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Editorial

Should We OPT to Induce "Dopamine Homeostasis" in the Long-Term Instead of Prescribing Powerful Opioids (Buprenorphine-Naloxone) to Treat Alcohol and Opioid use Disorders in the Face of the Drug Abuse Epidemic?

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Addiction clinicians and scientists face an enormous challenge in fighting the global opioid and alcohol use disorder (OUD/AUD) pandemics. Despite significant advances, the number of deaths attributed to narcotic overdose in the United States (US) alone exceeded 100,000 in 2021. The National Institute on Drug Abuse (NIDA) and The National Institute on Alcohol Abuse and Alcoholism (NIAAA) are struggling to generate novel approaches to tackle the severity of the present substance abuse epidemic.

Medication-assisted treatments (MAT) that have been approved by the FDA function predominantly by inhibiting dopamine release and function in the nucleus accumbens' pre-neuron [1,2]. MAT has been shown to reduce overdose deaths, costs, and health care events; but, a long-term approach that enables MAT patients to return to premorbid functionality is required. MATs frequently fail [3], and when terminated, relapse and overdose ensue at rates comparable to untreated patients. Neurologically, MAT can cause long-term alterations in acetylcholine, cannabinoid, dopamine, endorphin, serotonin, GABA, glutamate, and various brain systems (Figure 1). Due to a lack of options, chronic use of agonist treatments may be needed; nevertheless, research on chronic vs. acute

use harm reduction is limited [4,5]. However, evidence exists that treatments themselves, such as long-term agonist therapy for OUD, can also lead to Reward Deficiency Syndrome (RDS) [5], resulting in harm and fatalities that dwarf the existing viral epidemic.

Although drug overdose deaths are highest in the US, they are also a global problem that requires extraordinary solutions. Opioid substitution therapy used short-term can help to reduce harm; but long-term patients may suffer from substance use disorder for the rest of their lives [5]. Alternatively, Naltrexone, a narcotic antagonist, blocks Mu and delta opioid receptors causing "psychological extinction" by diminishing a conditioned response over time [6]. However, one challenge with narcotic antagonism is that compliance is controlled by the individual's genetic antecedents [7], while the other FDA-approved treatments for alcoholism block dopaminergic transmission [8,9].

There is growing support for using the non-addictive narcotic antagonist Naltrexone to treat both AUD and OUD. Recent studies have demonstrated that Naltrexone is useful in preventing relapse and attenuating cravings through "psychological extinction". The current MAT of choice is Buprenorphine, however injectable Naltrexone combined with a drug that improves dopaminergic tone and function may rekindle interest amongst addiction specialists and patients. However, poor compliance is present even when extended injectable treatment options are used. As a result, our group published an open-label study that found that dopamine augmentation with the pro-dopamine regulator KB220 (262 days) improved naltrexone outcomes and compliance in people compared to naltrexone alone (37days) [6]. In comparison to standard treatment, this well-researched complex is comprised of amino-acid neurotransmitter precursors and enkephalinase inhibitor therapy. Consideration of this unique paradigm change could help to solve not only the current opioid and alcohol epidemics, but also the larger issue of reward deficiency.

The ingredients that make up the most recent variation of KB220Z (powdered form) utilized in the recent studies include: Vitamin B6, 10 mg (500%); Thiamine, 15 mg (1033% of Daily Value); Chromium poly nicotinate 200 mcg (166%); and a fixed dose of Synaptose. Synaptose is comprised of herbs and amino acids including: L-Tyrosine, DL-Phenylalanine, Passionflower Extract; a Complex containing Arabinogalactans, N-Acetylglucosamine, Astragalus, Aloe Vera, Frankincense Resin, White Pine Bark Extract, and Spirulina; Rhodiola; L-Glutamine; 5-Hydroxytryptophan (5-HTP); Thiamine Hydrochloride; Pyroxidal-5-phosphate and Pyridoxine HCl [9]. The powder was manufactured by Cephram, Inc. (New Jersey). Prior to imaging, fresh solutions were made in double distilled water, had a total concentration of 33 mg/ml (based on weighed powder), and delivered in a total volume of 0.1ml over the course of 30 seconds.

Understanding the aforementioned presupposition, as well as the growing acceptance of the general premise of RDS, conceived by Dr. Blum in 1995, which is now published in ENCLYCLOPEDIA.COM, and Pubmed with 219 listed articles and 1,466 articles listed under "reward deficiency" as of 4-1-22, facilitates the widespread mechanism hypothesis for behavioral and chemical addictions [10]. The traditional neuromodulating characteristics of neurotransmission, as well as the disruption caused by chronic exposure to behavioral and substance addictions, requires an approach that focuses on achieving "dopamine homeostasis," particularly in the case of AUD [11].

