Acta Scientific NEUROLOGY

Volume 8 Issue 5 May 2025

Review Article

Dopaminergic Homeostatic Therapy (DHT™) as a Putative Anti-Addiction Seeking Intervention and Early Identification of Genetic Preaddiction with Genetic Addiction Risk Severity (GARS®) Screening

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Received: March 21, 2025

Published: April 30, 2025

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Abstract

In spite of the ongoing exquisite work of a multitude of researchers worldwide including governmental institutions like the National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and for example in the United States the FDA Medication Assisted Therapy (MAT) embracing Opioid Replacement Therapy (ORT) in 2022, 111,000 people prematurely died from opioid induced overdose. It is estimated that if treatment stays as usual by 2025 the death rate will increase to 165,00.Therefore, we are encouraging the scientific and clinical community to at least consider our "out of the box" thinking whereby we are proposing a new paradigm shift involving the " dopaminergic homeostatic modeling approach and Genetic screening to early identify preaddiction. In this novel approach following detoxification from for example powerful opioids, the patient is administered the validated RDSQ29 to access potential psychological profiling of Reward Deficiency Syndrome (RDS); obtain a cheek cell sample of the patient and perform genetic screening utilizing the Genetic Addiction Risk Severity (GARS); analyze mRNA to identify specific protein deficits/surfeits based on the measured reward genes involved in the Brain Reward Cascade (BRC); produce a customized pro-dopamine regulator (KB220) guided by GARS resulting polymorphisms; objectively employ the mRNA profiling assessment every week during the treatment phase to determine improvement; each treatment program could add on at their choice, for example, cognitive behavioral therapy, brain spotting, trauma therapy, electrotherapy (h-wave device to reduce pain, subluxation repair etc.) mindfulness, exercise, neuromodulation (PrTMS) amongst other modalities. The utilization of this model could prove beneficial to both substance and non-substance behavioral addictions (e. g. gaming). WC261 .

Keywords: Behavioural Addictions; Dopamine, Neurotransmitters; GARS; Preaddiction; MAT; Harm Avoidance

Introduction

One major step in the addiction psychiatry field is the inclusion within the ICD-11, a new category of non-substance-related addictive disorders due to addictive behaviors [1-5]. Drug addiction or Reward Deficiency Syndrome (RDS) [6,7] in spite of naysayers that believe that all substance and non-substance seeking behavior is due to one moral fabric [8], is indeed a brain disorder caused by the repetitive use of various substances, despite catastrophic consequences, which alter normal functioning of the central nervous system.

However, most importantly is the concept of pre-addiction espoused in the 70s and now invigorated by McLellan, Koob and Volkow [9] involving both DNA polymorphic antecedents and/or epigenetics [10] . In the search to comprehend which neurotransmitter systems (at least nine) play a role in all addictive behaviors and pathology thereof [11], dopamine has long been thought to play a primary role [12]. However, its major role is commonly and erroneously attributed to the known increase in function and release presynaptically, after acute administration of all addicting agents and even behaviors [13].

On the other hand, the mesolimbic dopamine transmission appears to be drastically reduced in its tonic activity when measured in animal models [14] and in humans [15]. Along these lines many reviews and experiments strongly support the concept of hypodopaminergic trait/state [see 16]. There is indeed a long history evoking dopamine depletion and as such a hypodominergia in substance seeking behavior like cocaine, alcohol, cannabis and morphine abuse [17-20]. It is quite noteworthy, that many experimental approaches including electrophysiological [21], biochemical [22], behavioral [23], biomolecular and even anatomical [24,25] , reveal that dopamine neurons function in the critical phases of the entire addiction cycle.

This hypodopaminergic trait/state triggers drug/behavioral seeking. Moreover, in spite of decrease in its activity, the system unfortunately induces a hypersensitivity to both substance and non-substance behavioral 'wanting" to confer long-lasting vulnerability to the system [26-28]. We propose that targeting the dopamine system with mild non-addicting agonistic agents, albeit not necessarily classic receptor-oriented drugs, instead complex nutraceuticals like KB2220 or any other modalities that induce dopamine balance

or homeostasis, aimed at restoring dopamine transmission may induce useful *'out of the box thinking* " instead of blocking dopaminergic function as observed with a number of FDA approved MATs for alcohol [29] or opioids[30] the treatment of ' reward dysregulation " a societal pathological dilemma [31-34]. Specifically, Acamprosate dose-dependently attenuated ethanol intake and preference. Acamprosate inhibited ethanol-stimulated increases in nucleus accumbens dopamine release [29]. Olive., *et al*. [29] suggested that acamprosate seems to attenuate ethanol intake by interfering with ethanol's ability to stimulate the mesolimbic dopamine reward system. In addition, Sorge and Stewart [30] reported that chronic administration with the partial mu-opioid receptor agonist, buprenorphine, blocks the NAc dopamine response to an acute injection of heroin, in contrast it potentiates the response to an acute injection of cocaine after 4-5 days of treatment. Unfortunately, even though buprenorphine/naloxone combinations significantly reduce harm [35], has been shown to negatively impact one's affect. Hill., *et al*. [31] utilized emotion-detection in speech as a measure of "true" emotionality in 36Suboxone (SUBX) patients compared to 44 subjects from the general population (GP) and 33 members of Alcoholics Anonymous (AA). This study revealed that current opioid users have abnormal emotional experiences, characterized by heightened response to unpleasant stimuli and blunted response to pleasant stimuli. The authors found that in long-term SUBX patients a significantly flat affect ($p < 0.01$), and they had less self-awareness of being happy, sad, and anxious compared to both the GP and AA groups. Along similar lines the FDA approved antismoking pharmaceutical Varenicline known to block nicotine-evoked dopamine increases in the NAc through action on nicotinic acetylcholine receptors.

