Editorial Commentary

Offering a putative neurobiological "dopamine homeostatic" solution to overcome the perils of the reward deficiency syndrome pandemic: emergence of "precision behavioral management"

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In addition to the COVID-19 pandemic, an addiction crisis is currently sweeping the entire world (1). This is extremely troubling, especially given that illicit drug usage can increase the risks associated with the coronavirus. Specifically, the psychological and social risks of the pandemic, which can also promote and augment drug abuse, in a possibly toxic cycle. Our latest figures have revealed that approximately 26.8 million people globally suffered from opioid use disorder (OUD) in 2016, with more than 100,000 opioid overdose deaths yearly, including more than 100,000 in the United States (US) in 2021 (2). While drug overdose is most prevalent in the US, it is a global issue requiring "out of the box" thinking to prevent further devastation and death (3).

Currently, the standard treatment of OUD and opioid addiction involves the use of powerful opioids, which seems inane and traps people in an unwanted cycle of addiction (4,5). This standard treatment is known as opioid agonist therapy (OAT), which functions by interacting with opioid receptors to reduce cravings and harm. However, OAT does not address the root cause, and this form of therapy may actually worsen the addiction pandemic worldwide. Therefore, a more prudent and effective treatment is needed. One solution, as espoused by Lee *et al.* (4), includes targeting various portions of the dopamine-dependent addiction pathway, identifying vulnerable genes, and modifying gene products such as, for example, precision Pro-dopamine Regulation (KKB220) or other gentle dopamine agonists (6).

Our group seeks to lessen harm while addressing the core underlying issue (7). Therefore, we are hereby suggesting that a hypodopaminergic state (epigenetic) and/or trait (genetic) is critical in terms of continued motivation to use/abuse licit and illicit substances and can lead to relapse. Although there are FDA-approved medications that can be utilized to treat substance addictions (e.g., alcohol, opiates, nicotine, etc.), these agents typically only offer a short-term advantage by blocking dopamine. Thus, it has been argued that instead of the utilization of long-term administration of these FDA-approved drugs, the goal should be to induce "dopamine homeostasis", or in simpler terms, "normalcy". Miller *et al.* (7), suggested that this could be accomplished through a variety of holistic modalities including, but not limited to, dopamine-boosting diets, exercise, yoga, meditation, hyper-oxygenation, heavy metal detoxification, and, most crucially, nutraceuticals like KB220 variants, which can help balance brain neurotransmitters.

Another strategy is to use a narcotic antagonist, such as naltrexone, to induce "psychological extinction" by blocking D2 receptors for not only opioids but methamphetamines as well (8). The latter approach appears to be more palatable, but compliance is a major problem. In addition, there is

poor compliance even with the extended-release injectable form of naltrexone. Another option is acamprosate, which is an NMDA receptor antagonist as well as a positive allosteric modulator of GABAA receptors that disrupts dopaminergic signaling (9). Our laboratory showed the novelty and profound enhancement of naltrexone compliance in patients who rapidly detoxed from long-term methadone utilization (10). In an open-label investigation in humans, Blum *et al.* (10) found that dopamine augmentation with the pro-dopamine regulator KB220 (262 days) improved naltrexone compliance and results when compared to naltrexone monotherapy (37 days). Compared to standard treatments, this well-studied complex consists of amino-acid neurotransmitter precursors, catabolism inhibition, and enkephalinase inhibitor therapy (11).

Understanding the above premise and the further emerging acceptance of the umbrella term reward deficiency syndrome (RDS), which was established by Blum in 1995, promotes the common mechanism hypothesis for drug and non-addictive behaviors and even anhedonia, an important endophenotype linked to relapse (12). Previously, we postulated that anhedonia is a by-product of hypodopaminergic traits and states resulting from the combination of hereditary traits and epigenetic neurobiological alterations as a result of environmental factors. Dopaminergic activity can cause a variety of pathophysiological conditions, including aberrant learning, incentive sensitization, and stress-like "anti-reward" phenomena (13). It seems prudent to suggest that neurogenetic antecedents to RDS and elucidation of reward gene polymorphisms could provide a framework for determining an individual's genetic risk for developing anhedonia as a subset of RDS. Thus, our prevention strategy encompasses the restoration of homeostatic balance through physiological activation of dopaminergic receptors (D2/D3) and might have heuristic value for targeting not only anhedonia but also drug craving and relapse.

