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Understanding Reward Deficiency Syndrome (RDS) as Common Root Cause of All Addictive Behaviors: Promoting "Precision Addiction Management"™

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Abstract

Worldwide, daily there are several millions of people that are increasingly unable to combat their frustrating and even fatal romance with getting high and/or experiencing "normal" feelings of well-being. One issue is that in the USA, the FDA has approved pharmaceuticals for drug and alcohol abuse: tobacco and nicotine replacement therapy. The National Institute on Drug Abuse (NIDA) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) because of outstanding research continue to provide an increasing understanding of the intricate functions of brain reward circuitry through sophisticated neuroimaging and molecular genetic applied technology. In addition similar work is intensely investigated on a worldwide basis with clarity and increased interaction between not only individual scientists but across many disciplines. However, while it is universally agreed that dopamine is a major neurotransmitter in terms of reward dependence, there remains controversy regarding how to modulate its role clinically to treat and prevent relapse for both substance and non-substance-related addictive behaviors. It is also agreed by most that there is a need to provide early genetic identification possibly through a novel researched technology referred to Genetic Addiction Risk Score(GARS).™ While the existing FDA-approved medications promote blocking dopamine, we argue that a more prudent paradigm shift should be biphasic-short-term blockade and long-term upregulation, enhancing functional connectivity of brain reward. Understanding that the real phenotype is not any specific drug or non –drug addictive behavior instead we are hereby proposing that a new paradigm should adopt the notion that Reward Deficiency Syndrome (RDS) is indeed the true phenotype of all addictive behaviors. Finally, we are suggesting that one way to combat the current out of control Opioid crisis worldwide is to seriously reconsider treating RDS by simply supplying powerful narcotic agents (e.g. Buprenorphine) keeping people addicted and turn to a more reasonable solution involving genetic testing , urine drug screens using Comprehensive Analysis of Reported Drugs (CARD) and dopamine homeostasis we call " Precision Addiction Management" ™

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Prolog

We are proposing a new paradigm shift in the prevention and treatment of all addictive behavioral seeking in humans. Following almost three decades of genetic based research related to what has been termed Reward Deficiency

Syndrome (RDS), we are poised for the novel adoption of "Precision Addiction Management."™ Certainly, more research is necessary to further pinpoint the most appropriate candidate genes utilizing accelerating personalized / precision medicine to identify highly convergent candidate gene SNPS associated with Reward Deficiency Syndrome (RDS) in not only the world population but especially in sub-served populations including but not limited to African Americans as part of a NIH grant awarded to Dr. Kenneth Blum (PI) and Marjorie Gondre-Lewis (Co-PI). [Drs. Blum and Gondré-–Lewis are the recipients of R41 MD012318/MD/NIMHD NIH HHS/United States.]. Our laboratory is confident that eventually the scientific community seriously augments research directed to up-regulation of dopamine in meso-limbic structures with the notion of achieving homeostasis.

INTRODUCTION

While the term Reward Deficiency Syndrome (RDS) was first coined by Dr. Blum in 1995 following many important studies from around the world, RDS is now listed in the SAGE *Encyclopedia of Abnormal and Clinical Psychology* edited by A. Wenzel (SAGE Publications 2017; 6: 2887-2891). To date there have been over 124 articles listed in PUBMED as well as 822 articles listed for Reward Deficiency.

In the early sixties we knew relatively very little about the workings of the brain especially the interrelatedness of the brain reward circuitry and the Pre-frontal cortices. Understanding the importance of the main neurotransmitters such as serotonin, GABA, dopamine and acetylcholine were unknown for the most part and endorphins was not even a part of our scientific acumen. The 1956 doctrine of Jellinek and the disease concept of alcoholism to some shocked the world, and as such without much scientific evidence and not generally accepted [1]. At that time most scientists working in the field of addiction agreed that alcoholism is the result -at least in part -of deficiencies or imbalances in brain chemistry-perhaps genetic in origin. However so little was known that nothing specific was espoused by the then newly called neuroscientists.

For thousands of years, human beings have had a love/hate relationship with alcohol. No one knows when the first beer was brewed, but it was earlier than 5,000 B.C. In fact, wine dates back to 3,000 B.C.; brandy appeared late in the

twelfth or early thirteenth century, but grain-based 'hard' liquors such as whiskey and gin had very little impact until the seventieth century.

In 1995, Blum questioned the validity of the theorized neurochemical mechanisms of a number of psychoactive drugs such as alcohol and opiates. This concern was highlighted by the original work of Virginia Davis [2], Gerald Cohen [3], Michael Collins [4] and others [5] related to common mechanisms between alcohol and opiates [6]. As such in 1996 Blum and his group coined the term *Reward Deficiency Syndrome (RDS)* publishing the concept in the Royal Society of Medicine [7].