Extant literature confirms that an array of polymorphic genes related to- neurotransmitters and second messengers govern the net release of dopamine in the NAc in the mesolimbic region of the brain. They are linked predominantly to motivation, anti-stress, incentive salience (wanting), and wellbeing [34]. In our opinion, while OPT has heuristic value in the very short term, for example acute pain only seven days of powerful opioids are recommended by the Center for Disease Control(CDC) [36], current clinical consensus is to treat opioid Use Disorder (OUD) , as if it were an opioid deficiency syndrome, with long-term to life-long opioid substitution therapy. Other than as harm reduction, is using opioids to treat OUD therapeutic or harmful in the long term? Our laboratory has argued for scholarly caution in the chronic utilization of ORT. We believe the molecular framework to comprehend the current underpinnings of endorphinergic/dopaminergic mechanisms linked to opioid deficiency syndrome (a subtype of RDS) and generalized reward processing depletion could enable more appropriate therapeutic targets.

In 1989, along with Gerald Kozlowski of Southwestern Medical School in Dallas, Texas and one of us (KB) , many scientifically sound research articles were reviewed, and the various ways that neurotransmitters interact within the brain were tracked [37]. Over many decades we have developed a detailed map that described the reward circuitry of the brain was developed initially at that time by embracing the work of Wise and Bozarth [38]. This basic conceptual framework termed *"Brain Reward Cascade"* (BRC) [SEE FIGURE1] described shared neurochemical correlates between drugs [39] and as common to all addictive behaviors [40]. The basic tenant of this work is that the feeling of well-being can be achieved only when the dopamine molecule is released in the NAc at balanced "homeostatic" levels. Any deviation induces *"dopamine resistance"* and as such, could result in cravings, whether liking or wanting [26-28]. Also, excessive dopamine can lead to schizophrenia [41] and too little dopamine could lead to unhappiness, anhedonia or depression [42].

Need new figure

Dopaminergic Homeostatic Therapy (DHT)

While various constituents of the proposed dopaminergic homeostatic modeling novel approach have been evaluated over many decades, unfortunately there are no studies to date to support this intervention. However, we will provide the readership with supporting material for each component [See Figures 2-13]

STEP 1. Detoxification

In order to explore the initiation of detoxification of addictive patients to opiates/opioids (along with some other anti-withdrawal agents), Blum., *et al*. [43] developed a protocol to be utilized in treatment centers particularly with heavily dependent opiate/opioid subjects. Out of 17 subjects, only three received Buprenorphine/Naloxone (Bup/nx) along with KB220Z. In this pilot, we first used a dose of KB220Z of 2 oz twice daily before meals along with

