Commentary

Precision Behavioral Management (PBM) and Cognitive Control as a Potential Therapeutic and Prophylactic Modality for Reward Deficiency Syndrome (RDS): Is There Enough Evidence?

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Abstract: This brief commentary aims to provide an overview of the available and relatively new precision management of reward deficiencies manifested as substance and behavioral disorders. Current and future advances, concepts, and the substantial evidential basis of this potential therapeutic and prophylactic treatment modality are presented. Precision Behavioral Management (PBM), conceptualized initially as Precision Addiction Management (PAM), certainly deserves consideration as an important modality for the treatment of impaired cognitive control in reward processing as manifested in people with neurobiologically expressed Reward Deficiency Syndrome (RDS).

Keywords: dopamine; hypodopaminergia; Genetic Addiction Risk Severity (GARS) test; pro-dopamine regulation (KB220); Restoregen®

1. Precision Behavioral Management

The Precision Behavioral Management (PBM) platform is related to addiction medicine, with the first USA and foreign patents related to the accurate Genetic Addiction Risk Severity (GARS®) test. Blum and Noble (JAMA, 1990) [1] found the first confirmed association of the DRD2 gene A1 allele with severe alcoholism and other Reward Deficiency Syndrome (RDS) behaviors, and Blum et al. have developed the GARS test and the pro-dopamine regulator, a nutraceutical neuronutrient (Research ID Code KB220) [2–102]. The basis of these addiction treatment interventions is research that identified a neurotransmitter network function within the Mesolimbic and Pre-Frontal Cortex (PFC) brain regions that regulates the final reward and motivational pathway of “wanting,” causing neuronal dopamine release (see Figures 1 and 2) [103–126].
Figure 1. Precision Behavioral Management (PBM) platform. Reprinted/adapted with permission from Ref. [127]. Gold et al. copyright 2021.

Figure 2. Mesolimbic Brain Reward Cascade [128]. This cartoon illustrates the interaction of the known major neurotransmitter pathways involved in the Brain Reward Cascade (BRC). In the hypothalamus, environmental stimulation results in the release of serotonin, which in turn, via, for example, 5HT-2a receptors, activates (green equal sign) the subsequent release of opioid peptides from opioid peptide neurons. Then, Substantia Nigra, the opioid peptides move to possibly two different opioid receptors with different effects. One inhibits (red hash sign) through the mu-opioid receptor (possibly via enkephalin) to GABA_A neurons. Another stimulates (green equal sign) cannabinoid neurons (the Anandamide and 2-archydonoglicerol, for example) through beta-endorphin-linked delta receptors, which inhibit GABA_A neurons. In addition, when activated, cannabinoids, primarily 2-arcydonoglerol, can indirectly disinhibit (green hash sign) GABA_A neurons through activation of G1/I0 coupled to CB1 receptors. In the Dorsal Raphe Nuclei (DRN), glutamate neurons can then indirectly disinhibit GABA_A neurons in the Substantia Nigra through activation of GLU M3 receptors (green hash sign). GABA_A neurons, when disinhibited, will, in turn, powerfully (red hash signs) inhibit VTA glutaminergic drive via GABAB 3 receptors. At the Nucleus, Accumbens ACH neurons may stimulate both muscarinic (red hash) and nicotinic (green hash). Finally, glutamate neurons in the VTA will project to dopamine neurons through NMDA receptors (green equal sign) to preferentially release dopamine at the Nucleus Accumbens (NAc), shown as a bullseye, indicating a euphoria, or “wanting” response. The result is dopamine release; low release is (endorphin deficiency), and unhappiness is felt. General (healthy) happiness depends on the dopamine homeostatic tonic set point (with permission) [22]. Notably, various hotheses have explained the findings that led to the modern known correlates of neurotransmitter interactions within this brain reward circuitry.
2. The Brain Reward Cascade

The cascading interaction of neurotransmitters and second messengers results in the correct release of dopamine within the NAc and across many brain regions. These regions are involved in motivation, cognition (memory), pleasure, stress reduction, drug reinstatement, decision making, recall, wellbeing, and cravings. The result is to provide *homo sapiens* with a usual happiness setpoint (i.e., dopamine homeostasis) [126], reflected in resting-state functional connectivity (rsFC) in neuroimaging studies [127].

In the neurophysiologic reward system, repeated frequent acute dopamine stimulation becomes chronic stimulation and leads to a dysfunctional hypodopaminergic state, rendering the reward system less responsive to natural reinforcers, a symptom of RDS [126,128]. The stimulation can be from euphorogenic substances, non-substances like gambling, or severe stressors like pain and anxiety. Chronic stimulation causes dopamine depletion (Hypodopaminergia). Reward deficiency results from depleted or hereditary hypodopaminergia, potentially reflected in a host of personality traits and mental and medical disorders that have been associated in genetic studies with dopamine depleting alleles. These symptoms and disorders create the diagnostic criteria for RDS and include, but are not limited to, novelty seeking, schizophrenia, obesity, chronic pain, post-traumatic stress disorder (PTSD), major depression, and attention deficit hyperactivity disorder (see Table 1) [129].

Table 1. Reward Deficiency Syndrome criteria.

| Set 1. Criteria DSM5 Disorders | A Present or Past Diagnosis or History of These Behavioral Disorders |
|-------------------------------|---------------------------------------------------------------------|
| Substance Use Process Disorders | Disorders: Alcohol Use Disorder, Opioid Use Disorder, Cannabis Use Disorder, Sedative, Hypnotic, Anxiolytic Use Disorder, Cocaine Use Disorder, Amphetamine Use Disorder, Hallucinogen Use Disorder, Nicotine Use Disorder, Inhalant Use Disorder, Other, Unknown Substance Use Disorder Specifiers: Mild, Moderate, Severe, Early Remission (6–12 months), Sustained Remission (12+ months), in a Controlled Environment, on Maintenance Therapy |
| Process Disorders | Gambling, Sex, Other Specified Process Disorders |
| Depressive (and related) Disorders | Major Depression, Dysthymia, Disruptive Mood Dysregulation, SUD/Medication/Medical Condition Inducted Depressive Disorder, Disruptive Premenstrual Dysphoric Disorder |
| Anxiety Disorders | Generalized Anxiety Disorder, Social Anxiety, Panic Attack Disorder, Separation Anxiety, Selective Mutism, Specific Phobia, SUD/Medication/Medical Condition Inducted Anxiety |
| Trauma and Stress Disorders | Reactive Attachment, Disinhibited Social Engagement, Post-Traumatic Stress Disorder (PTSD), Acute Stress Disorders |
| Disruptive, Impulse Control, and Conduct Disorders | Oppositional Defiant Disorder, Intermittent Explosive Disorder, Conduct Disorder, Pyromania, Kleptomania |
| Personality Disorders | General Personality Disorder, Paranoid Personality Disorder, Schizoid/Schizotypal Personality Disorder, Anti-Social Personality Disorder, Borderline Personality Disorder, Histrionic Personality Disorder, Narcissistic Personality Disorder, Avoidant Personality Disorder, Dependent Personality Disorder |
| Obsessive Compulsive Disorders and Related Disorders | Trichotillomania, Excoriation Disorder, SUD/Medication/Induced OCD Disorder, other Medical Condition, Induced Personality Disorder |
| Schizophrenic Disorders | Schizophrenia, Schizoaffective Disorder, Schizophreniform Disorder, Delusional disorder, Brief Psychotic Disorder, MH/Medical Catalonia, SUD/Medication/Medical Condition Inducted Psychotic Disorder |
| Dissociative Disorders | Dissociative Identity Disorder, Dissociative Amnesia, Depersonalization/Derealization Disorder |
| Other Not Otherwise Specified (NOS) Disorders | Gender Dysphoric Disorder, Paraphilic Disorders |
Table 1. Cont.

| Set 1. Criteria DSM5 Disorders |
|-------------------------------|
| A Present or Past Diagnosis or History of These Behavioral Disorders |
| Spectrum Disorders | Attention Deficient Disorder, Attention Deficient/Hyperactivity Disorder, Tourette’s Syndrome, Autism |

| Set 2. Criteria |
|-----------------|
| Reported history of these symptoms: |

| Novelty seeking | The y trait is associated with exploratory activity in response to novel stimulation, impulsive decision making, extravagance in approach to reward cues, quick loss of temper, and avoidance of frustration. |
| Impulsivity | The impulsivity construct includes at least two independent components: first, acting without an appropriate amount of deliberation, which may or may not be functional; and second, choosing short-term gains over long-term ones. |
| Difficulty feeling reward (Anhedonia) | Either a reduced ability to experience pleasure or a diminished interest in engaging in pleasurable activities. |
| Motivational Anhedonia | A decrease in motivation to participate in pleasurable activities. |
| Ruminative, Obsessive, and Intrusive Negative Thoughts | Possible causes and consequences, as opposed to its solutions. |

As alluded to above, reward deficiencies may also occur in the absence of dopaminergic stimulation by exogenous factors due to specific polymorphic alleles that alter the function of genes in the reward cascade. One example is the A1 allele of the D2 dopamine receptor gene that causes a reduced number of dopamine receptors in the mesolimbic NAc. An essential feature of RDS is the lack of integration between cognition, perception, and emotions occurring due to (1) substantial dopaminergic surges in reward, motivation, and learning centers leading to neuroplasticity in the striato-thalamic-frontal cortical loop, with ensuing top-down dissociation from the subcortical activity; (2) hypo-functionality of the excitatory glutamatergic afferents from the amygdala–hippocampus complex failing to produce bottom-up restraint of the striato-thalamic-frontal cortical loop [130–134].

