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Case Report

# OPIOID ADDICTION: That's "for the BRDS"

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## Introduction

This phrase" that's for the birds" is of American origin and, while still in use there, has never been commonly used elsewhere. It is US Army slang and originated towards the end of WWII. First use was from *The Lowell Sun*, October 1944. The phrase has a number of meanings as described in the 1944 edition of the American Speech. In our use of this phrase, it suggests that people do not want to experience addiction at all because it is contemptible. We also use it to designate that preaddiction based on both DNA antecedents and epigenetic insults due to negativity in the surrounds is due in-part to reward deficiency as in "Reward Deficiency Syndrome" first coined by Blum's group in 1995, thus aka BRDS.

Opioid use disorder (OUD) is the chronic use of opioids that induces clinically significant harm, addiction and neurological impairment. It is now known that OUD affect at least 16 million people worldwide, over 2.1 million in the United States, and there are over 120,000 deaths annually in America attributed to opioids. It is estimated that the overall cost of the illegal and legally prescribed opioid crisis exceeds one trillion dollars. In the US today, there are as many persons diagnosed with obsessive-compulsive disorder, psoriatic arthritis, and epilepsy combined as there are people regularly using opioids. The opioids include heroin, morphine, codeine, fentanyl, and synthetic opioids such as hydrocodone, oxycodone and methadone. Treatment for OUD primarily involves symptom management of acute withdrawal, rescue and stabilization of the patient using a single modality, opioid replacement therapy (ORT) ORTs include Suboxone (Burenorphrine and Natrexone), buccal administration of buprenorphine (Belcuca), and methadone. Although some patients can slowly taper off the MAT therapy, and become drug free, but this the uncommon exception. The pathophysiology of addictive disease is rooted in genetics, epigenetics one's developmental risks and life experience. The use of quickly cause neuroadaptation in the brain. Pre-teens and teens are the most vulnerable and prevalence data confirms that early onset use of any intoxicant increases the risk of addiction.

Persons with chronic pain rely of analgesic medication in order to participate and function in a manner congruent with their premorbid values and goals even though they remain physiologically dependent on the powerful opioid, Addiction may or may not include physiological dependence e.g., gambling, or pornography, or gaming, nevertheless the individuals premorbid values and goals are usurped by the effect of the drug on their emotional state via the hastened-release of dopamine, serotonin and other unknown mechanisms. A patient that presents with DNA polymorphic alleles of reward genes will increase the likelihood of substance and non-substance addictive behavioral seeking. Harm reduction is far from having any effect on the root cause of the SUD and OUDs in particular [1].

Naltrexone is often prescribed to prevent relapse. Based on our clinical outcome data, evidence has emerged showing that compliance and sustained recovery are associated with combining naltrexone with a pro-dopamine regulator that restores the bioavailability of central dopamine [2]. Combined with proven non-pharmacological therapeutic modalities such as twelve-step programs, peer support, and mental health professionals, individual and group therapy [3]. Unfortunately, long-term use or misuse of for example heroin (only $2.00 per bag), there is strong neuroimaging evidence that even abstinent heroin dependent patients experience brain reward circuitry abnormalities.

We are cognizant that others have found resting state functional connectivity patterns in heroin-dependent individuals that were significantly different from healthy subjects [4-7]. Undoubtedly, there is strong evidence that such impairments in functional connectivity may negatively impact decision-making and inhibitory control [8]. In addition, in earlier reports it was found that heroin addicts displayed reduced activation in right amygdala in response to the affective pictures when compared to normal controls [9]. Other studies showed persistent abnormalities in brain function following one month of heroin withdrawal in the orbitofrontal cortex [6]. Zijlstra., *et al*. found lower baseline dopamine D2 receptor (D2R) availability in opiate-dependent subjects than controls in the left caudate nucleus [7]. D2R availability in the putamen correlated negatively with years of opiate use. Opiate-dependent subjects demonstrated higher dopamine release after cue-exposure in the right putamen than controls. Chronic craving and anhedonia were positively correlated with altered DA release [7] in psychoactive drug dependent subjects.

Currently, the standard treatment of OUD and opioid addiction involves the use of powerful opioids, which seem inane and traps people in an unwanted cycle of addiction [8,9]. 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. We encourage additional novel but prudent and effective treatment as a future goal.

In our opinion, as espoused by Lee., *et al*. [8], future therapies should include targeting various portions of the dopamine-dependent addiction pathway, identifying vulnerable genes, and modifying gene products. In this regard, we propose as one solution precision Pro-dopamine Regulation (KKB220) or other gentle dopamine agonists [10].