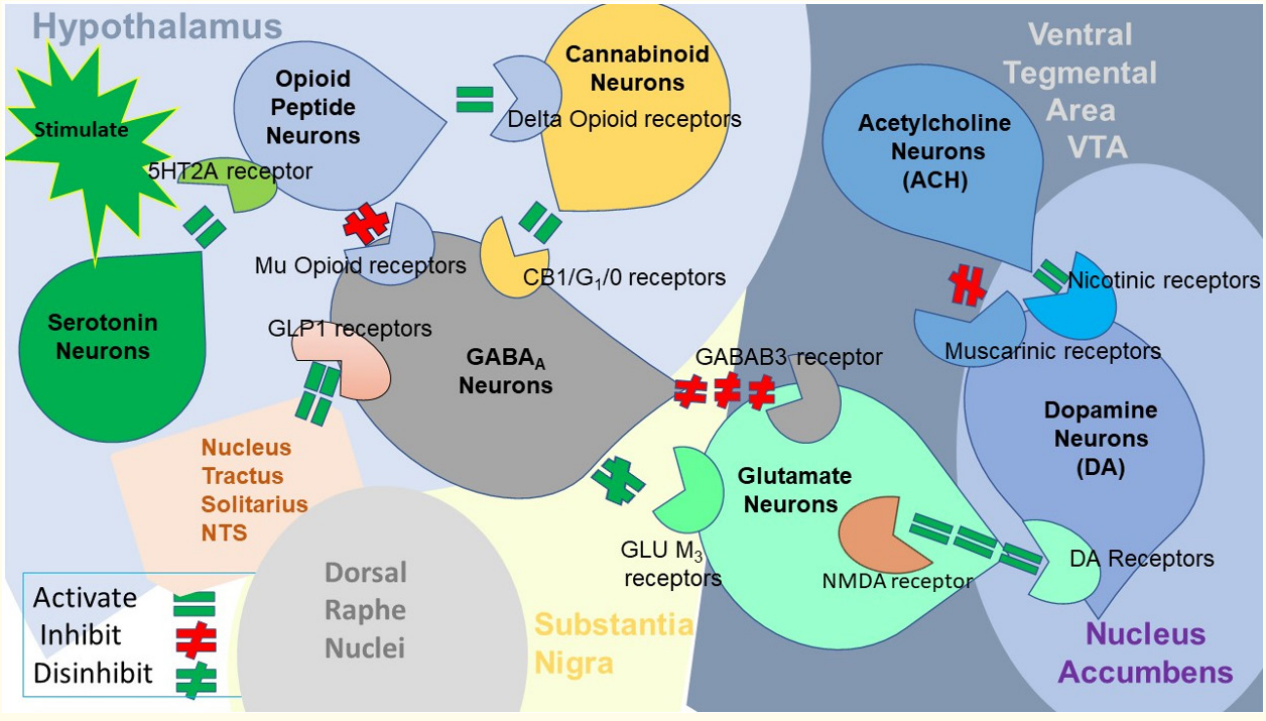

Figure 1: The interaction of some well-known brain reward cascade (BRC) neurotransmitter pathways are illustrated. Environmental stimulation initiates the release of serotonin in the hypothalamus, which in turn, for example, via 5 HT-2 A receptors activates (green equal sign) the subsequent release of opioid peptides from opioid peptide neurons. Then, in the Substantia Nigra, the opioid peptides move to two different opioid receptors with different effects. One is through the mu-opioid receptor that inhibits (red hash sign) GABAA neurons (possibly via an opioid peptide like enkephalins). The second stimulates cannabinoid neurons (for example, the Anandamide and 2-arachidonoylglycerol) (green equal sign) through beta-endorphin-linked delta receptors, which inhibit GABAA neurons. When activated, cannabinoids, primarily the 2-arachidonoylglycerol neurons, can disinhibit (green hash sign) GABAA neurons indirectly by G1/0 coupled to CB1 receptor activation. The Glutamate neurons in the Dorsal Raphe Nuclei (DRN) disinhibit GABAA neurons in the Substantia Nigra indirectly through GLU M3 receptor activation (green hash sign). When disinhibited, GABAA neurons will powerfully inhibit (red hash signs) VTA glutaminergic drive via GABAB 3 receptors. At the Nucleus Accumbens (NAc), Acetylcholine (ACH) neurons may inhibit (red hash sign) muscarinic and stimulate Nicotinic (green hash) receptors. Glutamate neurons in the VTA will project to dopamine neurons through (NMDA) receptors (green equal sign) to definitively release dopamine at the NAc. (WITH PERMISSION BLUM ET AL.)

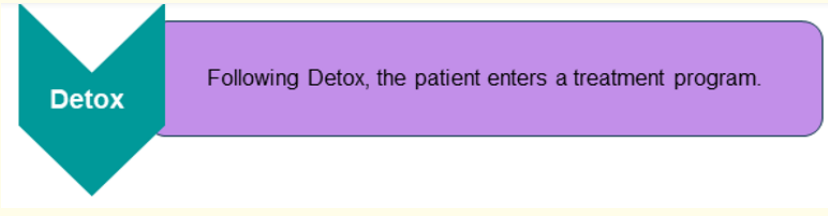

Figure 2

clonidine and benzodiazepines and other anti-nausea and sleep aids including Gabapentin. The dose of KB220Z was maintained for 6 days in five individuals. In a second scenario, we utilized a higher dose of 4 oz every 6 hours, over a 6-day period. The higher dose was employed in another 12 patients. It is noteworthy that only 3 people have relapsed utilizing these two protocols during the first two weeks of the study, allowing for the remaining 82% to be maintained on KB220Z. The patients have been maintained without any additional Bup/nx for a minimum of 120 days and in one subject, 214 days. Moreover, because of the utilization of standard detoxifying agents in this detoxification protocol, we cannot make any inference to KB220Z's effects. However, out of 17 subjects, only three required Bup/nx suggesting an interesting finding. If further confirmed in larger studies, the utilization for opiate/opioid detoxification may provide a novel way to eliminate the need for addictive opioids during withdrawal and detoxification. This paradigm shift may translate to a reduction in utilizing powerful and addictive opioids like buprenorphine and methadone (especially in these patients at high genetic risk for addiction) as not only detoxifying agents, but also maintenance drugs. While extensive research is required, this pilot paves the way for future investigations that could assist in the reduction of addictive opiate/opioid use and mortalities amongst both the young and old in America.

STEP 2. RDSQ29

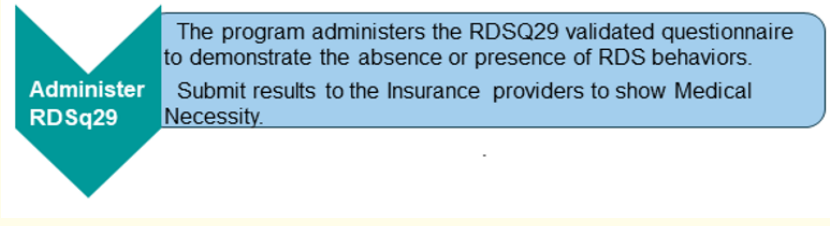

Figure 3

Reward deficiency syndrome (RDS) integrates psychological, neurological, and genetic factors of addictive, impulsive, and compulsive behaviors. According to Kótyuk., *et al*. [44] Data was collected on two college and university samples. Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) were performed on Sample 1 (N = 1726), and confirmatory analysis was conducted on an independent sample (N = 253). Impulsivity and sensation-seeking were assessed. Based on EFAs, a 29-item Reward Deficiency Syndrome Questionnaire (RDSQ-29) was developed, containing four subscales (lack of sexual satisfaction, activity, social concerns, and risk-seeking behavior). CFA indicated good fit (comparative fit index (CFI) = 0.941; Tucker-Lewis index (TLI) = 0.933; root mean square error of approximation (RMSEA) = 0.068). Construct validity analysis showed a strong relationship between sensation-seeking and the RDS scale. The RDSQ-29 is an adequate scale assessing psychological and behavioral aspects of RDS. The RDSQ-29 assesses psychological and behavioral characteristics that may contribute to addictions generally. In fact, we believe that this kind of data utilizing the RDSq29 when submitted to insurance companies will increase te chance for medical necessity to administer the GARS test.