The above aberrations may be a target of neuromodulation with therapeutic interventions and prophylaxis of addictive and related disorders. PBM combines the GARS test that identifies RDS risk polymorphisms and is used to ascertain the neuropathways involved in the tested individual’s hypodopaminergic risk neurotransmission finite pathways. These pathways are used in an algorithm to select a neuronutrient formulation of KB220 for that individual to induce the desired dopamine homeostasis by balancing genetic and epigenetic (neuro-molecular) brain reward activity [134].

3. Genetic Addiction Risk Severity (GARS)

The GARS test uses saliva samples and polymerase chain reaction (PCR) to identify dysfunctional polymorphisms of reward genes [135]. Genes express proteins that determine neurotransmitter function [136]. People who have Single Nucleotide Polymorphisms (SNPs) of genes in their DNA that cause dysfunctional dopaminergic neurotransmission are at risk of RDS behaviors, including addictions. The development of the GARS test used the reward cascade of neurotransmission to identify eleven SNPs that cause hypodopaminergia from ten reward genes [137–143].

Hypo-dopaminergia refers to a reduced dopamine function in the brain reward circuitry. As stated in the paper and indicated by the interrelatedness of at least seven main neurotransmitter pathways involving synthesis, vesicular pre-neuronal storage, mitochondrial catabolism, synaptic catabolism, neuronal clearance via transporters, receptor affinity, and number, carrying any one of the eleven polymorphic alleles could explain low dopamine function (see Table 1). One example is the finding by Noble and Blum that a progressively reduced Bmax was found in subjects with A2/A2, A1/A2, and A1/A1 alleles...
of the DRD2 gene, with subjects with A2/A2 having the highest and subjects with A1/A1, the lowest mean values (see Table 2).

### Table 2. Summary GARS test allele function and behavioral risk predisposition [138–144].

| Genetic Variant                  | Prime Function                                                                 |
|----------------------------------|--------------------------------------------------------------------------------|
| G-Allele COMT                    | Carriers of this allele will have a high activity of synaptic dopamine (DA) reabsorption leading to a reduced interaction at DA receptors. |
| A-Allele of the DRD1 receptor gene | Carriers of this allele will have a reduced number of DRD1 receptors and lower DA function within the brain reward circuitry. The DRD1 receptor is involved in promoting normal DA function. |
| A1 variant of the DRD2 receptor gene | Carriers of this allele will have a reduced number of DRD2 receptors up to 40% and, as such, will have a lower DA function within the brain reward circuitry, especially at the Ventral Tegmental Area (VTA) Nucleus Accumbens. |
| C variant of the DRD3             | Carriers of this allele will have a reduced number of DRD3 receptors and have a lower DA function within the brain reward circuitry. Studies have found that this allele associates with risk for Alcohol, Cocaine, and Opioid Use Disorder as well as opioid dependence, especially in the African American population. |
| C variant of the DRD4 receptor gene | Carriers of this allele will have a reduced number of DRD4 receptors and have a lower DA function within the brain reward circuitry. The DRD4 gene is responsible for normal DA function within the mesolimbic reward cascade, and the C variant is highly associated with risk for ADHD and novelty seeking. |
| G-Allele of the OPRM1 receptor gene | Carriers of this allele will have a reduced number of Mu opioid receptors. Reduced Mu opioid receptors reduce GABA transmission at the Raphe Nuclei and Substania Nigra, leading to a reduced DA release at the VTA via altered inhibition of the normal Glutaminergic drive. |
| 9 R allele of the DAT1 gene       | Carriers of this allele will have a high activity of synaptic dopamine (DA) reabsorption, leading to a reduced interaction at DA receptors. |
| S or LG allele of the 5-HTTLPR gene | Carriers of these alleles will have a high activity of synaptic serotonin reabsorption, leading to a reduced interaction at serotonin receptors. This paucity leads to a reduced serotonergic transmission at the hypothalamus in the mesolimbic system. The low serotonin activity results in a reduced interaction with the endogenous opioid peptides and, as such, a reduced inhibition at GABA sites. |
| 4 R variant of the MAOA gene      | Carriers of this allele will have a high activity of mitochondrial catabolism of both serotonin and dopamine. The high activity will reduce the projection of these neurotransmitters to storage at the pre-neuron vesicles for further release when fired with an action potential. |
| 181 allele of the GABRB3 gene      | Carriers of this allele will have an overexpressed GABRB3 that will lead to a higher GABA transmission at the VTA-Glutaminergic site, leading to hypodopaminergia. |

The GARS test examines the sum of many related polymorphisms instead of one gene alone to predict genetic risk for RDS behaviors. It is possible to find a significant association with the degree of risk for all addictive behaviors (RDS). In conjunction with the Institute of Behavioral Genetics at Colorado University, unpublished research compared the GARS test with the Addiction Severity Index (ASI) in 273 subjects from substance treatment centers to determine drug and alcohol risk severity. Alcohol risk severity \( p < 0.04 \) predicted with seven or more alleles, and drug risk severity \( p < 0.05 \) predicted with four or more alleles. Understanding the genetic antecedents to Alcohol Use Disorder (AUD) may help explain potential neuroplasticity in those dependent on alcohol or other substances of abuse [142].
4. Precision Behavioral Management (PBM) System

The PBM system uses the patented, commercially available GARS test with a nutraceutical Precision Neuronutrient-Research ID code: KB220 [143–146].

The GARS test identifies RDS risks and determines the neuopathways involved in hypodopaminergic risk to identify the neuronutrient formulation of KB220 via algorithm and create balanced genetic and epigenetic (neuro-molecular) brain function, the desired induction of dopamine homeostasis.

5. Cognitive Control of Reward Processing

This Special Issue is not only about risky behaviors (addiction) but also cognitive control of reward processing; here, we provide a few examples, emphasizing the role of dopamine in addiction and cognition. The neuronal release of dopamine in the limbic system relies on many neurotransmitters, peptides, and second messengers to impact the dopamine released at the NAc, which is critical to feeling good [127].

There are many examples of cognitive control of various aspects of drug and non-drug addictive behaviors. For example, the ability to resist the urge to eat is in part a function of the homeostatic functioning of neuronal circuits involved in top-down control to oppose the conditioned responses that predict reward from eating the food and the desire to eat the food. Moreover, imaging studies by Volkow’s group of this non-drug behavior have revealed that obese probands have impairments in dopaminergic pathways that regulate neuronal systems linked with reward sensitivity, conditioning, and control [147]. There is evidence that neuropeptides regulate energy balance (homeostatic processes) via the hypothalamus and subsequently modulate the activity of dopamine cells and their projections into the regions involved in the rewarding processes that modulate food intake.

Substance use disorders (SUDs), while effecting billions worldwide, are indeed preventable. Thousands of articles attest to the well-known effects of substance misuse that cause many physiological, molecular, and cellular changes in specific brain regions. Moreover, these neuroplastic changes have a role in seeking behaviors seen in substance and non-substance addictions [148,149].

Notably, many studies have focused on the dopamine neurons of the ventral tegmental area (VTA) and the regions where these neurons terminate: the striatum, the prefrontal cortex [148], and the amygdala. Specifically, decreases in dopamine receptors and transmission have been found in chronic users of psychostimulants [150], cannabis [151], opioids [152], alcohol [153], and nicotine [154].

