Overcoming reward deficiency syndrome by the induction of “dopamine homeostasis” instead of opioids for addiction: illusion or reality?

Abstract: Many individuals in the United States are plagued by addiction, and the rate at which it is affecting people in the United States only seems to be increasing. Research shows that addiction is a preventable disorder rather than a flaw in one’s moral fiber. It is driven by the imbalance of dopamine and the brain’s reward system. Although medication-assisted treatment (MAT), the most common treatment for addiction, is effective in reducing harm, they provide minimal aid in addressing the root cause of this preventable disorder. The authors aim to convey that the proper treatment should help restore dopamine balance so the quality of life can be improved in the recovering community. Osteopathic principles emphasize the importance of homeostasis and allostatics in allowing the body to heal itself. Viewing reward deficiency syndrome (RDS) through this osteopathic lens can bring about treatments that aim to restore the dopamine homeostasis. The article discusses various potential therapeutic modalities that can provide dopamine homeostasis via activation of dopaminergic pathways.

Keywords: addiction; dopamine homeostasis; reward deficiency syndrome.

In 2019, the US Centers for Disease Control and Prevention (CDC) provided vital statistics related to drug overdoses in the United States. They reported that the number of deaths in the United States was approximately 71,000, with opioid overdoses accounting for over 70% (49,000) of mortalities [1]. Unfortunately, the rate is increasing yearly and appears to be exacerbated by the COVID-19 pandemic. Despite the approval of highly effective vaccines for COVID-19, 2021 will likely continue the significant challenges resulting from increased drug usage related to the COVID-19 pandemic [2, 3]. It is important to realize that many factors are involved, including the issue with contaminated fentanyl in the drug supply. Specifically, in 2020, the death rate from opioid overdoses rose to 13% nationally and in some states was as high as 30% [4]. Moreover, for economic reasons, more than half of pre-existing addiction treatment centers have already closed their doors [5]. Although this seems like a loosely tied economic factor, the loss of available treatment facilities during this pandemic coupled with the rise of higher rates of relapse during recovery takes on real clinical importance. In fact, since 1999, the rate at which analgesic opioids have been prescribed in the United States has quadrupled, worsening the unwanted opioid playing field [6]. A review of the extant data since 2004 reveals that approximately 800,000 people have succumbed to opioid-induced overdoses [7]. Most strikingly, an in-depth analysis from Stanford University concluded that if we continue to indiscriminately utilize opioids to treat opioid dependence, 510,000 deaths from both prescription overdoses and heroin street misuse will occur between 2016 and 2025 [8].

While we agree with initiatives to educate healthcare providers in the use of and increased short-term utilization (6–12 months) of medication-assisted treatment (MAT) to reduce harm and potentially save lives (methadone, naltrexone, and buprenorphine), more needs to be done to address the stigma and its negative impact on help-seeking and overall treatment. Drug misuse should be viewed as a disease that requires treatment, and not a flaw in one’s moral fiber [9].

Burris [10] speculated that “Safe injection sites and other harm-reduction measures, better access to more effective drug treatment, and safer marketing of opioid medicines are
all viable ways to act on that compassionate concern.” However, even though this helps to reduce despair, it provides less benefit for the induction of an individual’s quality of life during recovery [11]. There is an emerging organizational need to help patients obtain some relief with their opioid addiction by utilizing MAT, including recovery community centers (RCCs), Probation departments across the United States and even professional treatment and nonprofessional mutual-help organizations (MHOs). However, the general consensus of these organizations is that MAT is treatment, not merely harm reduction [12]. Although we agree that MAT reduces harm for the most part, it does little to address the root cause of this preventable disorder, and other modalities that target known neurotransmitter deficits seem prudent [13]. While this is true, until we have better approved treatments other than opioid agonists or even antagonists like naltrexone with associated poor compliance, the addiction medicine community needs to continue to utilize, for example, buprenorphine-type drugs to reduce harm in the short term.

Expanding the understanding of substance use disorders (SUD) from an osteopathic perspective would also provide significant benefit to understanding SUD as a disease. In his original writings on osteopathic theory, Still [14] emphasized the concept of homeostasis and allostasis. His understanding of the body’s ability to “heal” itself when in proper balance is a core tenet of osteopathic philosophy. In fact, reward deficiency syndrome (RDS) can be viewed as an osteopathic concept. The imbalance of dopamine, and the brains reward system, is a core etiologic component of substance misuse, with effective treatments targeted at restoring this imbalance [14, 15].

Understanding this conundrum, we are proposing a paradigm shift in our thinking, as we approach a new era in 2021, with a promising inoculation for COVID-19 to reduce viral-induced mortality across the globe [16]. Certainly, if we could reduce the worldwide incidence of COVID-19, “fueling the flame”, supposedly opioid-induced fatalities should also decline [17]. To be clear, we applaud the intense and arduous efforts of our governmental institutes and professional societies (NIDA, NIAAA, ASAM, ABAM) in their extraordinary efforts in combating this continued dilemma, but out-of-the-box thinking for nonosteopathic physicians is necessary.