STEP 3. GARS

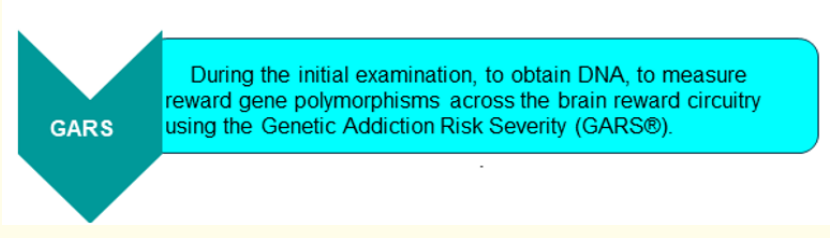

Figure 4

Since 1990, published addiction psychiatry articles have exceeded 11,495. Several from Blum., *et al*. showed the clinical relevance of the Genetic Addiction Risk Severity (GARS) test in identifying risk for reward deficiency behaviors in cohorts from polysubstance and pain clinics, post-surgical bariatrics, and DWI offenders facing prison time. Since Blum., *et al*. first published in JAMA (1990) concerning the association of the *DRD2* gene polymorphism and severe alcoholism, confirmation has been mixed and controversial. More recently, however, a meta-analysis of 62 studies showed a significant association between *DRD2* rs 1800497 and Alcohol Use Disorder (AUD). Other studies from Yale University showed that a haplotype block of the *DRD2* gene A1 allele was associated with AUD and heroin dependence. GWAS studies of depression and suicide in 1.2 million veterans confirmed the first psychiatric candidate gene study finding from Blum., *et al*. 1990; a significant association between the minor *DRD2* allele, Taq A1 (rs 1800497 C > T) and severe alcoholism. Additionally, the *DRD2* rs1800497 is associated with suicide behaviors robustly at $P = 1.77 \times 10^{-7}$. Furthermore, DNA polymorphic alleles underlying SUD with multiple substances were mapped via chromatin refolding, revealed that the *DRD2* gene and associated polymorphism(s) was the top gene signal (DRD2, $P = 7.9 \times 10^{-12}$). Additionally, based on these investigations, we conclude that GWAS should end the controversy about the *DRD2* gene being at least one determinant of Reward Deficiency Syndrome (RDS) first reported in the Royal Society of Medicine journaling 1996 [45].

When our laboratory published the association of the DRD2 Taq A1 allele and severe alcoholism in *JAMA*, there has been an explosion of genetic candidate association studies, including GWAS. To develop an accurate test to help identify those at risk for at least Alcohol Use Disorder (AUD), Blum's group developed the Genetic Addiction Risk Severity (GARS) test, consisting of ten genes and eleven associated risk alleles. In order to statistically validate the selection of these risk alleles measured by GARS, we applied strict analysis to studies that investigated the association of each polymorphism with AUD or AUD-related conditions published from 1990 until 2021. This analysis calculated the Hardy-Weinberg Equilibrium of each polymorphism in cases and controls. If available, the Pearson's χ^2 test or Fisher›s exact test was applied to comparisons of the gender, genotype, and allele distribution. The statistical analyses found the OR, 95% CI for OR, and a post-risk for 8% estimation of the population›s alcoholism prevalence revealed a significant detection. The OR results showed significance for DRD2, DRD3, DRD4, DAT1, COMT, OPRM1, and 5HTT at 5%. While most of the research related to GARS is derived from our laboratory, we are encouraging more independent research to confirm our findings [46].

STEP 4. CUSTOMIZED KB220

DNA Customization of nutraceutical products is here. In the truest sense, "Gene Guided Precision Nutrition™" and KB220 variants (a complex mixture of amino-acids, trace metals, and herbals) are the pioneers and standard-bearers for a state of the art DNA customization. Findings by both Kenneth Blum, Ph.D. and Ernest Noble, Ph.D. concerning the role of genes in shaping cravings and pleasure- seeking, opened the doors to comprehension of how genetics control our actions and affect our mental and physical health. Moreover, technology that is related to KB220 variants in order to reduce or eradicate excessive cravings by influencing gene expression is a cornerstone in the pioneering of the practical applications of nutrigenomics. Continuing discoveries have been an important catalyst for the evolution, expansion, and scientific recognition of the significance of nutrigenomics and its remark-