Another example is the role of cognitive control and reward processing in Internet Gaming Disorder (IGD). There are indeed common neurochemical mechanisms that have been observed with both IGD and SUD [155]. Specifically, Functional Magnetic Resonance Imaging (fMRI) investigations of the resting state and measures of gray matter volume have shown that Internet game playing is associated with changes to brain regions responsible for attention and control, impulse control, motor function, emotional regulation, sensory-motor coordination [156], and stress processing [157]. Most interestingly, IGD was associated with reduced white matter density in brain regions involved in decision making, behavioral inhibition, and emotional regulation [158]. Playing videogames is also associated with changes in reward inhibitory mechanisms and loss of control [159]. In addition, Tain et al. [160] reported that D2 receptor activity is significantly associated with glucose metabolism in subjects with IGD, suggesting that D2/5-HT2A receptor-mediated dysregulation of the orbitofrontal cortex could underlie a mechanism for loss of control and compulsive behavior in IGD individuals.

There is also evidence from experiments that used lentivirus tools for over-expression or silencing of the dopamine transporter (DAT) gene in animals. Behavioral profiles that evaluated motivation and self-control compared to controls revealed significant differences. Specifically, DAT over-expressing rats showed increased impulsivity. The authors concluded that an attenuated dopaminergic tone following altered accumbal DAT func-
tion may subserve a sensation-seeker phenotype with vulnerability to lack of impulse control [161–163].

6. Summary

In summary [2–102,164–166]:

- No matter what therapeutic strategy the clinical team chooses, a beneficial practice for treatment and recovery is genetic addiction risk testing and personalized induction of dopamine homeostasis based on genetic test results.
- Indeed, the use of any treatment that reduces stress and enhances resting-state functional connectivity along the brain reward circuitry seems prudent.
- From pre-authorization of very short-term use of opioids to reduce harm to cognitive behavioral therapy, trauma therapy, brain spotting, stress reduction, rsTMS to deep brain stimulation, and 12-stepping, the foundational induction, via epigenetics, of gentle up-regulation of dopaminergic function will be an evidenced basis for the induction of treatment (without complications or side effects) to keep people from any form of dopaminergic dysfunction.
- Genetic addiction risk testing for patients attending a pain clinic provides information about the likelihood of a predisposition for Opioid Use Disorder (OUD) and enables the utilization of less addicting analgesia at the onset of treatment.
- Genetic testing should be the standard of care for all patients attending substance and non-substance (process addictions) dependency programs (i.e., inpatient, outpatient, and intensive outpatient programs).
- Genetic addiction risk testing for early risk identification in children, especially if they have addiction issues in the family (for example, children of alcoholics), combined with precision pro-dopamine regulation prophylaxis, may attenuate or prevent addiction risk.
- Coupling of KB220 precision variants with naltrexone to improve compliance [43].
- Combat cannabis-induced anhedonia in adolescents and adults with RDS using “Precision Behavioral Management” (PBM) to provide precision KB220 formulations [144,146].

7. Conclusions

Billions worldwide are affected by SUDs and RDS, which are preventable with PBM, genetic testing for addiction risk, and pro-dopamine precision KB220 formulations selected to treat neurotransmitter deficits. The neurotransmitter deficits are caused by the tested person’s dysfunctional alleles, identified by their genetic test results. This required induction of “dopamine homeostasis” is recommended for frontline tertiary addiction treatment and relapse prevention.

While more in-depth and extensive double-blinded studies combining the GARS test with KB220 precision formulations are encouraged, we believe that this body of evidence presented to support PBM, an important therapeutic and prophylactic modality for the treatment of impaired cognitive control of reward processing as manifested in patients expressing RDS, deserves careful consideration.

