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Reward Deficiency Solution System (RDSS) "Repairing a Hypodopaminergic Trait/State: Reflection Over 50 Years

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Over the last 50 years of my journey in the exciting field of "Addiction Medicine", I have seen remarkable change in our scientific understanding of how psychoactive drugs influence behavior, through very complex actions on neuronal pathways especially in the mesolimbic system (craving) and the prefrontal cortex –cingulate gyrus (relapse) of the brain [1]. During this period I have had the distinct pleasure of not only working with some of the giants in the field but personally interacting with many of them. While the concept of recovery became a household word incorporating the 12 step program & fellowship [2], it is my belief that introducing a new definition of "addiction" espoused by the American Society of Addiction Medicine (ASAM) [3] will have tremendous impact on generations to come who will accept that addiction is indeed a brain disorder. My work with Ernest P. Noble and our esteemed associates, the discovery of the first gene to associate with severe alcoholism and sparked the current field of "Psychiatric Genetics," is certainly a highlight in my career [4].

We are now poised in the 21st century through the era of genomic medicine to begin to understand the true nature of this brain disorder, that I intuitively coined "Reward Deficiency Syndrome (RDS) [5,6]. Reflecting over these many years, there are a number of important examples of progress: understanding of the neurochemical mechanisms involved in the addiction process including withdrawal symptomatology [7]; understanding the physiological basis for brain neurotransmission [8]; understanding neurochemical mechanisms for synaptic function [9]; understanding the role of long-term potentiation in drug self- administration and sensitization [10]; understanding the neurobiological mechanisms of storage, release and catabolism of neurotransmitters in pre and post synaptic loci [11]; understanding the role of the" Brain Reward Cascade" in craving behavior and relapse [12]; neuroimaging dissecting dopaminergic activity in brain regions and understanding the role of neurogenetics in all aspects of drug seeking and process addictions [13].

However, with all of this positive and remarkable understanding we have a long way to go before we can say that science has caught up with this very complex brain disorder known as RDS. A priori, have we been looking at the genetics in a simplistic fashion (candidate gene approaches) compared to GWAS evaluation of a large body of genes (clusters)? [14] Should we pay more attention to epigenetic effects and continue our pursuit through EWAS studies? [15]. In regard to this rhetoric I submit to my scientific peers that it seems reasonable that based on well- known physiological mechanisms that we should not "toss the baby out with the bathwater." In my point of view, in spite of a number of GWAS studies having difficulty in finding significantly large associations with various gene candidates, (small associations) may be due to a number of factors such as the complex nature of the disorder being polygenic and most importantly, the flawed utilization of seemingly reasonable controls [16].

If indeed my associates and I are correct about the true phenotype of "addiction" which constitutes RDS and all of its subtypes (e.g. drugs, alcohol, nicotine, food, sex etc.) then it makes good scientific sense to rigorously screen controls for these RDS subtypes prior to systematic analysis whether one prefers the candidate or GWAS approach [17]. Having the disease as part of the controls will only lead to spurious and useless results. While this question will take years to resolve I would, like to turn my attention to the clinical management of the RDS patient. It is well known that patients especially when young, that present to a treatment center due to being coerced (court, family and friends intervention) will deny the real ongoing brain related issue there may be a number of reasons, including denial. To develop a non-invasive genetic test for RDS, RDS, such as The proposed "Genetic Addiction Risk Score (GARS) "based on known associations with alleles, that will "Genetic Addiction Risk Score (GARS) "that will allow for stratification of genetic risk in an individual, should at the very least provide a "mirror to the brain" thereby reducing some guessing in terms of brain function [18]. Obviously, there are other clinical benefits such as medical monitoring for pharmacogenetic response of a drug; metabolic issues of drug delivery; tailored customized treatment; medical necessity for type of clinical care; pharmacogenomic treatment targeting gene polymorphisms; and a host of other clinical benefits including family curiosity and wiliness to participate in the patients recovery plan.

The genetic test should be coupled with methodology involving drug urine testing evaluating both compliance to FDA approved treatment medications and abstinence from licit and illicit psychoactive drugs. Importantly, our recent research utilizing the Comprehensive Analysis of Reported Drugs (CARD) as developed by Dominion

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Diagnostics based on urine analysis n a large cohort, revealed that while a number patients complied to drug treatment medications and were abstinent during treatment (in-patient and out-patient) the majority 61% were not compliant and 39 were not abstinent [19]. This revelation suggests that for some treatment does work well but for many the rate of relapse remains high. Most treatment medications approved in the field of addiction medicine seem to be those that mimic the pharmacology of the drugs in question such as opioids and Buprenorphine; blocking opiate receptors with narcotic antagonists; reducing dopamine release with GABA agonists; and even vaccines against for example cocaine moieties [20,21].

Since the 1970s my associates and I have realized that extinction from drug abuse by the patient does not work in the long-term and must be replaced with a non-addictive substitute. This has led to many years of research in the development of a natural D2 agonist (as seen from neuroimaging experiments and over 25 clinical trials). In essence, we are causing a rather slow release of dopamine following neuronal synthesis buildup and inhibition of synaptic catabolism [22]. So instead of blocking dopamine in the long-term I am suggesting a different modus. Being cognizant that powerful D2 agonists like Bromocryptine may have significant anti-craving effects only to result in down – regulation of needed D2 receptors we opt for a less powerful but natural complex that may even increase D2 receptors in carriers, for example, with the dopamine D2 receptor ***Taq A1*** polymorphism [23].

Finally, I am proposing that utilizing mRNA analysis along with GARS when a patient enters a treatment center for addiction and or pain it would be parsonomiuos to determine gene expression pre and post –treatment [24]. This novel testing approach will provide third party payers with a further "mirror to the brain" that could show real objective improvement in the patient. Thus by following this set of rules we may have found what I am terming the "Reward Deficiency Solution System (RDSS)" [6].

As we approach 2014, I want to encourage the addiction scientific community in continued research success and enhanced efforts in areas involving early genetic diagnosis [25], improved medical monitoring, increased funding for required neuroimaging studies [26], careful selection of controls for genetic experiments and most importantly stronger support for a direct or indirect dopaminergic agonistic instead of antagonistic dopaminergic therapy.

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Conflict of Interest

Kenneth Blum, PhD holds a number of patents worldwide involving both natural D2 receptor agonist therapy and gene testing.

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