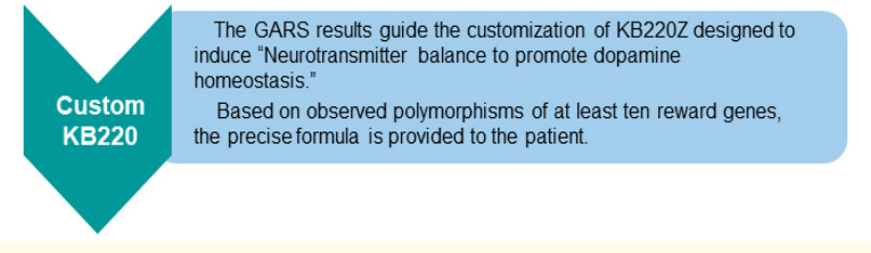

Figure 5

able contributions to human health. Neuro-Nutrigenomics is now a very important field of scientific investigation that offers great promise to improving the human condition. In the forefront is the development of the Genetic Addiction Risk Score (GARS™), which unlike 23andMe, has predictive value for the severity of drug and alcohol abuse as well as other non-substance related addictive behaviors. While customization of neuronutrients has not yet been commercialized, there is emerging evidence that in the future, the concept will be developed and could have a significant impact in addiction medicine [47].

STEP 5- Precision Behavioral Management

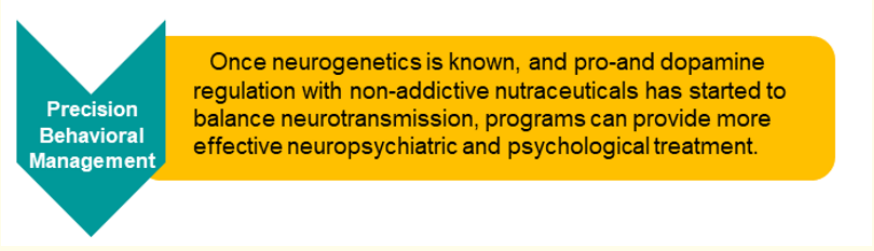

Figure 6

America is experiencing a high prevalence of substance use disorders, primarily involving legal and illegal opioid use. A 3000% increase in treatment for substance abuse occurred between 2000 and 2016. Unfortunately, present day treatment of opioid abuse involves providing replacement therapy with powerful opioids to, at best, induce harm reduction, not prophylaxis. These interventions do not enhance gene expression and restore the balance of the brain reward system's neurotransmitters. We are herein proposing a generalized approach called "Precision Behavioral Management". This approach includes 1) using the Genetic Addiction Risk Severity (GARS, a 10 candidate polymorphic gene panel shown to predict ASI-alcohol and drug severity) to assess early pre-disposition to substance use disorder; 2) using a validated reward deficiency syndrome (RDS) questionnaire; 3) utilization of the Comprehensive Analysis of Reported Drugs (CARD™) to assess treatment compliance and abstinence from illicit drugs during treatment, and, importantly; 4) utilization of a "Pro-dopamine regulator (KB220)" (via IV or oral [KB220Z] delivery systems) to optimize gene expression, restore the balance of the Brain Reward Cascade's neurotransmitter systems and prevent relapse by induction of dopamine homeostasis, and; 5) utilization of targeted DNA polymorphic reward genes to direct mRNA genetic expression profiling during the treatment process. Incorporation of these events can be applied to not only the under-considered African American RDS community, but all victims of RDS, as a demonstration of a paradigm shift that uniquely provides a novel putative "standard of care" based on DNA guided precision nutrition therapy to induce "dopamine homeostasis" and rebalance neurotransmitters in the Brain Reward Cascade. We are also developing a Reward Deficiency Syndrome Diagnostic Criteria (RDSDC) to assist in potential tertiary treatment [48].

STEP 6- Identify enhanced compromised proteins with mrna during treatment phase

Neural pathways and drugs interact to affect mRNA's expression of enzymes that produce neurotransmitters, consequent neurotransmission, and the neuronal receptors responsible for feelings of well-being in animals and humans [49] . Convergent input of the indirect striatopallidal and the direct striatonigral pathways, to the basal ganglia, and the dopaminergic modulation of these pathways, are very important in reward and aversion learning and substance dependence [50,51]. To understand the role of the basal ganglia in processing information from these two pathways, Hikida., *et al*. [52] developed a selective, reversible technique for blocking the activity of each pathway. Their results indicated that the effect of dopamine mediated psychostimulants required the coordinated modulation of the striatonigral and striatopallidal pathways. The direct striatonigral pathway was predominant in reward learning and cocaine sensitization, whereas the indirect, striatopallidal pathway was involved in aversive learning. These two pathways have different functional roles, the striatonigral pathway discriminating stimuli associated

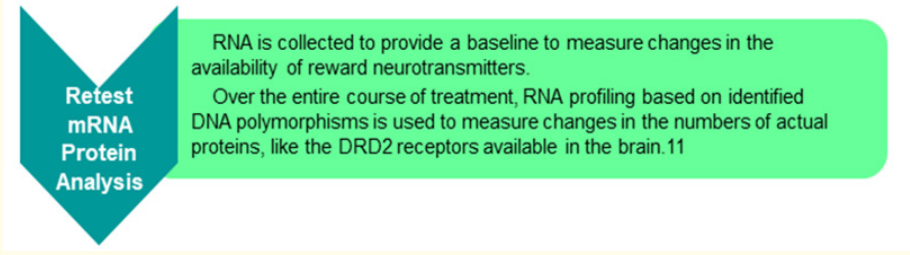

Figure 7

with reward and non-reward, and the striatopallidal pathway supporting memory for aversive stimuli. "What is the role of drugs of abuse on mRNA in these pathways?" We have carefully explored this concept especially since it has an important function in helping to determine treatment outcomes pre- and post-treatment. This has culminated in the development of a map yielding for the first time a comprehensive test involving multiple mRNA expressions utilizing array analysis to detect the type of expression (up or down) dependent upon the drug in question for a particular subject. Therefore, utilizing GARS, the mRNA outcome test for each patient follows the GARS test result as they enter the treatment facility or primary care program followed by a number of weekly retests to pinpoint any formidable changes in mRNA expression.