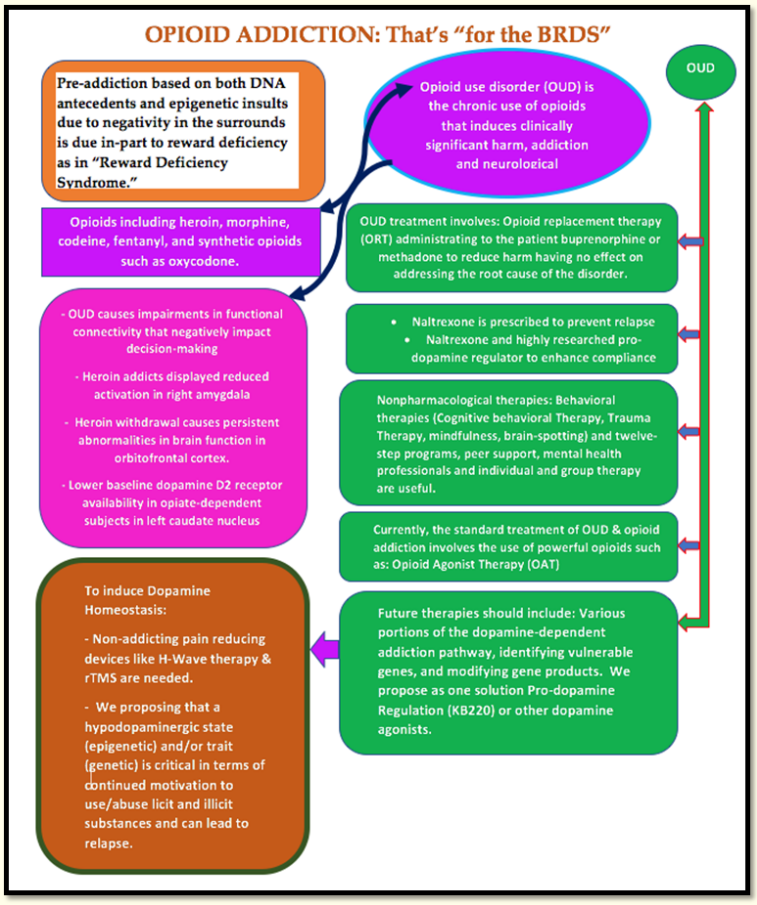
It is noteworthy that our team seeks to attenuate harm while addressing the core underlying issue [11]. Since 1995 when Blum's group coined the term "Reward Deficiency Syndrome (RDS)" there are now 233 articles listed in PUBMED (11-25-22) as well as 1,475 using the term reward deficiency" where only 9.3% has been contributed by our team. With this in mind, using Bayesian theorem, the Predictive Value (PV) of carriers of just the *DRD2 Taq A1* allele from birth to adulthood will have at least one RDS behavior (e.g., SUD) was found to be 74.4%. [12]. Specifically, the dopaminergic system, especially the dopamine D2 receptor, has been implicated in reward mechanisms in the meso-limbic circuitry of the brain [13]. Dysfunction of the D2 dopamine receptors leads to aberrant substance (alcohol, drug, tobacco and food) seeking behavior. Most importantly, many years of research strongly suggest that genetics plays an important role in predisposition to severe substance seeking behavior. Thus, we propose herein that polymorphisms of the D2 dopamine receptor gene along with at least ten other prominent "reward genes" are important common genetic determinants in predicting compulsive disease we call RDS. The consensus of the [18] literature suggests that alcohol and other SUD share comorbidity with other RDS disorders, i.e., a reduction or blunting in dopamine signaling within the reward pathway [14]. While ORT is the standard of care for patients displaying opioid dependence, a JAMA report in terms of pain relief revealed that non-opioid treatments fare better than chronic opioid treatments [15]. Other non-addicting pain reducing devices like H-Wave therapy and rTMS are better options especially in high risk for addictive behaviors [16,17]. One daunting statistic is that over 50% of all suicides are linked to abarrant drug use both egal and illicit [18]. Based on these statistics and others [19] we believe it is imperative to develop following more intensive research new novel non-addicting therapies to overcome the issue related to ORT with a resounding attempt to induce dopamine homeostasis.

Therefore, we are proposing 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. Unfortunately, there are FDA-approved medications that can be utilized to treat substance addictions (e.g., alcohol, opiates, nicotine, etc.), as previously mentioned, these agents typically only offer a short-term advantage by blocking dopamine [20]. 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".

