Tentative Outline

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

Title of the Thematic Issue: Neurobiological and Genetic Correlates of Reward Processing as a Therapeutic and Preventive determent of "Preaddiction" and Global Mental Health

Guest Editor: Panayotis K. Thanos

- **Scope of the Thematic Issue:** Addiction scientists and clinicians face an incredible challenge in combatting the current opioid and alcohol use disorder (OUD/AUD) pandemic worldwide. Significant progress has been made; however, the death toll from narcotic overdose managed to reach north of 100,000 fatalities in the United States alone in 2021 with as potentially as high as 165,000 for 2022. The National Institute on Drug Abuse (NIDA) and The National Institute on Alcohol Abuse and Alcoholism (NIAAA) continue to struggle with the generation of novel approaches to combat the severity of the current substance abuse epidemic. FDA-approved medication-assisted treatments (MAT) work primarily by blocking dopamine release and function at the pre-neuron in the nucleus accumbens [1,2]. Although MAT has reduced overdose deaths, costs, and health care events, a long-term strategy to return MAT patients to premorbid functioning is necessary. Medication-assisted treatments routinely fail [3], and when discontinued, relapse and overdose occur at rates similar to those of untreated patients. Neurologically, MAT may induce persistent changes that compromise endorphin, dopamine, and multiple brain systems. Chronic use of agonist therapies may be necessary for lack of other options; however, we caution that data on chronic vs. acute use harm reduction is lacking [4,5]. However, there is evidence that treatments themselves, like long-term agonist treatments for opioid use disorder (OUD), may also cause Reward Deficiency Syndrome (RDS) [5], causing harm and fatal consequences that eclipse the size of the current viral epidemic.

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

Unfortunately, despite the enormous efforts of the federal government to help fund and develop and deliver certain treatments (MAT) for people victims of SUD, albeit not a magic bullet or "cure", treatment penetration rates are less than 20%, [6]. In an article by Mclellan et al. [7] they correctly point out that in the diabetes field facing a similar dilemma, increased treatment penetration by early stage diabetes identification, termed "prediabetic". In fact, in 2001, the American Diabetes Association, suggested that the term 'prediabetic" could operationally be defined by augmented scores on 2 laboratory tests: impaired glucose tolerance and impaired fasting glucose [8]. This strategy led to a wide range campaign, partnership with third party payors, and over-time has shown increased risk detection rates, shortened delays between symptom onset and treatment entry, and success in halting progression to diabetes [9].

It is noteworthy that Volkow (Director of NIDA) and Koob (director of NIAAA) are encouraging the psychiatric field to include the concept of "preaddiction" as a plausible new inclusion for the DSM. Relevant to this suggestion is the possibility of developing a test to help categorize mild, moderate or high risk for future addictive -like behaviors. With this in mind based on our initial work and now with many other global scientists, the preaddiction classification is best captured with the construct of dopamine dysregulation (net attenuation of function due to the inappropriate or dysregulation involving at least seven major neurotransmitter systems - serotonergic, cannabinergic, opioidergic, GABA ergic, Glutaminergic, Acethylcholinergic and dopaminergic) or specifically in reward deficiency or net hypodopaminergia at the meso-limbic brain reward circuitry [10].

Our point here is that while the term preaddiction resonates well with the historical advance in the diabetic field, scientifically the real evidence resides in concepts related to brain neurotransmitter deficits or even in some cases surfeit (especially in adolescence as a neurodevelopmental event) referred to as "reward dysregulation [11]. It is noteworthy, as pointed out by McLellan et al.,[7] that while the DSM-5 the DSM-5 uses 11 equally weighted symptoms of impaired control to define SUDs along a 3-stage severity continuum. The

common name 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 (ie, addiction). However, treatment efforts and public health policies have focused almost exclusively on those with serious, usually chronic addictions, virtually ignoring the much larger population with early-stage SUDs. Although harmful substance misuse and early-stage SUDs can be identified and severity progression monitored, very little has been done, especially where it is most common, in mainstream health care settings. Indeed, neither clinicians nor the public even have a commonly understood name for early-stage SUD. In this regard, regard we are proposing "Reward Deficiency "(meaning lack of normal function) or "Reward Dysregulation" as a general term which does encompass the nosology of "Preaddiction." In stating this suggestion, we are cognizant that for the public awareness the latter terminology would be more understood. However, for the DSM and Psychiatrists and other clinicians 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 with RDS. In terms of GARS, albeit required additional research, there are 58 listed articles in PUBMED. Unfortunately, they are predominately from Blum's laboratory, and mostly narrative in content, but still encouraging. Importantly, there have been a number of studies published showing real utility and scientific benefit in terms of identifying both drug and alcohol risk utilizing objective DNA polymorphic identification rather than just subjective (but still useful) diagnostic surveys including 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 in1971,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 can be clinical presentations where a lesser number of criteria are present, but these criteria are indicative of presence of 'addiction'. Second, the clinical presentations that are captured by the mild and moderate severity are given a valid medical diagnosis as er 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:

The sub-topics to be covered within the issue should be provided:

- Preaddiction & mental Illness
- Preaddiction and NIDA Policy
- Preaddiction and NIAAA Policy
- Reward Deficiency Syndrome
- Exercise and Neurotransmitter Mechanisms
- Opioid Crisis from Bench to Bedside
- GWAS Studies and Addiction
- Epigenetics of 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 and a list of contributors:

Tentative titles of the articles and a list of contributors with their names, designations, updated affiliations, and email addresses should be provided (if available, however, please note that these details of contributors **would** be required before the acceptance of your finalized proposal).

Schedule:

- Thematic issue submission deadline: The deadline for submission should be set at august 15th 2023, this will provide enough time for completion of thematic issue

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