An early example of mRNA gene expression and SUD was the Noble., *et al.* [53] discovery that the brains of alcoholic and non-alcoholic subjects differed in the binding affinity and number of binding sites of the dopamine D2 receptor in the caudate nucleus. The binding affinity of the D2 receptor and the number of D2 receptor binding sites were lower in alcoholics compared to non-alcoholics. Furthermore, subjects with the A1 allele who also had alcoholism showed significantly reduced dopamine D2 receptor sites. The number of these sites was progressively reduced as the involvement of the A1 allele increased from the A2/A2, to A2/A1 to A1/A1 genotypes. Subjects with the A2/A2 genotype had the highest number of dopamine D2 receptor sites whereas subjects with the A1/A1 genotype had the lowest number of D2 binding sites. In fact, the A1/A1 subjects demonstrated decreased protein expression in association with a 30–40% reduction in dopamine D2 receptors. The differential expression of dopamine D2 receptors as a function of the polymorphic pattern of the dopamine D2 receptor gene supports the involvement of the dopamine system in vulnerability to a subtype of severe alcoholism. The Noble., *et al.* [52] study is an example of the effect of the dopamine receptor gene alleles on Reward Deficiency Syndrome. There are ten genes and eleven alleles[54] that influence RDS behaviors. Each allele changes the expression of RNA transcription with the effect of decreasing protein synthesis. In Noble., *et al.* [53] the A1/A1 allele showed reduced protein expression in association with reduced dopamine D2 receptors in the caudate nucleus.

STEP 7. Overdose opioid induced deaths

In the face of the current Opioid crisis in America killing close

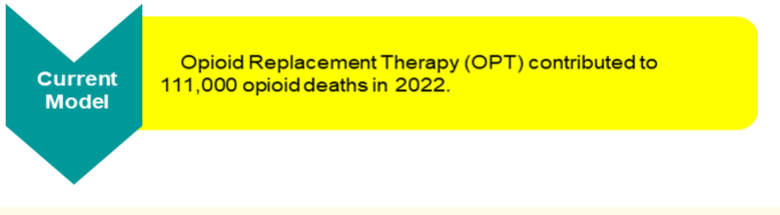

Figure 8

to 800,000 people since 2004, and 110,000 fatalities as of 2022, we are proposing a novel approach to assist in at least attenuating these unwanted premature deaths. While we applaud the wonderful efforts of our governmental institutes and professional societies (NIDA, NIAAA, ASAM, ABAM) in their extraordinary efforts in combating this continued dilemma, the current approach is failing, and other alternative approaches should at least be tested. These truths present a serious ethical dilemma to scientists, clinicians and counselors in the Reward Deficiency Syndrome (RDS) treatment community. It is important to realize that the current DSM-5 does not actually accurately display the natural brain reward process. The human brain has not been designed to carve out specific drugs like opioids, alcohol, nicotine, cocaine, benzodiazepines or cannabis and process addictions such as gambling as distinct endophenotypes. This is true in spite of natural ligands for cannabinoids, endorphins, or even benzodiazepines. The most accurate endophenotype is indeed reward dysfunction (e.g., hypodopaminergic or hyperdopaminergic). With this in mind, we are hereby proposing that the current Medication Assisted Treatment (i.e., 'MAT') expands to needed individuals as an initial "Band-Aid" to reduce harm avoidance, with the long-term goal of prophylaxis. So, to be clear, there may be other promising modalities other than MAT such as personalized repetitive transcranial magnetic stimulation (PrTMS), exercise and even new medications with positive allosteric modulators of GABA-A receptors, as well as the highly researched Genetic Addiction Risk Score (GARS) coupled with precision KB220Z. This will induce "dopamine homeostasis" to effectively rebalance and restore healthier brain function by promoting the cross talk between various brain regions (e.g., nucleus accumbens, cingulate gyrus, hippocampus etc.) resulting in dopamine homeostasis. Our laudable goal is to not only save lives, but to redeem joy and improve the quality of life in the recovery community through scientifically sound natural non-addicting alternatives [55].

