Tentative Outline

Special Thematic Issue for the journal "Current Pharmaceutical Design" (CPD)

Title of the Thematic Issue: Neurobiological, Behavioral and Genetic Correlates of Reward Processing as a Preventive and Therapeutic Target in "Preaddiction" and Health as a Whole

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Co-Guest Editors: Dr. Mark S. Gold, Kenneth Blum, Igor Elman

- **Scope of the Thematic Issue:**

Addiction scientists and clinicians alike face at times unsurmountable challenges in confronting the mounting worldwide 'pandemic' of opioid use disorder with or without co-occurring alcohol use disorder. Notwithstanding tremendous progress in understanding the underlying neurobiological mechanisms, the 2021 death toll from opioid overdose has already surpassed 100,000 fatalities in the United States alone and it is projected to be as high as 165,000 for 2022. The National Institute on Drug Abuse (NIDA) and The National Institute on Alcohol Abuse and Alcoholism (NIAAA) work tirelessly on generations of novel approaches to combat the ongoing pandemic. FDA-approved medication-assisted treatments (MAT) work primarily via opioid agonist replacement with long-acting opioids namely, buprenorphine and methadone [1]. Although MAT has reduced overdose deaths, health care expenses and many other societal costs, it is imperative to design long-term strategies for assisting MAT patients to regain as much of their premorbid level of functioning as possible [2]. Moreover, MAT non-adherences remains a major concern leading to relapses to illicit opioid consumption [3]; interruptions in the course of MAT are associated with similar to untreated patients rates of consequent overdoses. Neurologically, MAT may induce persistent changes that compromise neuroendocrine [4] and neurochemical systems including, but not limited to dopamine, glutamate, GABA, endorphin, norepinephrine and serotonin. While chronic MAT administration may be essential at the present time given the lack of superior alternatives, more research is warranted on chronic vs. acute MAT sequalae [4,5]. This is a timely endeavor in the context of recent concerns about Reward Deficiency Syndrome (RDS) [5] and metabolic derailments [4] arising in the course of MAT leading to detrimental outcomes, the gravity of which may even outweigh the current viral epidemic.

Can early genetic risk assessment of "Preaddiction" like "Prediabetes" provide the missing piece to help overcome Substance Use Disorder?

Notwithstanding the enormous efforts of the federal government to fund, refine and deliver MAT, these treatments have not become a magic bullet or "cure" partially explaining less than 20% treatment penetration rates [6]. Mclellan et al. [7] interestingly point out that in the diabetes field introduction of the prediabetes concept referring to very preliminary stages of diabetes substantially increased treatment penetration. According to the American Diabetes Association 'prediabetes' is operationally defined by augmented scores on 2 laboratory tests namely, impaired glucose tolerance and impaired fasting glucose [8]. This strategy awareness has sharpened the awareness and increased sensitivity to the importance of early detection and timely introduction of behavioral and medical therapeutic interventions to avert long-term detrimental outcomes as well as partnership with third party payers, and over-time has shortened the delays between symptom onset and treatment entry leading to a success in halting the progression to diabetes [9].

It was thanks to these successes that Volkow (Director of NIDA) and Koob (director of NIAAA) are encouraging the psychiatric field to consider the "preaddiction" for the inclusion among the categories of the Diagnostic and Statistical Manual of Mental Disorders (DSM). While the term preaddiction resonates well with the historical advance in the diabetic field, scientific evidence resides in concepts related to brain neurotransmitter dysregulation including excessive dopaminergic function in adolescence [11]. There is the possibility of developing a test to help identify even early and subtle risk for future addictive-like behaviors. Based on the large body of prior work by scientists around the globe including our lab, the preaddiction state may be helpfully characterized using the terms taken from the dopamine dysregulation literature such as Reward Deficiency Syndrome (RDS) derived from the net attenuation

of the mesolimbic brain reward circuitry dopaminergic function in conjunction with the altered function of at least six related neurotransmitter systems i.e., serotonergic, cannabinergic, opioidergic, GABA ergic, glutaminergic and cholinergic [10].