Our simple proposal to help restore brain neurotransmitter balance in the afflicted individual with a possible pharmacogenomic personalized approach involves the coupling of a genetic based addiction risk assessment, for example, the Genetic Addiction Risk Severity (GARS) test, and customized KB220 (14). Understanding the common neuromodulating aspects of neurotransmission and its disruption via chronic exposure to drugs and behavioral addictions requires a known approach involving "dopamine homeostasis". While there is an emerging push for the utilization of "psychedelic medicine" (15) in the short-term at low doses via patch delivery systems, we further propose that long-term treatment requires induction of "dopamine homeostasis" (16). However, along these lines of thinking, Bill Wilson's psychedelic experience, which led to his becoming alcohol-free (but not nicotine-free, which eventually killed him) and the founding of Alcoholics Anonymous, appears to be consistent with the current re-excitement of psychedelic medicine. A 2012 meta-analysis of lysergic acid diethylamide (LSD) therapy was found to be at least as efficacious a treatment as anything we currently have today (17). The work of Mash and associates has paved the way to implicate the idea of psychedelics like Ibogaine to treat addiction (18).

Snapshot review of evidence

Our "out of the box" novel approach requires the coupling of genetic risk polymorphic testing with the safe and well-studied complex KB220 or KB220Z customized to match the presence of resultant alleles and, as such, provides a precision nutraceutical known to have pro-dopamine regulatory pharmacological properties, including H-Wave therapy (19). There is a plethora of high-tier publications providing unequivocal evidence to establish a common overlap neuro-mechanism between substance and non-substance addiction (alcohol, opioids, food, etc.) (20). In addition, there are currently over 55 clinical studies involving this amino-acid based enkephalinase inhibitory Pro-Dopamine Regulator (PDR) with KB220 nutraceutical complex as the primary constituent ingredient (11,21). The basis of this complex is that it mimics the brain reward cascade (see *Figure 1*), an established model of reward processing.

KB220 has also been shown to have BOLD activation across the brain reward circuit, which has been observed in both animal and human heroin-dependent individuals (23,24). These include the nucleus accumbens, anterior thalamic nuclei, anterior cingulate gyrus, hippocampus, infralimbic, and prelimbic loci. The evidence for genetic vulnerability as an important antecedent to this unwanted behavior may be a determinant factor which must be identified early in life.

Based on a rather moderate published literature, the role of reward gene polymorphisms puts individuals at a higher risk for developing all RDS behavior subtypes, including anhedonia. With this in mind, our laboratory has created the novel patented GARS test to help identify one's risk for these addictive-like behaviors. Specifically, published studies illustrate the coupling of GARS with KB220Z variants