Mark Gold's theory, the "Dopamine Depletion Hypothesis", proposed an important role for dopamine in the effects of cocaine [8, 9]. Euphoric properties of cocaine lead to the development of chronic abuse, and appear to involve the acute activation of central DA neuronal systems. Dopamine depletion is hypothesized to result from overstimulation of these neurons and excessive synaptic metabolism of the neurotransmitter. DA depletion may underlie dysphoric aspects of cocaine abstinence, and cocaine urges. Neurochemical disruptions caused by cocaine are consistent with the concept of "physical" rather than "psychological" addiction. In follow-up research, it was proposed that one way to treat cocaine addiction was to embrace dopamine agonist therapy such as utilizing the powerful dopamine D2 agonist bromocriptine. This compound was found to significantly reduce cocaine craving after a single dose [10]. It was suggested that bromocriptine may be effective as a new, non-addictive pharmacological treatment for cocaine addicts and support the notion that functional dopamine depletion occurs with chronic cocaine use.

Open trials indicate that low-dose bromocriptine may be useful in cocaine detoxification. In 195, Lawford et al. [11] conducted a double-blind study, where bromocriptine or placebo was administered to alcoholics with either the A1 (A1/A1 and A1/A2 genotypes) or only the A2 (A2/A2 genotype) allele of the DRD2. The greatest improvement in craving and anxiety occurred in the bromocriptine treated A1 alcoholics and attrition was highest in the placebo-treated A1 alcoholics. However, we know now that chronic administration of this D2 agonist induces significant down-regulation of D2 receptors thereby preventing its use clinically [12].

Blum and Gold's groups continued to propose dopamine agonist therapy rather than dopamine antagonistic therapy, which is currently favored by the approved FDA drugs as medical assisted treatment [13]. Specifically, Blum et al. [14] proposed that D2 receptor stimulation can be accomplished via the use of KB220Z [15], a complex therapeutic "neuro-nutrient" formulation that potentially induces DA release, causing the same induction of D2-directed mRNA and thus proliferation of D2 receptors in the human.

This proliferation of D2 receptors in turn will induce the attenuation of craving behavior. The research of this model has shown DNA-directed compensatory overexpression (a form of gene therapy) of the DRD2 receptors, resulting in a significant reduction in alcohol craving behavior in alcohol preferring rodents [16] as well as self-administration of cocaine [17]. The promotion of long term dopaminergic activation by lower potency dopaminergic repletion therapy will lead to a common, safe and effective modality to treat RDS behaviors including Substance Use Disorders (SUD), Attention Deficit Hyperactivity Disorder (ADHD), obesity and other reward deficient aberrant behaviors. This concept is further supported by the more comprehensive understanding of the role of dopamine in the Nucleus Accumbens [NAc] as a "wanting" messenger in the mesolimbic DA system [18].

It is the author's hypothesis that D2 receptor stimulation signals a negative feedback mechanism in the mesolimbic system to induce mRNA expression causing proliferation of D2 receptors. Thus, we are proposing for the first time ever an holistic therapeutic model for RDS which includes Genetic Addiction Risk Score (GARS) (predisposition); Comprehensive Analysis of Reported Drugs CARD (urine drug screen outcome measure) and KB220PAM (restoreGen ™) or gentile prolonged D2 agonist therapy, along with 12 step fellowship, mindfulness, and other holistic modalities (e.g. low glycemic index diet; yoga, meditation etc.) known to naturally release neuronal dopamine [19]. We call this - ***"Precision Addiction Management"***

Can we overcome DNA polymorphisms by promoting positive epigenetic effects which can be transferred from generation to generation [20]? With this in mind we wonder if we have been "licking our pups" enough, so that we could potentially attenuate substance and non-substance seeking- behaviors through

love-understanding that as David E. Smith suggested in the late 60's "love needs care" [21, 22].

Summary

Understanding these basics will enable the potential of translational addiction related basic research to reach the multitude of victims of genetically induced RDS to become the recipient of better therapeutic and relapse preventive tactics. Generally, as neuroscientists and psychiatrists, working in the "addiction space" we encourage the global scientific community to take heed and reconsider the current utilization of dopaminergic blockade and adopt the goal of achieving dopamine homeostasis. We assert that failure to at least carry on more sophisticated research as proposed herein, attempts to overcome our current opioid crisis is doomed. Optimistically, achieving early diagnosis through genetic testing (including Pharmacogenetics (PGX) and pharmacogenomics) , pro-dopamine regulation along with appropriate urine drug screening should have the remarkable potential of actually combating the current devastating the global opioid crisis.

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Conflict of Interest

Kenneth Blum owns stock in a number of companies holding patents on genetic testing and KB220PAM.There are no other conflicts of interest to declare.

Contribution of Authors:

The original concept was developed by KB, MSG, DB, JN, PKT, RDB. The original draft was provided by KB, and MCGL. The entire paper was carefully vetted by RDB, MCGL, KB, ERB, PKT, MH, DB, JN, DS and approved.

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