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References

1. Blum, K.; Noble, E.P.; Sheridan, P.J.; Montgomery, A.; Ritchie, T.; Jagadeeswaran, P.; Nogami, H.; Briggs, A.H.; Cohn, J.B. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA 1990, 263, 2055–2060. [CrossRef] [PubMed]
2. Blum, K.; Wood, R.C.; Braverman, E.R.; Chen, T.J.; Sheridan, P.J. The D2 dopamine receptor gene as a predictor of compulsive disease: Bayes’ theorem. *Funct. Neurol.* 1995, 10, 37–44. [PubMed]
3. Blum, K.; Lott, L.; Siwicki, D.; Fried, L.; Hauser, M.; Simpatico, T.; Baron, D.; Howeedy, A.; Badgaiyan, R.D. Genetic addiction risk score (GARS™) as a predictor of substance use disorder: Identifying predisposition not diagnosis. *Curr. Trends Med. Diagn. Methods* 2018, 1, 1. [CrossRef]
4. Blum, K.; Briggs, A.H.; Trachtenberg, M.C.; Delallo, L.; Wallace, J.E. Enkephalinase inhibition: Regulation of ethanol intake in genetically predisposed mice. *Alcohol* 1987, 4, 449–456. [CrossRef]
5. Chen, A.L.; Chen, T.J.; Waite, R.L.; Reinking, J.; Tung, H.L.; Rhoades, P.; Downs, B.W.; Braverman, E.; Braverman, D.; Kern, M.; et al. Hypothesizing that brain reward circuitry genes are genetic antecedents of pain sensitivity and critical diagnostic and pharmacogenomic treatment targets for chronic pain conditions. *Med. Hypotheses* 2009, 72, 14–22. [CrossRef]
6. Blum, K.; Bowirrat, A.; Baron, D.; Lott, L.; Ponce, J.V.; Brewer, R.; Siwicki, D.; Boyett, B.; Gondre-Lewis, M.C.; Smith, D.E.; et al. Biotechnical development of genetic addiction risk score (GARS) and selective evidence for inclusion of polymorphic alleric risk in substance use disorder (SUD). *J. Syst. Integr. Neurosci.* 2020, 6, 1–20. [CrossRef]
7. Blum, K.; Chen, A.L.C.; Thanos, P.K.; Febo, M.; Demetroticves, Z.; Dushaj, K.; Kovoor, A.; Baron, D.; Smith, D.E.; Roy, A.K.; III; et al. Genetic addiction risk score (GARS)™, a predictor of vulnerability to opioid dependence. *Front. Biosci.* 2018, 16, 175–196. [CrossRef]
8. Blum, K.; Gondre-Lewis, M.C.; Modestino, E.J.; Lott, L.; Baron, D.; Siwicki, D.; McLaughlin, T.; Howeedy, A.; Krengetl, M.H.; Oscar-Berman, M.; et al. Understanding the scientific basis of post-traumatic stress disorder (PTSD): Precision behavioral management overrides stigmatization. *Mol. Neurobiol.* 2019, 56, 7836–7850. [CrossRef]
9. Blum, K.; Siwicki, D.; Baron, D.; Modestino, E.J.; Badgaiyan, R.D. The benefits of genetic addiction risk score (GARS™) and pro-dopamine regulation in combating suicide in the American Indian population. *J. Syst. Integr. Neurosci.* 2018, 4. [CrossRef]
10. Blum, K.; Simpatico, T.; Badgaiyan, R.D.; Demetroticves, Z.; Fratantonio, J.; Agan, G.; Febo, M.; Gold, M.S. Coupling neurogenetics (GARS™) and a nutrigenomic based dopaminergic agonist to treat reward deficiency syndrome (RDS): Targeting polymorphic reward genes for carbohydrate addiction algorithms. *J. Reward Defic. Syndr.* 2015, 1, 75–80. [CrossRef]
11. Fried, L.; Modestino, E.; Siwicki, D.; Lott, L.; Thanos, P.K.; Baron, D.; Badgaiyan, R.D.; Ponce, J.V.; Giordano, J.; Downs, W.B.; et al. Hypodopaminergia and “precision behavioral management” (PBM): It is a generational family affair. *Curr. Pharm. Biotechnol.* 2020, 21, 528–541. [CrossRef] [PubMed]
12. Blum, K.; Gold, M.; Modestino, E.J.; Baron, D.; Boyett, B.; Siwicki, D.; Lott, L.; Podesta, A.; Roy, A.K.; Hauser, M.; et al. Would induction of dopamine homeostasis via coupling genetic addiction risk score (GARS™) and pro-dopamine regulation benefit benzodiazepine use disorder (BUD)? *J. Syst. Integr. Neurosci.* 2018, 4. [CrossRef] [PubMed]
13. Blum, K.; Baron, D.; McLaughlin, T.; Gold, M.S. Molecular neurological correlates of endorphinergic/dopaminergic mechanisms in reward circuitry linked to endorphinergic deficiency syndrome (EDS). *J. Neurol. Sci.* 2020, 411, 116733. [CrossRef] [PubMed]
14. Blum, K.; Baron, D.; Lott, L.; Ponce, J.V.; Siwicki, D.; Boyett, B.; Steinberg, J.; Modestino, E.J.; Fried, L.; Hauser, M.; et al. In search of reward deficiency syndrome (RDS)-free controls: The “holy grail” in genetic addiction risk testing. *Curr. Psychopharmacol.* 2020, 9, 7–21. [CrossRef]
15. Blum, K.; Madigan, M.A.; Fried, L.; Braverman, E.R.; Giordano, J.; Badgaiyan, R.D. Coupling genetic addiction risk score (GARS) and pro-dopamine regulation (KB220) to combat substance use disorder (SUD). * Glob. J. Addict. Rehabil. Med.* 2017, 1, 555556. [CrossRef]
16. Blum, K.; Thanos, P.K.; Badgaiyan, R.D.; Febo, M.; Oscar-Berman, M.; Fratantonio, J.; Demetroticves, Z.; Gold, M.S. Neurogenetics and gene therapy for reward deficiency syndrome: Are we going to the Promised Land? *Expert Opin. Biol. Ther.* 2015, 15, 973–985. [CrossRef]
17. Blum, K.; Chen, T.J.; Meshkin, B.; Waite, R.L.; Downs, B.W.; Blum, S.H.; Mengucci, J.F.; Arcuri, V.; Braverman, E.R.; Palomo, T. Manipulation of catechol-O-methyl-transferase (COMT) activity to influence the attenuation of substance seeking behavior, a subtype of Reward Deficiency Syndrome (RDS), is dependent upon gene polymorphisms: A hypothesis. *Med. Hypotheses* 2007, 69, 1054–1060. [CrossRef]
18. Blum, K.; Oscar-Berman, M.; Barb, D.; Giordano, J.; Gold, M. Dopamine genetics and function in food and substance abuse. *J. Genet. Syndr. Gene Ther.* 2013, 4, 1000121. [CrossRef]
19. Blum, K.; Oscar-Berman, M.; Demetroticves, Z.; Barb, D.; Gold, M.S. Genetic addiction risk score (GARS): Molecular neurogenetic evidence for predisposition to reward deficiency syndrome (RDS). *Mol. Neurobiol.* 2014, 50, 765–796. [CrossRef]
20. Blum, K.; Baron, D.; Hauser, M.; Henriksen, S.; Thanos, P.K.; Black, C.; Siwicki, D.; Modesto, E.J.; Downs, B.W.; Badgaiyan, S.; et al. Americas’ opioid/psychostimulant epidemic would benefit from general population early identification of genetic addiction risk especially in children of alcoholics (COAs). J. Syst. Integr. Neurosci. 2019, 5, 1–3.
21. Blum, K.; Downs, B.W.; Dushaj, K.; Li, M.; Braverman, E.R.; Fried, L.; Waite, R.; Demetrovics, Z.; Badgaiyan, R.D. The benefits of customized DNA directed nutrition to balance the brain reward circuitry and reduce addictive behaviors. Precis. Med. 2016, 1, 18–33.
22. Blum, K.; Modesto, E.J.; Neary, J.; Gondré-Lewis, M.C.; Siwicki, D.; Moran, M.; Hauser, M.; Braverman, E.R.; Baron, D.; Steinberg, B.; et al. Promoting precision addiction management (PAM) to combat the global opioid crisis. Biomed. J. Sci. Tech. Res. 2018, 2, 1–4. [CrossRef] [PubMed]
23. Chen, A.L.; Blum, K.; Chen, T.J.; Giordano, J.; Downs, B.W.; Han, D.; Barh, D.; Braverman, E.R. Correlation of the Taq1 dopamine D2 receptor gene and percent body fat in obese and screened control subjects: A preliminary report. Food Funct. 2012, 3, 40–48. [CrossRef] [PubMed]
24. Blum, K.; Modesto, E.J.; Gondré-Lewis, M.C.; Neary, J.; Siwicki, D.; Hauser, M.; Barh, D.; Steinberg, B.; Badgaiyan, R.D. Global opioid epidemic: Doomed to fail without genetically based precision addiction medicine (PAM(TM)): Lessons learned from America. Precis. Med. 2017, 2, 17–22.
25. Thanos, P.K.; Hamilton, J.; O’Rourke, J.R.; Napoli, A.; Febo, M.; Volkow, N.D.; Blum, K.; Gold, M. Dopamine D2 gene expression interacts with environmental enrichment to impact lifespan and behavior. Oncotarget 2016, 7, 19111–19123. [CrossRef]
26. Blum, K.; Badgaiyan, R.D.; Aman, G.; Fratantonio, J.; Simpatico, T.; Febo, M.; Haberstick, B.C.; Smolen, A.; Gold, M.S. Molecular genetic testing in reward deficiency syndrome (RDS): Facts and fiction. J. Reward Defic. Syndr. 2015, 1, 65–68. [CrossRef]
27. Blum, K.; Chen, A.L.; Oscar-Berman, M.; Chen, T.J.; Lubar, J.; White, N.; Lubar, J.; Bowirrat, A.; Braverman, E.; Schoolfield, J.; et al. Generational association studies of dopaminergic genes in reward deficiency syndrome (RDS) subjects: Selecting appropriate phenotypes for reward dependence behaviors. Int. J. Environ. Res. Public Health 2011, 8, 4425–4459. [CrossRef]
28. Blum, K.; Badgaiyan, R.D.; Dunston, G.M.; Baron, D.; Modesto, E.J.; McLaughlin, T.; Steinberg, B.; Gold, M.S.; Gondré-Lewis, M.C. The DRD2 Taq1A A1 Allele may magnify the risk of Alzheimer’s in aging African-Americans. Mol. Neurobiol. 2018, 55, 5526–5536. [CrossRef]
29. Noble, E.P.; Blum, K.; Khalsa, M.E.; Ritchie, T.; Montgomery, A.; Wood, R.C.; Fitch, R.J.; Oskaragoz, T.; Sheridan, P.J.; Anglin, M.D.; et al. Allelic association of the D2 dopamine receptor gene with cocaine dependence. Drug Alcohol Depend. 1993, 33, 271–285. [CrossRef]
30. Blum, K.; Febo, M.; Smith, D.E.; Roy AK 3rd Demetrovics, Z.; Cronjé, F.J.; Femino, J.; Agan, G.; Fratantonio, J.L.; Pandey, S.C.; Badgaiyan, R.D.; et al. Neurogenetic and epigenetic correlates of adolescent predisposition to and risk for addictive behaviors as a function of prefrontal cortex dysregulation. J. Child Adolesc. Psychopharmacol. 2015, 25, 286–292. [CrossRef]
31. Chen, T.J.; Blum, K.; Mathews, D.; Fisher, L.; Schnautz, N.; Braverman, E.R.; Schoolfield, J.; Downs, B.W.; Comings, D.E. Are dopaminergic genes involved in a predisposition to pathological aggression? Hypothesizing the importance of “super normal controls” in psychiatricgenetic research of complex behavioral disorders. Med. Hypotheses 2005, 65, 703–707. [CrossRef] [PubMed]
32. Blum, K.; Noble, E.P.; Sheridan, P.J.; Montgomery, A.; Ritchie, T.; Oskaragoz, T.; Fitch, R.J.; Wood, R.; Finley, O.; Sadlack, F. Genetic predisposition in alcoholism: Association of the D2 dopamine receptor Taq1 B1 RFLP with severe alcoholics. Alcohol 1993, 10, 59–67. [CrossRef]
33. Moran, M.; Blum, K.; Konce, J.V.; Lott, L.; Gondré-Lewis, M.C.; Badgaiyan, S.; Brewer, R.; Downs, B.W.; FYnnan, P.; Weingarten, A.; et al. High addiction risk score (GARS) in chronically prescribed severe chronic opioid probands attending multi-pain clinics: An open clinical pilot trial. Mol. Neurobiol. 2021, 58, 3335–3346. [CrossRef] [PubMed]
34. Bowirrat, A.; Chen, T.J.; Blum, K.; Madigan, M.; Bailey, J.A.; Chuan Chen, A.L.; Downs, B.W.; Braverman, E.R.; Radi, S.; Waite, R.L.; et al. Neuro-psychopharmacogenetics and neurogenetic antecedents of posttraumatic stress disorder: Unlocking the mysteries of resilience and vulnerability. Curr. Neuropharmacol. 2010, 8, 355–358. [CrossRef]
35. Blum, K.; Braverman, E.R.; Wood, R.C.; Gill, J.; Li, C.; Chen, T.J.; Taub, M.; Montgomery, A.R.; Sheridan, P.J.; Cull, J.G. Increased prevalence of the Taq 1 A1 allele of the dopamine receptor gene (DRD2) in obesity with comorbid substance use disorder: A preliminary report. Pharmacogenetics 1996, 6, 297–305. [CrossRef]
36. Bowirrat, A.; Chen, T.J.; Oscar-Berman, M.; Madigan, M.; Chen, A.L.; Bailey, J.A.; Braverman, E.R.; Kernier, M.; Giordano, J.; Morse, S.; et al. Neuropsychopharmacology and neurogenetic aspects of executive functioning: Should reward gene polymorphisms constitute a diagnostic tool to identify individuals at risk for impaired judgment? Mol. Neurobiol. 2012, 45, 298–313. [CrossRef] [PubMed]
37. Blum, K.; Gondré-Lewis, M.C.; Baron, D.; Thanos, P.K.; Braverman, E.R.; Neary, J.; Elman, I.; Badgaiyan, R.D. Introducing precision addiction management of reward deficiency syndrome, the construct that underpins all addictive behaviors. Front. Psychiatry 2018, 9, 548. [CrossRef]
38. Bisagno, V.; Cadet, J.L. Expression of immediate early genes in brain reward circuitries: Differential regulation by psychostimulant and opioid drugs. Neurochem. Int. 2019, 124, 10–18. [CrossRef]
39. Blum, K.; Oscar-Berman, M.; Dinubile, N; Giordano, J.; Braverman, E.R.; Truesdell, C.E.; Barh, D.; Badgaiyan, R. Coupling genetic addiction risk score (GARS) with electrotherapy: Fighting iatrogenic opioid dependence. J. Addict. Res. Ther. 2013, 4, 1000163. [CrossRef]
40. Blum, K.; Oscar-Berman, M.; Blum, S.H.; Madigan, M.A.; Waite, R.L.; McLaughlin, T.; Barh, D. Can genetic testing coupled with enhanced dopaminergic activation reduce recidivism rates in the workers compensation legacy cases? J. Alcohol Drug Depend. 2014, 2, 161. [CrossRef]

