Journal of Addiction Science

https://doi.org/10.17756/jas.2020-043

Editorial

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Addiction by Any Other Name is Still Addiction: Embracing Molecular Neurogenetic/Epigenetic Basis of Reward Deficiency

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Received: December 09, 2019
Accepted: January 16, 2020
Published: January 21, 2020

Citation: Edwards D, Roy III AK, Boyett B, Badgaiyan RD, Thanos PK, et al. 2020. Addiction by Any Other Name is Still Addiction: Embracing Molecular Neurogenetic/Epigenetic Basis of Reward Deficiency. *J Addict Sci* 6(1): 1-4.

Published by United Scientific Group

The Human Genome Project and the database it created established a plausible observatory, so to speak, for scientists to identify the etiology of genetic variants and their expression. It is well-known that "Single Nucleotide Polymorphisms" (SNPs) which involve the cumulative presence of nucleic acids in sufficient volume and proximity along the DNA strands to create novel variants in the transcription and encoding of replicate genes--thus creating phenotypical risk for pathological expression [1]. One of these created phenotypes involves the molecular rearrangement of known base pairs sitting in chromosomes leading to an uncontrollable desire to self-administrate various drugs and even risky behaviours to overcome a known neurochemical deficiency or hypodopaminergia resulting in drug or non-drug seeking behaviours [2].

In the field of *behavioral and addiction medicine researchers* [3-6] have identified numerous SNPs and genetic variants in several candidate genes. For example, CADM2, is associated with sensation seeking and drug experimentation. CADM2 is just one of many candidate genes associated with Substance Use Disorder [7]. However, following the seminal work of our group on the first association of the DRD2 A1 allele and severe alcoholism the field of Psychiatric Genetics was born. A PUBMED search (12-6-19) reveals that there are now over 22,981. Along these lines is it well known that there over 393 genes that have associated with drug and alcohol seeking behaviours, whereby the two major pathways that have been consistently identified are glutaminergic and dopaminergic [8] While there have been many reports trying to untangle the specific role of dopamine in reward processing, the idea of "liking" and "wanting" revealed that in terms of dopaminergic mechanisms "wanting" seems to be the most relevant [9, 10]. However, it is well-established that dopamine especially in the brain reward circuitry is responsible in-part for motivation, cognitive abilities, achievement of pleasure, pain tolerance and even anti-stress functions [11]. One important aspect that requires consideration in terms of both treatment and prophylaxis of addictive behavioral seeking is balancing the

Brain Reward Cascade (BRC) with the net effect of ensuring "dopamine homeostasis". Failure to do so will result in high relapse rates [12]. One major issue that we take issue with has to do with the long term implications of treating opioid addiction with agonistic (methadone) or even partial agonistic opioids (buprenorphine) or even blocking opioid receptors with injectable Naltrexone [13]. In spite of the positive life saving aspects of using MAT to treat opioids and even alcohol, especially linked to reducing "societal harm" there is benefit in terms of quality of life especially in terms of prevention of overdose. However, while on these pharmaceuticals long term, they could impair cognitive abilities [14]. In fact, Hill et al., [15] evaluating emotional reactivity as measured by automatic detection of speech, found that long-term combinations of buprenorphine and naloxone resulted in a flattening of affect among some patients, compared to the general population and early attenders of Alcoholics Anonymous groups ($p< 0.01$). From as early as the late 60's notable work from Myers group [16] showing the role of serotonin in alcohol intake and the initial work of Blum's group [17] showing the blocking of ethanol dependence with the narcotic antagonist naloxone, and Davis's group [18] showing the involvement of isoquinolones (an opioid like condensation product of dopamine and acetaldehyde among others) initiated the concept of common mechanisms for opioids and alcohol [19]. This early work provided the actual framework for Blum's original concept he termed Reward Deficiency Syndrome (RDS) [20]. Following many years of study globally with 185 PubMed listed articles, RDS is featured as an abnormal psychological disorder in Sage Encyclopaedia of Clinical and abnormal Psychology [21].

These findings are supported through transcriptome analysis (the volume of messenger RNA molecules). Addictive disease (drug and non- drug (process) [22], depression [23], anxiety disorder [24], attention-deficit/hyperactivity disorder (ADHD) [25] and post-traumatic stress disorder (PTSD) [26] are all phenotypical conditions. Because these conditions share candidate genes and the co- occurring expression of neuropsychiatric conditions affecting the midbrain, ventral striatum, the term Reward Deficiency Syndrome has been coined to describe their shared etiology and pathophysiology [27].