DSM-5 uses 11 equally weighted symptoms of impaired control to define substance use disorders (SUDs) along a 3-stage severity continuum [7]. In the common parlance the term “addiction” is reserved for severe SUD, defined by 6 or more symptoms and found in approximately 4% to 5% of adults. Those with mild to moderate SUD (ie, 2-5 symptoms) comprise a much larger proportion of the adult population (13%) and thus account for far more substance use–related harms to society than those with severe SUD (i.e., addiction). However, treatment efforts and public health policies have focused predominately on those with serious and chronic addiction-related problems, apparently ignoring the much larger population with early-stage SUDs. Although harmful substance misuse and early-stage SUDs can be identified and severity progression can be monitored, very little has been done for a much more common (than full blown addiction) condition in the mainstream health care settings. Indeed, neither clinicians nor the public ever used a specific term for early-stage SUDs. In this regard, we put forward “Reward Deficiency “(i.e., lack of normal function) or “Reward Dysregulation” as a general terms which encompass the nosology of “Preaddiction.” In stating this suggestion, we are cognizant that for the public awareness the latter terminology would be more understandable from the intuitive standpoint whereas for professional audiences the former seems more parsimonious [12].

Independent of the appropriate name, similar to the idea of “prediabetes”, developing a reliable way to early identify people with risk for future serious issues with substance and non-substance behavioral addictions (preaddiction), we are hereby proposing the Genetic Addiction Risk Severity (GARS) test along with the RDSQ29 [13] pencil and paper test to capture the psychological correlates of RDS. Importantly, there have been numerous published studies showing real utility and scientific benefit in terms of identifying both drug and alcohol risk utilizing objective DNA polymorphic identification rather than just subjective (albeit useful) diagnostic surveys including clinical and family history [14].

Our understanding of the daunting polygenicity of mental illness, Hyman [15] discussed this perplexing issue. A momentous opportunity to elucidate the pathogenic mechanisms of psychiatric disorders has emerged from advances in genomic technology, new computational tools, and the growth of international consortia committed to data sharing. Moreover, as espoused by Hyman 81, the resulting large-scale, unbiased genetic studies have yielded new biological insights and, with them, the hope that a half-century of stasis in psychiatric therapeutics will come to an end. However, and we agree, "a sobering picture is coming into view; it reveals daunting genetic and phenotypic complexity, portending enormous challenges for neurobiology."

Additionally, successful exploitation of results from genetics will require past avoidance of long-successful reductionist approaches to the investigation of gene function, a commitment to supplanting much research now conducted in model organisms with human biology, and the development of new experimental systems and computational models to analyze polygenic causal influences. Furthermore, psychiatric neuroscience must develop a new scientific map to guide investigation through a polygenic "terra incognita" [15] and a reconsideration of what constitutes the real brain map. In our view, while finding new and novel GWAS discovered clusters of genes is highly important to translate genetic risk for at least Preaddiction, it is prudent to consider finite candidate genes involved in the dynamic systems biologic approach of at least the major neurotransmitter pathways.

With the idea of preaddiction which was first introduced in 1971, thus not a new term [16], while a potentially smart idea the concept espoused by McLellan et al [7] is fraught with some misjudgments. Most recently Yatan Pal Singh Balhara, from National Drug Dependence Treatment Center and Department of Psychiatry, All India Institute of Medical Sciences (AIIMS), New Delhi, India, commented. The authors McLellan et al.[7] make an argument for introduction of the concept of pre-addiction. They also propose that the existing categories of mild and moderate substance use disorders in DSM- 5 can be used to operationalize ‘preaddiction’ in the interim. There are two points