41. Downs, B.W.; Blum, K.; Baron, D.; Bowirrat, A.; Lott, L.; Brewer, R.; Boyett, B.; Siwicki, D.; Roy, A.K.; Podesta, A.; et al. Death by opioids: Are there non-addictive scientific solutions? J. Syst. Integr. Neurosci. 2019, 5. [CrossRef] [PubMed]

42. Blum, K.; Febo, M.; Fried, L.; Baron, D.; Braverman, E.R.; Dushaj, K.; Li, M.; Demetrincis, Z.; Badgaiyan, R.D. Pro-dopamine regulator—(KB220) to balance brain reward circuitry in reward deficiency syndrome (RDS). J. Reward Defic. Syndr. Addict. Sci. 2017, 3, 3–13. [CrossRef] [PubMed]

43. Blum, K.; Modestino, E.J.; Badgaiyan, R.D.; Baron, D.; Thanos, P.K.; Elman, I.; Siwicki, D.; Febo, M.; Gold, M.S. Analysis of evidence for the combination of pro-dopamine regulator (KB220PAM) and naltrexone to prevent opioid use disorder relapse. EC Psychol. Psychiatry 2018, 7, 564–579.

44. Blum, K.; Modestino, E.J.; Gondre-Lewis, M.; Downs, B.W.; Baron, D.; Steinberg, B.; Siwicki, D.; Giordano, J.; McLaughlin, T.; Neary, J.; et al. “Dopamine homeostasis” requires balanced polypharmacy: Issue with destructive, powerful dopaminergic agents to combat America’s drug epidemic. J. Syst. Integr. Neurosci. 2017, 3. [CrossRef] [PubMed]

45. Blum, K.; Giordano, J.; Downs, B.W.; Barh, D.; Braverman, E.R.; Hauser, M.; Smith, D.E.; Roy, A.K.; et al. The Benefits of Genetic Addiction Risk Score (GARS™) Testing in Substance Use Disorder (SUD). Int. J. Genom. Data Min. 2018, 2018, 115. [CrossRef]

46. Blum, K.; Febo, M.; Fried, L.; Li, M.; Dushaj, K.; Braverman, E.R.; McLaughlin, T.; Steinberg, B.; Badgaiyan, R.D. Hypothesizing that neuropharmacological and neuroimaging studies of glutaminergic-dopaminergic optimization complex (KB220PAM) are associated with “dopamine homeostasis” in reward deficiency syndrome (RDS). Subst. Use Misuse 2017, 52, 535–547. [CrossRef]

47. Blum, K.; Modestino, E.J.; Gondre-Lewis, M.; Chapman, E.J.; Neary, J.; Siwicki, D.; Baron, D.; Hauser, M.; Smith, D.E.; Roy, A.K.; et al. The Benefits of Genetic Addiction Risk Score (GARS™) Testing in Substance Use Disorder (SUD). Int. J. Genom. Data Min. 2018, 2018, 115. [CrossRef]

48. Blum, K.; Febo, M.; Bagchi, D.; Kushner, S.; Bagchi, M.; Galvin, J.M.; Lewis, M.; Siwicki, D.; Brewer, R.; Boyett, B.; et al. Neuro-epidemiological and systemic health benefits of achieving dopamine homeostasis in the face of a catastrophic pandemic (COVID-19): A mechanistic exploration. J. Syst. Integr. Neurosci. 2020, 7. [CrossRef]

49. Schoenthaler, S.J.; Blum, K.; Fried, L.; Oscar-Berman, M.; Giordano, J.; Modestino, E.J.; Badgaiyan, R. The effects of residential dual diagnosis treatment on alcohol abuse. J. Syst. Integr. Neurosci. 2017, 3. [CrossRef]

50. Roy, A.K.; Bowirrat, A.; Smith, D.E.; Braverman, E.R.; Jalali, R.; Badgaiyan, R.D.; Barh, D.; Llanos-Gomez, L.; Barh, D.; Blum, K. Neurobiology and Spirituality in Addiction Recovery. Acta Sci. Neural. 2021, 4, 64–71.

51. Blum, K.; Febo, M.; Badgaiyan, R.D.; Braverman, E.R.; Dushaj, K.; Li, M.; Demetrincis, Z. Neuronutrient Amino-Acid Therapy Protects Against Reward Deficiency Syndrome: Dopaminergic Key to Homeostasis and Neuropsychology. Curr. Pharm. Des. 2016, 22, 5837–5854. [CrossRef] [PubMed]

52. Blum, K.; Noble, E.P.; Sheridan, P.J.; Finley, O.; Montgomery, A.; Ritchie, T.; Ozkaragöz, T.; Fitch, R.J.; Sadlack, F.; Sheffield, D.; et al. Association of the A1 allele of the D2 dopamine receptor gene with severe alcoholism. Alcohol 1991, 8, 409–416. [CrossRef]

53. Blum, K.; Febo, M.; Fahlke, C.; Archer, T.; Berggren, U.; Demetrincis, Z.; Dushaj, K.; Badgaiyan, R.D. Hypothesizing Balancing Endorphinergic and Glutaminergic Systems to Treat and Prevent Relapse to Reward Deficiency Behaviors: Coupling D-Phenylalanine and N-Acetyl-L-Cysteine (NAC) as a Novel Therapeutic Modality. Clin. Med. Rev. Case Rep. 2015, 2, 76. [CrossRef] [PubMed]

54. Vitali, M.; Napolitano, C.; Berman, M.O.; Minuto, S.F.; Battagliese, G.; Attilia, M.L.; Braverman, E.R.; Romeo, M.; Blum, K.; Ceccanti, M. Neurophysiological measures and alcohol use disorder (AUD): Hypothesizing links between clinical severity index and molecular neurobiological patterns. J. Addict. Res. Ther. 2016, 5, 182. [CrossRef] [PubMed]

55. Blum, K.; Thanos, P.K.; Gold, M.S. Dopamine, obesity, and reward deficiency syndrome. Front. Psychol. 2014, 5, 919. [CrossRef] [PubMed]

56. Duquette, L.L.; Mattiace, F.; Blum, K.; Waite, R.L.; Boland, T.; McLaughlin, T.; Dushaj, K.; Febo, M.; Badgaiyan, R.D. Neurobiology of KB220Z-glutaminergic-dopaminergic optimization complex [GDOC] as a liquid nano: Clinical activation of brain in a highly functional clinician improving focus, motivation and overall sensory input following chronic intake. Clin. Med. Rev. Case Rep. 2016, 3, 104. [CrossRef]

57. Blum, K.; Oscar-Berman, M.; Giordano, J.; Downs, B.; Simpatico, T.; Han, D.; Femino, J. Neurogenetic impairments of brain reward circuitry links to reward deficiency syndrome (RDS): Potential nutrigenomic induced dopaminergic activation. J. Genet. Syndr. Gene Ther. 2012, 3, 535–547. [CrossRef]

58. Blum, K.; Jacobs, W.; Modestino, E.J.; DiNubile, N.; Baron, D.; McLaughlin, T.; Siwicki, D.; Elman, I.; Moran, M.; Braverman, E.R.; et al. Insurance companies fighting the peer review empire without any validity: The case for addiction and pain modalities in the face of an American drug epidemic. SEJ Surg. Pain 2018, 1, 1–11.

