Editorial Commentary

"Preaddiction" construct and reward deficiency syndrome: genetic link via dopaminergic dysregulation

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From 1999–2020, over 932,000 Americans died from a drug overdose, and over 564,000 of those deaths involved opioids (1,2). Since 1999, practically every year, excluding 2018, has seen a record-setting number of deaths and overdoses (1-13). According to preliminary data from the Centers for Disease Control and Prevention's (CDC) National Center for Health Statistics (NCHS), there were approximately 100,306 drug overdose deaths in the United States (US) during a 12-month period that ended in April 2021, which is a 28.5% increase when compared to the 78,056 deaths that occurred during the same period the year before (3). This trend is particularly disturbing given the new drug czar's projection of the annual number of overdose deaths to reach 165,000 by 2025.

Approximately 9.5 million Americans, aged 12 or older, misused opioids in 2020 (13). In addition, in 2020, approximately 2.5 million Americans, aged 12 or older, suffered from opioid use disorder (OUD), but only about 11% (278,000 individuals) received medication-assisted treatment (13). Untreated individuals are more likely to experience increased criminal activity, HIV infection, and mortality (14). Additionally, it is estimated that these individuals will cost society more than $500 billion annually (15). Hence, there is a need to revisit our pathophysiological conceptualizations and ensuing therapeutic approaches (16).

As pointed out in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, (DSM-5), substance use disorder (SUD) is defined using 11 equally weighted symptoms of impaired control along a three-stage severity continuum (17). In terms of severity, mild is characterized as having two to three symptoms, moderate as having four to five symptoms, and severe (also commonly referred to as "addiction") as having six or more symptoms (17). In 2020, 14.5% (40.3 million) of Americans aged 12 or older were diagnosed with SUD. Only 1.4% (4 million) of Americans aged 12 or older received any substance use treatment, and 1% (2.7 million) received substance use treatment at a specialty facility in 2020 (13). In addition, treatment efforts and public health policies have typically focused on those with severe, usually chronic addictions, largely individuals with early-stage SUDs. Although harmful substance misuse and early-stage SUDs can be identified and severity progression monitored, relatively little has been done, especially where it is most prevalent, in mainstream health care settings. In fact, early-stage SUD lacks a broadly accepted term among clinicians or the general public (18).

One of the novel conceptualizations, suggested for inclusion in the DSM, is the "preaddiction" construct, as it is juxtaposed to "prediabetes" (19). The American Diabetes Association defines prediabetes as having abnormal insulin sensitivity (hemoglobin A1c of 5.7–6.4) and/or glucose

tolerance tests [fasting blood glucose of 100–125 mg/dL; oral glucose tolerance test (OGTT) 2-hour blood glucose of 140–199 mg/dL] (20). Prediabetes has a wide range of campaigns and partnerships with third party payors, which over time have contributed to a quantum leap in the efficiency of early detection, shortened delays between symptom onset and treatment entry, and success in halting the progression to diabetes (21). While prediabetes is a manifestation of failing homeostatic function, preaddiction may be linked to closely related (22) hedonostatic derailments (23), namely, hypodopaminergia in the meso-limbic brain reward circuitry (9), as well as the associated opioidergic-, serotonergic-, cannabinergic, GABA-ergic, glutaminergic, and cholinergic abnormalities and clinical manifestations (24,25), collectively termed reward deficiency syndrome (RDS) (24-28).

The implication here is that reward is a key element of mental operation that has evolved beyond immediate survival, and it is crucial for most individual and social activities, including emotional attachments, group affiliations, free will, conformity, and obedience to societal norms and edicts (29-33). Consequently, the lives of individuals with RDS may be intolerable due to their inability to gain full satisfaction from their accomplishments while overcoming the same challenges as others. As a result, they may turn to addictive substance use, which may temporarily alleviate their RDS symptoms but ultimately worsens their clinical condition and pushes them toward eventual full-blown addiction (34,35), which in turn will increase their stress and psychiatric and medical comorbidities (36-38).

RDS encompasses many mental health disorders, characterized by heightened stress, a propensity for the development of addictions, as well as compulsive and impulsive behaviors (39,40). This may be why large-scale genome-wide association studies showed a significant dopaminergic gene risk polymorphic allele overlap between schizophrenic and depressed cohorts (25). A growing body of literature has also identified post-traumatic stress disorder, attention deficit hyperactivity disorder, and spectrum disorders (41,42) as having the typical neurogenetic and psychological RDS underpinnings (43). In addition, several prior studies showed clinical benefit in identifying drug and alcohol risks by utilizing objective DNA polymorphic identification rather than sole reliance on subjective diagnostic surveys (44).

Even though the term "preaddiction" bodes well given the historical advancement of the diabetic field with prediabetes, scientifically the real evidence resides in concepts related to brain neurotransmitter alterations (e.g., in adolescence as a neurodevelopmental event) referred to as RDS (45). Therefore, we suggest "Reward Deficiency" (namely, lack of normal function) or even "Reward Dysregulation" as a more general term encompassing the nosology of "preaddiction." In stating this suggestion, we are cognizant that for the lay public, the "preaddiction" terminology may be more recognizable. However, for the clinical and scientific community, reward deficiency/dysregulation may be more parsimonious (46).

Such conceptualization offers immediate benefits in the form of early screening to detect high-risk individuals through the Genetic Addiction Risk Severity (GARS) (19) test and the Reward Deficiency Syndrome Questionnaire (47), which capture both genetic and clinical aspects of RDS (48). Moreover, epigenetic repair may be possible with precision gene-guided therapy using formulations of KB220, a nutraceutical that has demonstrated pro-dopamine regulatory function in animal and human neuroimaging and clinical trials (49), and thus, clinical trials aimed at restoring dopamine homeostasis (i.e., hedonostasis) look promising (50-60).

In sum, we put forward an RDS-derived complementary measure of "preaddiction" that may provide further impetus for the optimal characterization of the construct, including its early detection, staging, and therapeutic management. The heuristic value of our proposal will be determined by its ability to account for specific clinical, genetic, and therapeutic aspects of the preaddiction phenomenon. Further research is warranted to uncover the distinctive aspects of RDS in addictive- *vs.* other psychiatric- and medical conditions and their interactions in the comorbid states (61-64). In essence, our proposal relates to the importance of early genetic testing to identify preaddiction or RDS in children (65,66).

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Footnote

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