It is well-known and agreed that a major culprit in motivational drug-seeking behavior relates to impairments across the brain reward circuitry [18]. Volkow’s group [19] points out that dopaminergic signaling is not only a major culprit in opioid-seeking behavior, but its upregulation is indeed an important therapeutic requirement and laudable goal. Hyman [20] and others [21] have argued that the current DSM-5 does not accurately display the natural brain reward process. In fact, our group has further argued that 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 [22]. This later concept has led to the emerging understanding that the common genetic thread and its interrelatedness to the environment (epigenetic) has at its rubric alterations in normal dopaminergic function (surfeit or deficit) identified by Blum’s group [23] as RDS. Indeed, currently, dependent upon gender, age, ethnicity, diet, and exercise, drug taking as an accurate endophenotype related to dopaminergic function could be either hypodopaminergic or hyper-dopaminergic [24–27], while Dackis and Gold [28] correctly suggested that dopamine D2 receptor agonist therapy (e.g., bromocriptine) seemed prudent to treat cocaine-induced dopamine depletion, long-term administration resulted in down-regulation of dopamine, limiting its clinical usefulness [29–31]. In contrast, instead of proposing powerful D2 agonists [32], our proposition is to provide dopamine balance (homeostasis) via the incorporation of pro-dopamine brain circuit regulation [33].

The scientific community is interested in methodology related to optimizing the regulation of dopamine function either up or down dependent upon the specific dysfunction [34–37]. There are a number of therapeutic modalities that potentially activate dopaminergic pathways and as such may provide useful anti-RDS approaches. These include and are not limited to repetitive transcranial magnetic stimulation (rTMS), exercise, and even new medications with positive allosteric modulators of GABA-A receptors [38–40]. In response to the opioid/other drugs and behavioral addiction crisis, our group has investigated the role of genetics as a DNA polygenic risk factor in RDS behaviors. Since the first paper by Blum et al. [41] in JAMA related to the association of the DRD2 Taq A1 in severe alcoholism, there has been a plethora of genetic risks in psychiatric genetics, with 25,781 listed in PubMed (06/16/21). Along these lines of investigation, our laboratory has developed “precision addiction management” (PAM). PAM couples the Genetic Addiction Risk Severity (GARS®) [42] with a precision-matched pro-dopamine regulation complex known as KB220 [43–45]. Ultimately, an important goal is to activate mesolimbic D2 receptors with dopamine agonist therapy capable of supplementing biochemical mechanisms mediating synthesis, control, and release of dopamine, particularly at D2 target sites. The nutraceutical KB220z was assembled based on the cascade of neurotransmission that results in reward. The
brain reward cascade involves the enzymatic synthesis in midbrain dopamine neurons controlled by hypothalamic, serotonergic, enkephalinergic, and GABAergic neurons, as well as their targets in the nucleus accumbens (NAc) that contain high levels of D2 receptors.

Preclinical studies and human trials involving KB220 variants have been previously reviewed [43–45]. Prior KB220 variants have enhanced brain enkephalin levels in rodents and reduced alcohol-seeking behavior in C57/BL mice by pharmacogenetic conversion of ethanol-prefering C57/BL mice to the same level of nonpreference as DBA mice. In humans, KB220Z has been reported to reduce drug and alcohol withdrawal symptomatology. A pilot study of abstinent heroin addicts found that, compared to placebo, a single dose of KB220Z resulted in improved prefrontal-cerebellar-occipital neural network connectivity and NAc activation. Thus, based on these and other studies, the use of KB220Z might be an ideal strategy to treat RDS, particularly to counteract underlying brain hypodopaminergia [43].

Utilizing fMRI neuroimaging, we showed that KB220z induced not only enhanced brain resting-state connectivity across specific reward brain regions in naïve rats [46] but also induction of dopamine homeostasis in abstinent heroin addicts [47]. To be clear, PAM and other known prodopamine regulating agents or approaches could induce “dopamine homeostasis” to effectively rebalance and restore brain function by promoting the crosstalk between various brain regions (e.g., NAc, cingulate gyrus, hippocampus, etc.), resulting in dopamine homeostasis [48, 49].

Finally, while the current FDA-approved MAT is what we have, future investigation is required with the emphasis that MAT should be expanded to individuals in need as an initial frontline way to reduce harm, with the long-term goal of prophylaxis [50]. However, one futuristic goal is to not only induce harm reduction and save lives, but also to achieve a hierarchical way to redeem joy and improve the quality of life in the recovering community and to assist them in getting out of a hypodopaminergic ditch [51]. Based on the current literature, the idea of balancing dysfunctional brain reward dopamine [14, 15] is not as illusionary as some might think. To be clear, there are a number of important ways to induce potential dopamine homeostasis besides KB220 variants and even include psychedelic medicine, exercise, and other modalities [49, 52–54]. For us, it seems like a reachable reality.

Osteopathic approach

The principles of osteopathy focus on providing treatment with a holistic approach and keeping biopsychosocial factors in consideration rather than focusing on treating just the organ system in question. Pain, through the biopsychosocial model, can be viewed as a dynamic interplay between physiological, psychological, and social factors [55]. An asymmetry of these factors can diminish homeostatic balance and an individual’s inherent capability to heal. Rather than prescribing opioids as the first line of defense, physicians should aim to understand “who, what, where, when.” [56] Effective communication between patients and physicians is the key to addressing all three of these factors so that homeostatic balance can be restored.

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Competing interests: Dr. Blum is the inventor and owner of a number of patents related to Genetic Addiction Risk Severity (GARS®) and KB220. Through his company Synaptamine, Inc. he has licensed his patents related to KB220 to iVitalize Inc. (Los Angeles, CA) with a sublicense to Victory Nutrition International (Lederach, PA).

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