that highlight the limitation and challenges with this approach to this operationalization. First, there was a significant shift in the way the disorders due to use of psychoactive substances was diagnosed by the introduction of the diagnostic category of 'substance use disorders' in the DSM- 5.2 The terms 'abuse', 'dependence' and 'addiction' were not used in the DSM-5. Additionally, the severity of the substance use disorders was assessed based on the number of the diagnostic criteria (out of a total of 11) that were met. The DSM-5 continuum of the severity of substance use disorders does not demarcate those 'without addiction' (commonly equated with 'mild' and 'moderate' severity categories) from those with 'addiction' (commonly equated with 'severe' category). Some of the core features of the concept of 'addiction' can be present even in those with mild and moderate severity of substance use disorders. For example, in case a person uses a substance in a pattern that is characterized by 'substance being taken in larger amounts over a longer period than was intended; a persistent desire or unsuccessful efforts to cut down or control substance use; recurrent substance use resulting in a failure to fulfill major job obligations; tolerance; and withdrawal' the severity rating in such a case shall be moderate. This presentation would fit into the conceptualization of 'addiction' and using the term 'preaddiction' in such a case shall fail to capture the clinical presentation accurately.

In fact, there is little logic in mixing different criteria to designate mild, moderate, or severe category. There can be clinical presentations where a lesser number of criteria are present, but these criteria are indicative of presence of 'addiction' e.g., continued use in a presence of a physical (e.g., cirrhosis or chronic obstructive pulmonary disease) problem that could be worsened by the substance vs. giving up social activity attributable to the substance. Second, the clinical presentations that are captured by the mild and moderate severity are given a valid medical diagnosis as per the DSM- 5. This should warrant appropriate clinical interventions (brief intervention, laboratory investigations, promotion of health and wellbeing, prevention of progression, treatment, disability limitation, rehabilitation focused, recovery- oriented, etc.). If the aim of introduction of the concept of 'preaddiction' is to offer appropriate interventions to those at risk of developing 'addiction' later in their life, then these persons need to be identified using criteria that does not overlap with an existing diagnostic category [17].

Keywords: Reward Processing, Preaddiction, Addiction, Reward Deficiency, Mental Health

Sub-topics:

- Preaddiction & mental Illness
- Preaddiction and NIDA Policy
- Preaddiction and NIAAA Policy
- (Pre)Addiction and (Pre)Diabetes: Is There a Link?
- Reward Deficiency Syndrome
- Exercise and Neurotransmitter Mechanisms
- Opioid Crisis from Bench to Bedside
- Genetic and GWAS Studies on Addiction
- Prenatal and Epigenetics effects of Drug abuse and Impact on Reward Processing
- Overlapping Neuroimaging Evidence for Substance Use Disorder & Obesity
- Reward Deficiency Syndrome & Anti-Reward Symptomatology: Neurobiology of Pain Mechanisms

Tentative titles of the articles:

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- Epigenetics of Reward Processing
- Epigenetics of Binge Drinking

- Bariatric Surgery Genetic Assessment of Patient and Transfer of Addiction Prophylaxis
- Overlapping Neuroimaging Evidence for Substance Use Disorder & Obesity
- Epigenetics of Psychostimulant Abuse
- Psychopharamcology of Dopaminergic Receptors and Drug Self Administration
- Reward Deficiency Syndrome & Anti-Reward Symptomatology: Neurobiology of Pain Mechanisms
- Animal Models of Addictive Behaviors
- Dopaminergic Dynamics in ADHD
- Alcohol: effects on neurobehavioral functions and the brain-Marlene Oscar
- The Role of Impulsivity and Reward Deficiency in Problematic Behaviors and Substance Uses
- Psychological and Neurobiological Correlates of Gaming Behavior
- Psychological Risk Factors in all Behavioral Addictions with Empasis on Pathological Gambling
- Vaporized Delta-9-tetrahydrocannabinol inhalation and vulnerability on offspring:A pharmacokinetic and behavioral assessment
- Epigenetic Effects of Psychostimulants: A Review
- The Role of Estrogen Signaling and Exercise on Drug Abuse
- Behavioral and Neurochemical Effects of Chronic Oral Methylphenidate
- Theorizing Rejection Sensitivity Dysphoria as part of Attention-Deficit/Hyperactivity Disorder: Differentiating it from other Psychopathologies.
- (Pre)Addiction and (Pre)Diabetes: Is There a Direct Link?
- Brain Reward Circuit and Pain
- Modulation of pain, nociception, and analgesia by the brain reward center

Schedule:

- ✧ Thematic issue submission deadline: August 15th, 2023

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