STEP 8-Naloxone treatment with kb220

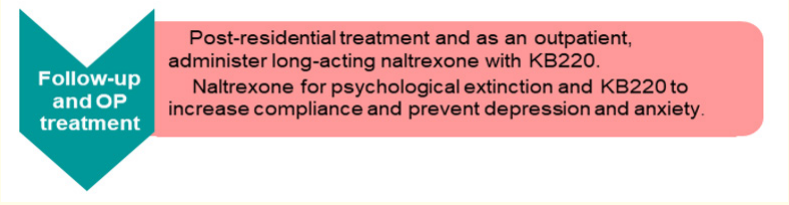

Figure 9

A recent analysis from Stanford University suggested that without any changes in currently available treatment, prevention, and public health approaches, we should expect to have 510,000 deaths from prescription opioids and street heroin from 2016 to 2025 in the US. In a recent review, Mayo Clinic Proceedings (October 2019), Gold and colleagues at Mayo Clinic reviewed the available medications used in opioid use disorders and concluded that in private and community practice adherence is more important as a limiting factor to retention, relapse, and repeat overdose. It is agreed that the primary utilization of known opioid agonists like methadone, buprenorphine and naloxone combinations, while useful as a way of reducing societal harm, is limited by 50% of more discontinuing treatment within 6 months, their diversion, and addiction liability. Opioid agonists may have other unintended consequences, like continuing the down regulation of dopamine systems. While naltrexone would be expected to have opposite effects, adherence is also low even after detoxification and long acting naltrexone injections. Recent studies have shown Naltrexone is beneficial by attenuation of craving via "psychological extinction" and reducing relapse. Buprenorphine is the MAT of choice currently but injectable Naltrexone plus an agent to improve dopaminergic function and tone may renew interest amongst addiction physicians and patients. Understanding this dilemma there is increasing movement to opt for the non-addicting narcotic antagonist Naltrexone. Even with the extended injectable option there is still poor compliance. As such, we point to an open label investigation in humans showing improvement of naltrexone compliance and outcomes with dopamine augmentation with the pro- dopamine regulator KB220 (262 days) compared to naltrexone alone (37days) [56]. This well studied complex consists of amino-acid neurotransmitter precursors and enkephalinase inhibitor therapy compared to treatment as usual. Consideration of this novel paradigm shift may assist in not only addressing the current opioid epidemic but the broader question of reward deficiency in general [57].

STEP 9- Evidence-based treatment options

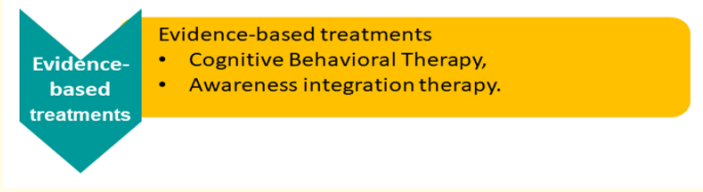

Figure 10

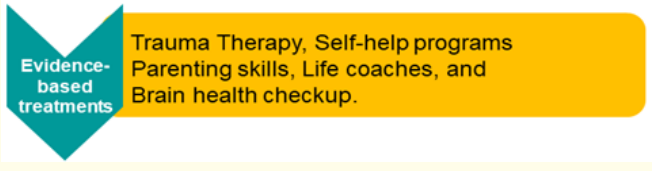

Figure 11

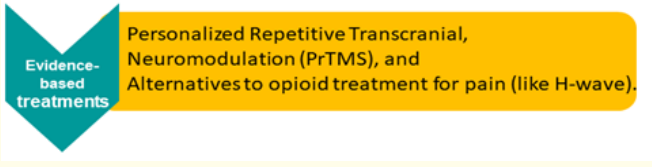

Figure 12

Since 2000 there have been 915,515 people who have died from a drug overdose in the United States (US).As mentioned earlier, this number continues to increase and in 2022 drug overdose deaths reached a record high of 111,000, and opioids involving Fentanyl, specifically were responsible for most of those deaths. This unprecedented rate of drug overdose deaths is the direct result of increasing rates of illicit drug use in the US. It was estimated that in the US in 2020, approximately 59.3 million individuals had used illicit drugs, 40.3 million had a substance use disorder (SUD), and 2.7 million had opioid use disorder (OUD). Typical treatment for OUD involves an opioid agonist (i.e., buprenorphine or methadone) along with a variety of psychotherapeutic interventions (i.e., motivational interviewing, cognitive-behavioral therapy (CBT), behavioral family counseling, mutual help groups, H-wave, PrTMS, etc.). In addition to the aforementioned treatment options, there is an urgent need for new therapies and screening methods that are reliable, safe, and effective. Similar to the concept of prediabetes is the novel concept of "preaddiction." Preaddiction is defined as individuals with mild to moderate SUD or those at risk for developing a severe SUD/addiction. Screening for preaddiction could be achieved through genetic testing (i.e., the genetic addiction risk severity (GARS) test) and/or through other neuropsychiatric testing (i.e., Memory (CNSVS), Attention (TOVA), Neuropsychiatric (MCMI-III), Neurological Imaging (qEEG/P300/EP). The concept of preaddiction, when used in conjunction with standardized and objective diagnostic screening/testing, would halt the rise of SUD and overdoses with early detection and treatment [58]. Currently, there is a thrust to invigorate the carefully monitored psychedelic assisted-therapy micro-dosing for all RDS behaviors [59]. Specifically, psilocin (3-[2-(dimethylamino)ethyl]-1*H*-indol-4-ol) is a hallucinogenic component of the Mexican mushroom *Psilocybe mexicana* and a skeletal serotonin (5-HT) analogue. Psilocin is the active metabolite of psilocybin (3-[2-(dimethylamino)ethyl]-1*H*-indol-4-yl dihydrogen phosphate). Sakashita., *et al.* (2014) examined the effects of systemically administered psilocin on extracellular dopamine and 5-HT concentrations in the ventral tegmental area

(VTA), nucleus accumbens, and medial prefrontal cortex of the dopaminergic pathway in awake rats using *in vivo* microdialysis. Intraperitoneal administration of psilocin (5, 10 mg/kg) significantly increased extracellular dopamine levels in the nucleus accumbens. Psilocin did not affect the extracellular 5-HT level in the nucleus accumbens. Conversely, systemic administration of psilocin (10 mg/kg) significantly increased extracellular 5-HT levels in the medial prefrontal cortex of rats, but dopamine was decreased in this region. Behaviorally, psilocin significantly increased the number of head twitches. Thus, data suggest that psilocin increased both the extracellular dopamine and 5-HT concentrations in the mesoaccumbens and/or mesocortical pathway [60].