Large-scale genomics research have had limited success in discovering alleles linked to addiction and RDS. Although Genome-Wide Association Studies (GWAS) and next-generation sequencing are powerful genetic tools, they are not without flaws. Certainly, GWAS, for example, is assisting in the discovery of novel gene clusters that may be associated with an etiological component as a genetic antecedent to specific RDS behaviors such as AUD. Convergence to specific candidate genes is the next essential step after GWAS results. Therefore, if there is any evidence that a specific known gene and associated polymorphic risk allele is associated with a specific phenotype, i.e., AUD/OUD, even if the contribution of each gene is miniscule, then it's pursuit is valuable. Our strategy has always involved identifying addiction liability by determining DNA associated polymorphisms at finite pathways.

Numerous neurotransmitters are implicated in the processing of reward and punishment. At least seven quintessential neurotransmitters along with various second messengers are involved in these pathways, which are associated with the mesolimbic and Pre-Frontal Cortex (PFC). To reiterate and emphasize, one function is the regulation of the final pathway of "wanting," which results in the net neuronal release of dopamine. Figure 1 offers a schematic representation of the Brain Reward Cascade (BRC) demonstrating the interaction of acetylcholine, cannabinoidergic, dopaminergic,

GABAergic, glutaminergic, opioidergic, and serotonergic, systems related to the net neuronal release of dopamine at the Nucleus Accumbens (NAc).

Dopamine is highlighted because it is understood that healthy processing of an initial action potential in the brain requires the integrity of the entire neurotransmitter complex of the brain reward circuitry. The cascade interactions cause balanced dopamine release at the NAc and throughout various brain regions. These various regions in the brain are involved in cognition (memory), recall, decision-making, motivation, pleasure, well-being, stress reduction, drug reinstatement, and cravings [12]. Additionally, the Genetic Addiction Risk Severity (GARS) test can be utilized to measure DNA polymorphisms in order to provide customized KB220 [13,14].

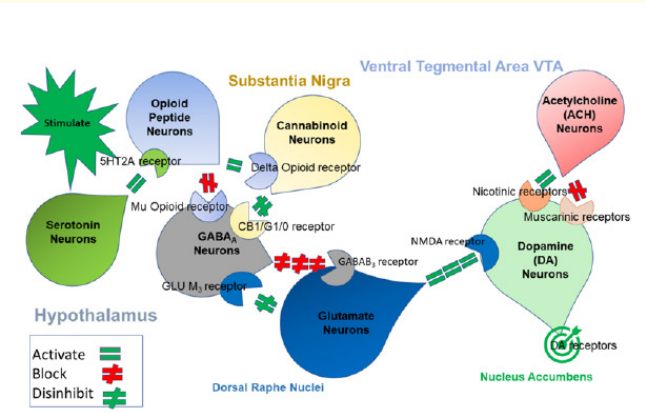

Figure 1

Figure 1 illustrates the interaction of at least seven major neurotransmitter pathways involved in the Brain Reward Cascade (BRC). In the Hypothalamus, environmental stimulation causes the release of serotonin, which in turn, via, for example, 5HT-2a receptors activate (the green, equal sign) the subsequent release of opioid peptides into the Hypothalamus. Then, the opioid peptides have two distinct effects, possibly via two different opioid receptors. A) inhibits (the red hash sign) through the mu-opioid receptor (possibly via enkephalin) and projects to the Substania Nigra to GABAA neurons. B) stimulates (the green, equal sign) Cannabinoid neurons (e.g., Anandamide and 2-archydonoglcerol) through Beta –Endorphin linked delta receptors, which in turn inhibit GABAA neurons at the Substania Nigra. Cannabinoids, primarily 2-archydonoglcerol, when activated, can also indirectly disinhibit (the red hash sign) GABAA neurons in the Substania Nigra through activation of G1/0 coupled to CB1 receptors. Similarly, Glutamate neurons located in the Dorsal Raphe Nuclei (DRN) can indirectly disinhibit GABAA (neurons in the Substania Nigra by activating GLU M3 receptors (the red hash sign). GABAA neurons, when stimulated, will, in turn, powerfully (the red hash signs) inhibit Ventral Tegmental Area (VTA) glutaminergic drive via GABAB 3 neurons. Finally, Glutamate neurons in the VTA will project to dopamine neurons through NMDA receptors (the green, equal sign) to preferentially release dopamine at the NAc shown as a bullseye indicating well-being (Blum owns copyright).

Author Contribution

All authors contributed equally to this editorial.

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Conflict of Interest

KB is the inventor and patent holder of KB220Z and the Genetic Addiction Risk Severity (GARS) test.

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