59. McLaughlin, T.; Han, D.; Nicholson, J.; Steinberg, B.; Blum, K.; Febo, M.; Braverman, E.; Li, M.; Fried, L.; Badgaiyan, R. Improvement of long-term memory access with a pro-dopamine regulator in an elderly male: Are we targeting dopamine tone? J. Syst. Integr. Neurosci. 2017, 3. [CrossRef]
(TAAR-1) and induce anti-craving of psychostimulants in the long-term. J. Reward Defic. Syndr. Addict. Sci. 2016, 2, 14–21. [CrossRef] [PubMed]
82. Blum, K.; Whitney, D.; Fried, L.; Febo, M.; Waite, R.L.; Braverman, E.R.; Dushaj, K.; Li, M.; Giordano, J.; Demetrovics, Z.; et al. Hypothesizing that a pro-dopaminergic regulator (KB220z™ liquid variant) can induce “dopamine homeostasis” and provide adjunctive detoxification benefits in opiate/opioid dependence. Clin. Med. Res. Case Rep. 2016, 3, 125. [CrossRef] [PubMed]
83. Beitscher-Campbell, H.; Blum, K.; Febo, M.; Madigan, M.A.; Giordano, J.; Badgaiyan, R.D.; Braverman, E.R.; Dushaj, K.; Li, M.; Gold, M.S. Pilot clinical observations between food and drug seeking derived from fifty cases attending an eating disorder clinic. J. Behav. Addict. 2016, 5, 533–541. [CrossRef] [PubMed]
84. McLaughlin, T.; Febo, M.; Badgaiyan, R.D.; Barh, D.; Dushaj, K.; Braverman, E.R.; Li, M.; Madigan, M.A.; Blum, K. KB220Z™ a pro-dopamine regulator associated with the protracted, alleviation of terrifying lucid dreams. Can we infer neuroplasticity-induced changes in the reward circuit? J. Reward Defic. Syndr. Addict. Sci. 2016, 2, 3–13. [CrossRef]
85. McLaughlin, T.; Blum, K.; Oscar-Berman, M.; Febo, M.; Demetrovics, Z.; Agan, G.; Fratantonio, J.; Gold, M.S. Using the neuroadaptagen KB220z™ 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, 24–35. [CrossRef]
86. McLaughlin, T.; Blum, K.; Oscar-Berman, M.; Febo, M.; Agan, G.; Fratantonio, J.L.; Simpatico, T.; Gold, M.S. 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, 4, 106–115. [CrossRef]
87. Steinberg, B.; Blum, K.; McLaughlin, T.; Lubar, J.; Febo, M.; Braverman, E.R.; Badgaiyan, R.D. Low-resolution electromagnetic tomography (LORETA) of changed brain function provoked by pro-dopamine regulator (KB220Z) in one adult ADHD case. Open J. Clin. Med. Case Rep. 2016, 2, 1121.
88. McLaughlin, T.; Blum, K.; Trachtenberg, M.C.; Febo, M.; Braverman, E.R.; Badgaiyan, R.D. Pro-dopamine regulator, KB220Z, attenuates hoarding and shopping behavior in a female, diagnosed with SUD and ADHD. J. Behav. Addict. 2018, 7, 192–203. [CrossRef]
89. Barh, D.; Garcia-Solano, M.E.; Tiwari, S.; Bhattacharya, A.; Jain, N.; Torres-Moreno, D.; Ferri, B.; Silva, A.; Azevedo, V.; Ghosh, P.; et al. BARHL1 Is Downregulated in Alzheimer’s Disease and May Regulate Cognitive Functions through ER1 and Multiple Pathways. Genes 2017, 8, 245. [CrossRef]
90. Blum, K.; Trachtenberg, M.C.; Elliott, C.E.; Dingler, M.L.; Sexton, R.L.; Samuels, A.I.; Cataldi, L. Enkephalinine 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 1988, 5, 481–493. [CrossRef]
91. Blum, K.; McLaughlin, T.; Modestino, E.J.; Fried, L.; Baron, D.; Siwicky, D.; Braverman, E.R.; Badgaiyan, R.D. Pro-dopamine regulator, KB220Z, attenuates hoarding and shopping behavior in a female, diagnosed with SUD and ADHD. J. Behav. Addict. 2018, 7, 192–203. [CrossRef]
92. Brown, R.J.; Blum, K.; Trachtenberg, M.C. Neurodynamics of relapse prevention: A neuronutrient approach to outpatient DUI offenders. J. Psychoact. Drugs 1990, 22, 173–187. [CrossRef] [PubMed]
93. Blum, K.; Trachtenberg, M.C.; Ramsay, J.C. Improvement of inpatient treatment of the alcoholic as a function of neurotransmitter restoration: A pilot study. Int. J. Addict. 1988, 23, 991–998. [CrossRef] [PubMed]
94. DeFrance, J.F.; Hymel, C.; Trachtenberg, M.C.; Ginsberg, L.D.; Schweitzer, F.C.; Estes, S.; Chen, T.J.; Braverman, E.R.; Cull, J.G.; Blum, K. Enhancement of attention processing by Kantroll in healthy humans: A pilot study. Clin. Electroencephalogr. 2017, 49–51. [CrossRef] [PubMed]
95. Blum, K.; Gold, M.S. Neuro-chemical activation of brain reward meso-limbic circuitry is associated with relapse prevention and drug hunger. A hypothesis. Med. Hypotheses 2011, 76, 576–584. [CrossRef]
96. Blum, K.; Cadet, J.L.; Gold, M.S. Psychostimulant use disorder emphasizing methamphetamine and the opioid-dopamine connection: Digging out of a hypodopaminergic ditch. J. Neurol. Sci. 2021, 420, 117252. [CrossRef] [PubMed]
97. Blum, K.; Futterman, S.; Wallace, J.E.; Schwertner, H.A. Naloxone-induced inhibition of ethanol dependence in mice. Nature 1977, 265, 49–51. [CrossRef] [PubMed]
98. Blum, K.; Braverman, E.R.; Holder, J.M.; Lubar, J.F.; Monastra, V.J.; Miller, D.; Lubar, J.O.; Chen, T.J.; Comings, D.E. Reward deficiency syndrome: A biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J. Psychoact. Drugs 2000, 32 (Suppl. I–IV), 1–112. [CrossRef]
99. Trachtenberg, M.C.; Blum, K. Improvement of cocaine-induced neuromodulator deficits by the neuromodulator Tropanime. J. Psychoact. Drugs 1988, 20, 315–331. [CrossRef]
100. Blum, K.; Allison, D.; Trachtenberg, M.C.; Williams, R.W.; Loeblich, L.A. Reduction of both drug hunger and withdrawal against advice rate of cocaine abusers in a 30-day inpatient treatment program by the neuromodulator tropeamin’. Curr. Ther. Res. 1988, 43, 1204–1214.
101. Blum, K.; Chen, T.J.H.; Downs, B.W.; Meshkin, B.; Blum, S.H.; Martinez Pons, M.; Mengucci, J.F.; Waite, R.L.; Arcuri, V.; Varshafski, M.; et al. Synaptamine (SG8839) an amino-acid enkephalinase inhibition nutraceutical improves recovery of alcoholics, a subtype of reward deficiency syndrome (RDS). Trends Appl. Sci. Res. 2007, 2, 132–138. [CrossRef]
102. Mechelmanns, D.J.; Strelchuk, D.; Donhamayor, N.; Banca, P.; Robbins, T.W.; Baek, K.; Voon, V. Reward sensitivity and waiting impulsivity: Shift towards reward valuation away from action control. Int. J. Neuropsychopharmacol. 2017, 20, 971–978. [CrossRef] [PubMed]
103. Kötyük, E.; Urbán, R.; Hende, B.; Richman, M.; Magi, A.; Király, O.; Barta, C.; Griffiths, M.D.; Potenza, M.N.; Badgaiyan, R.D.; et al. Development and validation of the Reward Deficiency Syndrome Questionnaire (RDSQ-29). J. Psychopharmacol. 2022, 36, 409–422. [CrossRef] [PubMed]