There is plethora of data to evoke cognitive behavioral therapy [61], awareness integration therapy [62], and neuromodulation [63-65].

Futuristic perspecrive

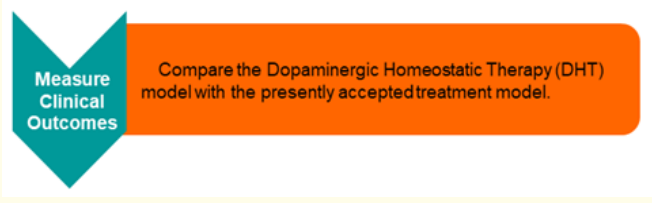

Figure 13

In face of the unwanted global opioid and other psychoactive abuse we are compelled to find reasonable solutions. While it is true that very short term Opioid Replacement Therapy (OPT) successfully reduces harm, it is also true that long-term use and subsequent loss of insurance leads to the uncanny use of fentanyl laced heroin followed by death [66]. As of December 2022, the MAT Act has eliminated the DATA-Waiver (X-Waiver) program. All DEA-registered practitioners with Schedule III authority may now prescribe buprenorphine for OUD in their practice if permitted by applicable state law, and SAMHSA encourages them to do so. Prescribers who were registered as DATA-Waiver prescribers will receive a new DEA registration certificate reflecting this change; no action is needed on the part of registrants. Blum., *et al*. has argued the wisdom of this expansion with caution [67]. In an effort to reduce potential overdose rated many clinicians and scientists have opted to switch the frontline modality to treat opioid dependence and alcoholism with the non-addictive narcotic antagonist naltrexone, however, there is poor compliance even with the injectable form [68] . As mentioned earlier, this poor compliance has been overcome by adding the pro-dopamine regulator KB220 [69] and as such should be seriously considered in te future .It seems reasonable to engage in intensive research comparing DHT with the presently acceptable treatment model including ORT. Addiction is a substantial health issue with limited treatment options approved by the FDA and as such currently available. The advent of neuroimaging techniques that link neurochemical and neurogenetic mechanisms to the reward circuitry brain function provides a framework for potential genomic-based therapies. Through candidate and genome-wide association studies approaches, many gene polymorphisms and clusters have been implicated in drug, food and behavioral dependence linked by the common rubric reward deficiency syndrome (RDS). New targets for addiction treatment and relapse prevention, treatment alternatives such as gene therapy in animal models, vaccines, gene editing, and pharmacogenomics and nutrigenomics methods to manipulate transcription and gene expression should be explored. The recognition of the clinical benefit of early genetic testing to determine addiction risk stratification and dopaminergic agonistic, rather than antagonistic therapies are potentially the genomic-based wave of the future [70]. In addition, further development, especially in gene transfer work and viral vector identification as first explored by Thanos and Volkow and associates [71-73] could make gene therapy for RDS a possibility in the future. Finally, additional research related to least dopaminergic genetics and epigenetics including binding studies along the array of RDS seems parsimonious [74]. Finally, there is strong evidence that various exercise programs affect dopaminergic and other important neurotransmitters (e ,g, mu opioid receptor, GABA, serotonin, endorphins etc.), integrity and these effects translates to reduced addictive behaviors [75-100].

Conclusion

In conclusion, there is an urgent need for new therapies and screening methods that are reliable, safe, and effective. In addition, a standardized approach for how we approach addiction is necessary. Similar to the concept of prediabetes is the novel concept of "preaddiction." Screening for preaddiction could be achieved through genetic testing (i.e. the genetic addiction risk severity (GARS) test) and/or through other neuropsychiatric testing (i.e., Memory (CNSVS), Attention (TOVA), Neuropsychiatric (MCMI-III), Neurological Imaging (qEEG/P300/EP)). The concept of preaddiction, when used in conjunction with standardized and objective diagnostic screening/testing, along with the above novel theories discussed , would greatly improve brain/mental health and stop/prevent the rise of SUD and overdoses with early detection and treatment. Based on these and possibly other tenants we are encouraging independent research to prove or disprove the novel concept referred to as *"Dopaminergic Homeostatic Therapy (DHT)*.

Figure 14

To enhance comprehension, we have developed an informative schematic represented in figure 14.

Acknowledgements

The authors appreciate the graphics by Margaret A. Madigan RN.

Author Contribution

KUL,KB, MSG AND BF developed the first working draft and CD Checked all references and formatting and edits, IE,PKT,CH. AS, ZF,NJ,KS,MPL,ALPL KTM, added comments and references, EJM, ERB, DS, DB, reviewed and edited entire manuscript and added comments, and GM reviewed the manuscript and added references to psychedelic assisted therapy. All authors approved the final version prior to submission.

Conflict of Interest

KB is the inventor of GARS, KB220 and RDS. He is the recipient of both domestic and foreign patents, issued and pending.

Funding

R41 MD012318/MD/NIMHD NIH HHS/United States.
UL1 TR001409/TR/NCATS NIH HHS/United States.

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