In addition, new imaging technology has shed much needed light on the brain's "functional anatomy." Over the last five decades of research concerned with the role and significance of specific neurotransmitters, their bioavailability, and the neurocircuitry that enables the brain to communicate electrochemically, has framed our modern-day view of all addictive behaviours [28]. Pleasure, contentment, mood, focus and cognition all conspire to determine our mental and behavioral health, our life trajectory, and quality. For those with Addictive Disease, and its most common comorbidities, life can seem empty and hopeless.

It's important to note that SNPs and phenotypical risk factors are not in themselves causal. Environmental and familial stressors combined with genomic variants may result in a disease or condition being expressed. Over the last two decades our new understanding of the role environmental factors play in terms of gene expression termed epigenetics, has paved the way to understanding the simple well-known equation P = G + E. Where P = Addiction Phenotype; G = Genetic Trait; E = Epigenetic impact which could occur without changing DNA per se [29]. One strong example of the role of epigenetics as studied by Szutorisz et al. [30] whereby they found that parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subsequent generation. Thus based on this and other definitive work [31], we can now ascribe a better understanding of why persons without genetic risk factors who persistently use intoxicants, or chronic stressors can cause epigenetic changes that redefine pleasure and reward through neuroadaptation for up to at least subsequent generations.

Finally, the good news is that genetic testing technology currently exists which can identify SNPs and determine one's specific risk for phenotypical Reward Deficiencies. This test is known as the Genetic Addiction Risk Score (GARS) coupled with a precision matched Pro-dopamine regulator (KB220) and this system has been referred to as Precision Behavioral Management (PBM) [32, 33]. Who knows, perhaps one day CRISPR or other gene editing technologies (gene splicing, editing) will prevent the expression of some phenotypical risks for addictive disease. This in-part could be accomplished for example by editing the DNA code to change the mRNA expression of DRD2 A1 carriers to expressing the so called normal variant A2 and as such attenuation of self- medicating for a "dopamine fix".

However, we and most experts agree these newer concepts will not end addiction, as humans are hedonically inclined and, likely, will continue seeking more diverse pleasures, convenience and shortcuts toward reward attainment. In support of this statement, based on the now thousands of subjects GARS tested in the America, it has been found (unpublished) that there is a very high genetic risk for RDS.

But, for now, treatment for addictive disease is most effective when

1. Treatment is individualized, patient and family centered.

2. Delivered within a chronic disease, multimodal framework of optimal intensity and duration.

3. Provided by a highly trained multidisciplinary professional team [34].

It is now well established that genetic and epigenetic risks factors underlie disease manifestation. Accordingly, the expansion of a bio-psycho-social model of treatment as outlined in Gustin et al. [35], will incorporate GARS or other empirically proven testing for genetic and epigenetic risk factors. This advancement in how addicted persons are assessed will serve to direct treatment intervention toward hastening "dopamine homeostasis", thusly improving treatment success and quality of life for those suffering from addictive disease [34].

As a preventative strategy, identifying those at risk for RDS could be implemented throughout our healthcare system in much the same way as identification and quantification of Adverse Childhood Experiences (ACEs) are now being integrated into primary care settings. In both cases, early

identification prompts early intervention strategies so that patients at risk can be saved from a pathologically driven life trajectory and diverted toward early intervention of appropriate treatment. In the case of RDS, restorative and brain-building care, including the use of precision pharmacological intervention as suggested by Shonesy et al. may prevent serious psychopathology from fully manifesting [36].

The more we learn, the more we know that addictive disease is a complex multifaceted neuropsychiatric disease in which no single intervention modality is sufficient. The best available evidence reveals that the integration of the appropriate use MATs for life saving intervention, and within a chronic disease treatment framework, delivered by competent and experienced professional, are yielding the best outcomes to date. The addition of genetic testing serves to streamline and focus clinical and precision pharmacological interventions to further improve outcomes for this disabling and deadly disease.

While many names have been used to accurately define and describe addiction and RDS [38], e.g., the other side of darkness [39], anti- reward [40], dopamine deficiency [41], endorphin deficiency [42], etc., our message is simply this: Addiction by any other name is still addiction--but what one becomes addicted to serves as a modifying , and often confusing, nosology [37, 43]. As William Shakespeare, so eloquently wrote: "A rose by any other name is still a rose.".

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