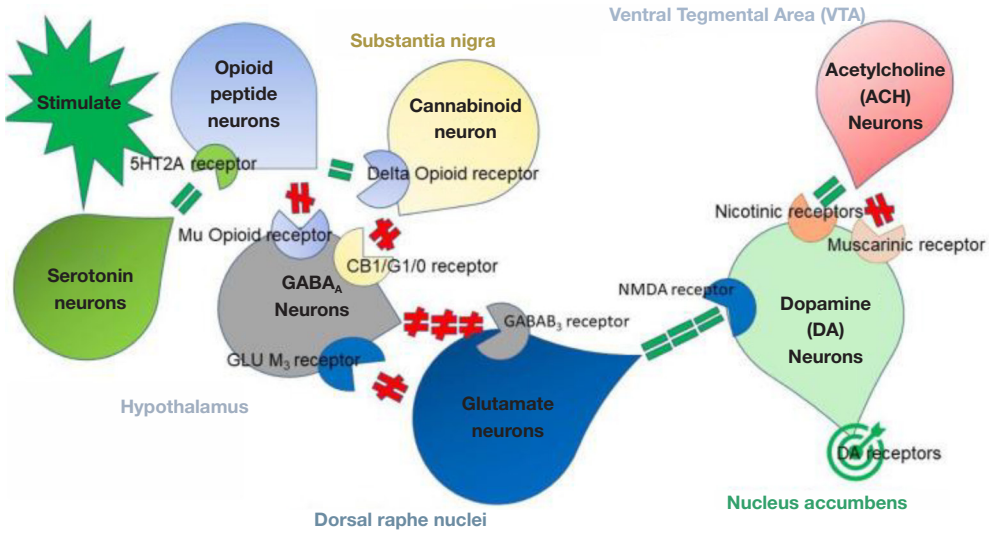

Figure 1 The brain reward cascade. The interaction of at least seven major neurotransmitter-pathways involved in the BRC. In the hypothalamus environmental stimulation results in the release of serotonin, which in turn via, for example, 5HT-2a receptors activate (green equal sign) the subsequent release of opioid peptides from opioid peptide neurons, also in the hypothalamus. Then, in turn, the opioid peptides have two distinct effects, possibly via two different opioid receptors. One that inhibits (red hash sign) through the mu-opioid receptor (possibly via enkephalin) and projects to the Substania Nigra to GABAA neurons. Another stimulates (green equal sign) cannabinoid neurons (the Anandamide and 2-archydonoglcerol, for example) through Beta-Endorphin linked delta receptors, which in turn inhibit GABAA neurons at the Substania Nigra. Also, when activated, cannabinoids primarily 2-archydonoglcerol, can indirectly disinhibit (red hash sign) GABAA neurons through activation of G1/0 coupled to CB1 receptors in the Substania Nigra. In the DRN, glutamate neurons can then indirectly disinhibit GABAA neurons in the Substania Nigra through activation of GLU M3 receptors (red hash sign). GABAA neurons, when stimulated, will, in turn, powerfully (red hash signs) inhibit VTA glutaminergic drive via GABAB 3 neurons. It is also possible that stimulation of ACH neurons at the Nucleus Accumbens ACH can stimulate both muscarinic (red hash) or 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 NAc shown as a bullseye indicates a euphoria, or "wanting" response. The result is that when dopamine release is low (endorphin deficiency), unhappiness is felt while general (healthy) happiness depends on the dopamine homeostatic tonic set point (22) (used with permission). BRC, brain reward cascade; DRN, dorsal raphe nuclei; NAc, nucleus accumbens.

utilizing a semi-customized precision matched to one's GARS. This novel modality linked to a systems biological approach provides an increased efficacy as well as clinical outcomes in terms of treating RDS (25,26).

We present herein new evidence related to the utilization of precision behavioral management (PBM) to effect clinical outcomes of (I) alcohol use disorder (AUD) (27); (II) identification of high addiction genetic risk in pain clinics (26); (III) bariatric surgery outcomes associated with GARS (28); (IV) conversion of incarceration to rehabilitation in Drug Court (29). There is even growing evidence that epigenetic insult, for example, methylation and histone modification of the *DRD2* gene, has been shown in people with lifetime gambling use disorder (30). This argues for the need to induce dopamine homeostasis.

Conclusions

It is generally accepted that balancing the brain reward circuit or achievement of "dopamine homeostasis" is a laudable goal instead of inhibiting natural dopamine or prescribing a potent opioid to treat opioid addiction (31). We are encouraging both the neuroscience and clinical science communities to potentially embrace this disruptive technology with a futuristic view of addressing the notion of what constitutes "standard of care" in the face of the ongoing addiction (alcohol, opioid, psychostimulant, food, etc.) pandemic (32).

While additional research is needed, it is pertinent to begin establishing guidelines that incorporate the knowledge of RDS as an umbrella term for all addictive behaviors. Comprehending the neurogenetics and using a

systems biological approach (PBM), as previously stated, appears to be the most prudent and marks a breakthrough in restoring joy to the billions suffering globally, particularly in terms of early detection (33).

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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