104. Mies, G.W.; Ma, I.; de Water, E.; Buitelaar, J.K.; Scheres, A. Waiting and working for rewards: Attention-Deficit/Hyperactivity Disorder is associated with steeper delay discounting linked to amygdala activation, but not with steeper effort discounting. Cortex 2018, 106, 164–173. [CrossRef] [PubMed]

105. Jimura, K.; Chushak, M.S.; Braver, T.S. Impulsivity and self-control during intertemporal decision making linked to the neural dynamics of reward value representation. J. Neurosci. 2013, 33, 344–357. [CrossRef]

106. Voon, V.; Irvine, M.A.; Derbyshire, K.; Worbe, Y.; Lange, I.; Abbott, S.; Morein-Zamir, S.; Dudley, R.; Caprioli, D.; Harrison, N.A.; et al. Measuring “waiting” impulsivity in substance Gold MSaddictions and binge eating disorder in a novel analogue of rodent serial reaction time task. Biol. Psychiatry 2014, 75, 148–155. [CrossRef]

107. Kazemi, T.; Huang, S.; Avci, N.G.; Waits, C.M.K.; Akay, Y.M.; Akay, M. Investigating the influence of perinatal nicotine and alcohol exposure on the genetic profiles of dopaminergic neurons in the VTA using miRNA-mRNA analysis. Sci. Rep. 2020, 10, 15016. [CrossRef]

108. Barlow, R.L.; Gorges, M.; Wearn, A.; Niessen, H.G.; Kassubek, J.; Dalley, J.W.; Pekcec, A. Ventral striatal D2/3 receptor availability is associated with impulsive choice behavior as well as limbic corticostriatal connectivity. Int. J. Neuropsychopharmacol. 2019, 21, 705–715. [CrossRef]

109. Robinson, E.S.; Eagle, D.M.; Economidou, D.; Theobald, D.E.; Mar, A.C.; Murphy, E.R.; Robbins, T.W.; Dalley, J.W. Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: Specific deficits in ‘waiting’ versus ‘stopping’. Behav. Brain Res. 2009, 196, 310–316. [CrossRef] [PubMed]

110. Barlow, R.L.; Gorges, M.; Wearn, A.; Niessen, H.G.; Kassubek, J.; Dalley, J.W.; Pekcec, A. Ventral striatal D2/3 receptor availability is associated with impulsive choice behavior as well as limbic corticostriatal connectivity. Int. J. Neuropsychopharmacol. 2019, 21, 705–715. [CrossRef] [PubMed]

111. Adriani, W.; Laviola, G. Delay aversion but preference for large and rare rewards in two choice tasks: Implications for the dopamine depletion hypothesis. J. Neurosci. 2003, 23, 9395–9402. [CrossRef]

112. Robinson, E.S.; Eagle, D.M.; Economidou, D.; Theobald, D.E.; Mar, A.C.; Murphy, E.R.; Robbins, T.W.; Dalley, J.W. Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: Specific deficits in ‘waiting’ versus ‘stopping’. Behav. Brain Res. 2009, 196, 310–316. [CrossRef] [PubMed]

113. Zhang, Y.; von Deneen, K.M.; Tian, J.; Gold, M.S.; Liu, Y. Food addiction and neuroimaging. Curr. Pharm. Des. 2011, 17, 1149–1157. [CrossRef]

114. Berridge, K.C. The debate over dopamine’s role in reward: The case for incentive salience. Psychopharmacology 2007, 191, 391–431. [CrossRef]

115. Gardner, E.L. Addiction and brain reward and antireward pathways. Adv. Psychosom. Med. 2011, 30, 22–60. [CrossRef]

116. Koob, G.F.; Le Moal, M. Plasticity of reward neurocircuitry and the ‘dark side’ of drug addiction. Nat. Neurosci. 2005, 8, 1442–1444. [CrossRef]

117. Zhang, Y.; von Deneen, K.M.; Tian, J.; Gold, M.S.; Liu, Y. Food addiction and neuroimaging. Curr. Pharm. Des. 2011, 17, 1149–1157. [CrossRef]

118. Berridge, K.C. Wanting and liking: Observations from the neuroscience and psychology laboratory. Inquiry 2009, 52, 378. [CrossRef]

119. Tindell, A.J.; Smith, K.S.; Berridge, K.C.; Aldridge, J.W. Dynamic computation of incentive salience: “Wanting” what was never liked. J. Neurosci. 2009, 29, 12220–12228. [CrossRef]

120. Peciña, S.; Cagniard, B.; Berridge, K.C.; Aldridge, J.W.; Zhuang, X. Hyperdopaminergic mutant mice have higher “wanting” but not “liking” for sweet rewards. J. Neurosci. 2003, 23, 9395–9402. [CrossRef]

121. Sharot, T.; Shiner, T.; Brown, A.C.; Fan, J.; Dolan, R.J. Dopamine enhances expectation of pleasure in humans. Curr. Biol. 2009, 19, 2077–2080. [CrossRef] [PubMed]

122. Kornetsky, C. Brain-stimulation reward, morphine-induced oral stereotypy, and sensitization: Implications for abuse. Neurosci. Biobehav. Rev. 2004, 27, 777–786. [CrossRef] [PubMed]

123. Dackis, C.A.; Gold, M.S. New concepts in cocaine addiction: The dopamine depletion hypothesis. Neurosci. Biobehav. Rev. 1985, 9, 469–477. [CrossRef]

124. Di Chiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 1988, 85, 5274–5278. [CrossRef] [PubMed]

125. Elman, I.; Borsook, D. Common brain mechanisms of chronic pain and addiction. Neuron 2016, 89, 11–36. [CrossRef]

126. Gold, M.S.; Baron, D.; Bowirrat, A.; Blum, K. Neurological correlates of brain reward circuitry linked to opioid use disorder (OUD): Do homo sapiens acquire or have a reward deficiency syndrome? J. Neurol. Sci. 2020, 418, 117137. [CrossRef]

127. Elman, I.; Borsook, D.; Lukas, S.E. Food intake and reward mechanisms in patients with schizophrenia: Implications for metabolic disturbances and treatment with second-generation antipsychotic agents. Neuropsychopharmacology 2006, 31, 2091–2120. [CrossRef]

128. Blum, K.; Sheridan, P.J.; Wood, R.C.; Braverman, E.R.; Chen, T.J.; Cull, J.G.; Comings, D.E. The D2 dopamine receptor gene as a determinant of reward deficiency syndrome. J. R. Soc. Med. 1996, 89, 396–400. [CrossRef]

129. Elman, I.; Borsook, D. Threat response system: Parallel brain processes in pain vis-à-vis fear and anxiety. Front. Psychiatry 2018, 9, 29. [CrossRef]
130. LeDoux, J.E.; Pine, D.S. Using neuroscience to help understand fear and anxiety: A two-system framework. *Am. J. Psychiatry* 2016, 173, 1083–1093. [CrossRef]

131. Murck, H.; Schubert, M.I.; Schmid, D.; Schüssler, P.; Steiger, A.; Auer, D.P. The glutamatergic system and its relation to the clinical effect of therapeutic-sleep deprivation in depression - an MR spectroscopy study. *J. Psychiatr. Res.* 2009, 43, 175–180. [CrossRef] [PubMed]

132. Salimpoor, V.N.; Benovoy, M.; Larcher, K.; Dagher, A.; Zatorre, R.J. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. *Nat. Neurosci.* 2011, 14, 257–262. [CrossRef] [PubMed]

133. Volkow, N.D.; Michaelides, M.; Baler, R. The neuroscience of drug reward and addiction. *Physiol. Rev.* 2019, 99, 2115–2140. [CrossRef] [PubMed]