Blum., *et al*. [21], 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. In addition, there is ongoing research related to the promise of effective anti-opioid vaccines. In terms of vaccines while intriguing it is not actually clinically friendly. The reason for this bold statement is that vaccines against one chemical moiety like heroin will not cross react with morphine and reduce its penetration into the brain, being too specific. So, with that stated in order to be effective there must be a specific vaccine for every known opioid to prevent effectiveness of each individualized opioid. However, one smart vaccine is targeted against the very potent and deadly adulterate Fentanyl. Along these lines, it would be potentially wise to develop a specific vaccine against this extremely potent synthetic opioid. Raleigh., *et al.* [22] developed a vaccine consisting of a fentanyl-based hapten (F) conjugated to keyhole limpet hemocyanin (KLH) carrier protein or to GMP-grade subunit KLH (sKLH). A number of key points here is the following: 1) F-KLH in mice and rats reduced fentanyl-induced hotplate antinociception; 2) F-KLH did not reduce the antinociceptive effects of equianalgesic doses of heroin or oxycodone in rats, showing specificity ; 3) F-KLH in rats reduced fentanyl distribution to the brain compared with controls ; 4) F-sKLH shifted the dose-response curves to the right for both fentanyl-induced antinociception and respiratory depression; 5) Naloxone reversed fentanyl effects in both groups, showing that its ability to reverse respiratory depression was preserve. According to the authors "*These data demonstrate preclinical selectivity and efficacy of a fentanyl vaccine and suggest that vaccines may offer a therapeutic option in reducing fentanyl-induced side effects [like death]".*

To reiterate, there is well-established evidence for hypodopaminergia [23], a blunted reward processing system [24], attenuated resting state functional connectivity [25], DNA antecedents [26], anti- reward symptomatology [27], poor compliance with MAT [28], and generalized RDS (AKA BRDS) [29]. The take home message here is that understanding this evidence it is conceivable that pursuit through intensive future research could involve an approach that incorporates "dopamine homeostasis". This required novel paradigm shift might consist of many beneficial modalities including but not limited to exercise [30], pro-dopamine regulation [31], nutrition [32], cognitive behavioral therapy [33], hedonic hot spot targets brain [34], rTMRS [35], deep brain stimulation [36], diet, genetic edits [37], genetic guided therapeutics [38], epigenetic repair [39], amongst others related to augmented resting state functional connectivity [40].

Certainly, "out of the box thinking" in the face the of the continued drug/behavioral addiction crisis, requires innovative systems biological approaches. The multi-faceted treatment approach should be holistic in that it combines a number of the above cited modalities. This therapeutic multi-targeted approach might just become a frontline defense to prevent and or treat "BRDS" like behavior. It is anticipated that effective fellowship programs and spirituality acceptance, nutrigenomic therapies (e.g., KB220Z) optimize gene expression, rebalance neurotransmitters, and restore neurotransmitter functional connectivity. One laudable goal is that Nutrigenomics may assist the millions of people of getting out of a "hypodopaminergic ditch" [41] (Figure 1).



## Conclusion

To reiterate, the literal meaning of the phrase, "That's for the BRDS" refers to a meaningless act only the gullible would be interested in engaging. This old American notion believes that humans inherently avoid acts they find contemptible. Then why do individuals blatantly engage in the use of addictive and harmful substances? Opioids change the individual's brain chemistry thus impairing perception, cognition, judgment, complex decision-making, and normal brain functioning. A chemically impaired neural system can no longer distinguish contemptible acts and thus engages the person in self-harming behavior such as addiction, so where and how the tendency to such risk-taking behavior can be found? Scientific studies allude to the presence of pre-genetic tendencies, existing DNA markers, and epigenetic setbacks, which can lead to inadequacies in dopamine function "Reward Deficiency Syndrome" aka BRDS.

The traditional one size fits all approach in addressing a globally charged opioid crisis is no longer working. It is time for a Multisystemic approach that includes Nutrigenomics (connections between nutrients, diet, and gene expression) [42]. The Human Genome Project, which was launched in the 1990s, led scientists to the discovery of human DNA sequencing, and the eventual DNA mapping. This phenomenal discovery opened possibilities for multimodality treatments such as dopamine regulators, genetic editing, and nutrigenomics [43].

The acknowledgment of such early developmental markers, genetic pre-disposition, and DNA structure emphasizes the importance of early detection and basal diagnostic strategies. These strategies include but are not limited to early childhood Multi- Assessment Developmental Tests (MADT), RDSq29, [44] Genetic Addiction Risk Severity (GARS), Multisystemic treatment approach, and Nutrigenomics (Nutritional genomics). To shift the addiction paradigm from the high rate of failure in opioid recovery, it is imperative that these early markers are identified during sensitive developmental periods. Finally, to help assess "preaddiction" [45] or "BRDS" [46], taking the proposed GARS test combined with a the KB220Z semi-customized nutrigenomic supplement has been shown via neuroimaging to effectively restores dopamine homeostasis [47].

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## Contribution of Authors

KB developed the first draft. AB provided the schematic. NJ reviewed the manuscript and provided information on nutrigenomics. IG, DB, PKT, MSG, CD, DE, JK, ERB RDB made edits and comments and approved manuscript.

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## Conflict of Interest

K.B. is the inventor of GARS and KB220 and is credited with domestic and foreign patents. The other authors declare no conflict of interest.

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