134. Volkow, N.D.; Fowler, J.S.; Wolf, A.P.; Schlyer, D.; Shiue, C.Y.; Logan, J.; Bendriem, B.; Christman, D.; et al. Effects of chronic cocaine abuse on postsynaptic dopamine receptors. *Am. J. Psychiatry* 1990, 147, 719–724. [CrossRef] [PubMed]

135. Blum, K.; Raza, A.; Schultz, T.; Jalali, R.; Green, R.; Brewer, R.; Thanos, P.K.; McLaughlin, T.; Baron, D.; Bowirrat, A.; et al. Should we embrace the incorporation of genetically guided “dopamine homeostasis” in the treatment of reward deficiency syndrome (RDS) as a frontline therapeutic modality? *Acta Sci. Neurol.* 2021, 4, 17–24. [CrossRef] [PubMed]

136. Russo, S.J.; Nestler, E.J. The brain reward circuitry in mood disorders. *Nat. Rev. Neurosci.* 2013, 14, 609–625. Erratum in *Nat. Rev. Neurosci.* 2013, 14, 736. [CrossRef] [PubMed]

137. Cooper, S.; Robison, A.J.; Mazei-Robison, M.S. Reward circuitry in addiction. *Neurotherapeutics* 2017, 14, 687–697. [CrossRef] [PubMed]

138. Walker, D.M.; Nestler, E.J. Neuroepigenetics and addiction. *Handb. Clin. Neurol.* 2018, 148, 747–765. [CrossRef] [PubMed]

139. Archer, T.; Oscar-Berman, M.; Blum, K.; Gold, M. Neurogenetics and epigenetics in impulsive behaviour: Impact on reward circuitry. *J. Genet. Syndr. Gene Ther.* 2012, 3, 1000115. [CrossRef] [PubMed]

140. Handbook of Clinical Neurology. 2018, 147, 719–724. [CrossRef] [PubMed]

141. Hansson, A.C.; Rimondini, R.; Neznanova, O.; Sommer, W.H.; Heilig, M. Neuroplasticity in brain reward circuitry following a history of ethanol dependence. *Eur. J. Neurosci.* 2008, 27, 1912–1922. [CrossRef] [PubMed]

142. Blum, K.; Bowirrat, A.; Lewis, M.C.; Simpatico, T.A.; Ceccanti, M.; Steinberg, B.; Modesto, E.J.; Thanos, P.K.; Baron, D.; McLaughlin, T.; et al. Exploration of epigenetic state hyperdopaminergia (Surfeit) and genetic trait hypodopaminergia (Deficit) during adolescent brain development. *Curr. Psychopharmacol.* 2021, 10, 181–196. [CrossRef] [PubMed]

143. Blum, K.; Modesto, E.J.; Gondre-Lewis, M.G.; Baron, D.; Steinberg, B.; Thanos, P.K.; Downs, W.B.; Siwicki, D.; Lott, L.; Braverman, E.R.; et al. Pro-dopamine regulator (KB220) a fifty year sojourn to combat reward deficiency syndrome (RDS): Evidence based bibliography (annotated). *CPQ Neurol. Psychol.* 2018, 1. Available online: https://www.cientperiodique.com/journal/fulltext/CPQNP/1/2/13 (accessed on 22 February 2022).

144. Blum, K.; Oscar-Berman, M.; Braverman, E.R.; Febo, M.; Li, M.; Gold, M.S. Enhancing brain pregnenolone may protect cannabis intoxication but should not be considered as an anti-addiction therapeutic: Hypothesizing dopaminergic blockade and promoting anti-reward. *J. Reward Defic. Syndr.* 2015, 1, 20–23. [CrossRef] [PubMed]

145. Gold, M.S.; Blum, K.; Febo, M.; Baron, D.; Modesto, E.J.; Elman, I.; Badgaiyan, R.D. Molecular role of dopamine in anhedonia linked to reward deficiency syndrome (RDS) and anti-reward systems. *Front. Biosci.* 2018, 10, 309–325. [CrossRef] [PubMed]

146. Noble, E.P.; Blum, K.; Ritchie, T.; Montgomery, A.; Sheridan, P.J. Alleric association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. *Arch. Gen. Psychiatry* 1991, 48, 648–654. [PubMed]

147. Volkow, N.D.; Wang, G.J.; Baler, R.D. Reward, dopamine and the control of food intake: Implications for obesity. *Trends Cogn. Sci.* 2011, 15, 37–46. [CrossRef] [PubMed]

148. Tanabe, J.; Regner, M.; Sakai, J.; Martinez, D.; Gowin, J. Neuroimaging reward, craving, learning, and cognitive control in substance use disorders: Review and implications for treatment. *Br. J. Radiol.* 2019, 92, 20180942. [CrossRef] [PubMed]

149. Weele, C.M.V.; Siciliano, C.A.; Tye, K.M. Dopamine tunes prefrontal outputs to orchestrate aversive processing. *Brain Res.* 2019, 1713, 16–31. [CrossRef] [PubMed]

150. Richer, K.; Regner, M.; Sakai, J.; Martinez, D.; Gowin, J. Neuroimaging reward, craving, learning, and cognitive control in substance use disorders: Review and implications for treatment. *Br. J. Radiol.* 2019, 92, 20180942. [CrossRef] [PubMed]

151. T. Nicotine, alcohol and cocaine coupling to reward processes via endogenous morphine signaling: The dopamine-morphine hypothesis. *Med. Sci. Monit.* 2007, 13, RA91–RA102. [CrossRef] [PubMed]

152. Weele, C.M.V.; Siciliano, C.A.; Tye, K.M. Dopamine tunes prefrontal outputs to orchestrate aversive processing. *Brain Res.* 2019, 1713, 16–31. [CrossRef] [PubMed]
156. Green, C.L.; Nahhas, R.W.; Scoglio, A.A.; Elman, I. Post-traumatic stress symptoms in pathological gambling: Potential evidence of anti-reward processes. *J. Behav. Addict.* 2017, 6, 98–101. [CrossRef]

157. Li, Q.; Wang, Y.; Yang, Z.; Dai, W.; Zheng, Y.; Sun, Y.; Liu, X. Dysfunctional cognitive control and reward processing in adolescents with internet gaming disorder. *Psychophysiology* 2020, 57, e13469. [CrossRef]

158. Chamberlain, S.R.; Derbyshire, K.; Daws, R.E.; O'dlaug, B.L.; Leppink, E.W.; Grant, J.E. White matter tract integrity in treatment-resistant gambling disorder. *Br. J. Psychiatry* 2016, 208, 579–584. [CrossRef]

159. Wang, L.; Tian, M.; Zheng, Y.; Li, Q.; Liu, X. Reduced loss aversion and inhibitory control in adolescents with internet gaming disorder. *Psychol. Addict. Behav.* 2020, 34, 484–496. [CrossRef]

160. Tian, M.; Chen, Q.; Zhang, Y.; Du, F.; Hou, H.; Chao, F.; Zhang, H. PET imaging reveals brain functional changes in internet gaming disorder. *Eur. J. Nucl. Med. Mol. Imaging* 2014, 41, 1388–1397. [CrossRef]

161. Adriani, W.; Boyer, F.; Gioiosa, L.; Macri, S.; Dreyer, J.L.; Laviola, G. Increased impulsive behavior and risk proneness following lentivirus-mediated dopamine transporter over-expression in rats’ nucleus accumbens. *Neuroscience* 2009, 159, 47–58. [CrossRef] [PubMed]

162. Zuckerman, M.; Kuhlman, D.M. Personality and risk-taking: Common biosocial factors. *J. Pers.* 2000, 68, 999–1029. [CrossRef] [PubMed]

163. Badgaiyan, R.D.; Sinha, S.; Sajjad, M.; Wack, D.S. Attenuated tonic and enhanced phasic release of dopamine in attention deficit hyperactivity disorder. *PLoS ONE* 2015, 10, e0137326. [CrossRef] [PubMed]

164. El Hayek, S.; Allouch, F.; Razafsha, M.; Talih, F.; Gold, M.S.; Wang, K.K.; Kobeissy, F. Traumatic brain injury and methamphetamine: A double-hit neurological insult. *J. Neurol. Sci.* 2020, 411, 116711. [CrossRef] [PubMed]

165. Gold, M.S. The role of alcohol, drugs, and deaths of despair in the U.S.’s falling life expectancy. *MO Med.* 2020, 117, 99–101.

166. Oesterle, T.S.; Kolla, B.P.; Rummans, T.A.; Gold, M.S. Medication-assisted therapies for opioid use disorders in patients with chronic pain. *J. Neurol. Sci.* 2020, 411, 116728. [CrossRef]