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Short Communication

Genetic Addiction Risk Testing to Identify Preaddiction: Reality or Rolling the Dice

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Abstract

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 and new drug czar's projection of the annual number of overdose deaths to reach 165,000 by 2025. One of the novel conceptualizations,

suggested for inclusion in the DSM, is the "preaddiction" construct, as it is juxtaposed to "prediabetes". While prediabetes is a manifestation of failing homeostatic function, preaddiction may be linked to closely related hedonostatic derailments, namely, hypodopaminergia in the meso-limbic brain reward circuitry, as well as the associated opioidergic-, serotonergic-, cannabinergic, GABA-ergic, glutaminergic, and cholinergic abnormalities and clinical manifestations, collectively termed reward deficiency syndrome (RDS). A few naysayers have argued that Pre-addiction is not real. One potential explanation for this argument is that there is a disconnect in understanding that the term "addiction" is misunderstood, and it refers to a predisposition linked to DNA polymorphic antecedents and even epigenetic methylation causing dopamine dysregulation. There is also an argument with very little evidence, that objective genetic addiction risk testing is akin to "rolling the dice". We disagree with this non-factual retort and provide scientific evidence to support the potential benefits of our laboratories developed Genetic Addiction Risk Severity (GARS) test.

Keywords: Genetic; Preaddiction; DNA

Introduction

From 1999–2020, over 932,000 Americans died from a drug overdose, and over 564,000 of those deaths involved opioids [1-10]. 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.

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 [11]. 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 [12]. One of the novel conceptualizations, suggested for inclusion in the DSM, is the "preaddiction" construct, as it is juxtaposed to "prediabetes" [13]. While prediabetes is a manifestation of failing homeostatic function, preaddiction may be linked to closely related hedonostatic derailments, namely, hypodopaminergia in the meso-limbic brain reward circuitry, as well as the associated opioidergic-, serotonergic-, cannabinergic, GABA-ergic, glutaminergic, and cholinergic abnormalities and clinical manifestations, collectively termed reward deficiency syndrome (RDS) [14-19].

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. RDS encompasses many mental health disorders, characterized by heightened stress, a propensity for the development of addictions, as well as compulsive and impulsive behaviors [20-23]. Several prior studies showed clinical benefits in identifying drug and alcohol risks by utilizing objective DNA polymorphic identification rather than sole reliance on subjective diagnostic surveys [24-30]. 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.

A few naysayers with little experience in the fields related to nosology of neurological issues have argued that Pre-addiction is not real. One potential explanation for this argument is that there is a disconnect in understanding that the term "addiction" is misunderstood, and it refers to a predisposition linked to DNA polymorphic antecedents and even epigenetic methylation causing dopamine dysregulation. 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. Such conceptualization offers immediate benefits in the form of early screening to detect high-risk individuals through the Genetic Addiction Risk Severity (GARS) test [31,32] and the Reward Deficiency Syndrome

Questionnaire which capture both genetic and clinical aspects of RDS [33].

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 many peer reviewed clinical trials, and thus, clinical trials aimed at restoring dopamine homeostasis (i.e., homoeostasis) look promising [34-38]. In terms of the importance and potential usefulness of GARS or genetic addiction test in principle naysayers suggest that this genetic testing is like" rolling the dice" and in fact might make the seeking of both substances and possibly even behavioral addictions (e.g., gambling) worse and labeling of for example "preaddiction" will further stigmatize and give people an excuse to be locked into their unwanted seeking behaviors [39-41].

Moreover, neuroscientist like Mark Lewis's unrealistic notion that there is no such a thing as a brain disorder like RDS or any of its subclasses like SUD, Eating Disorders, Gaming Disorders linked to molecular biological or genetic antecedents to this type of behavior. Accordingly, to Lewis and his followers they seem blinded to the actual existence as with any other disorder the magnitude of data published throughout the entire scientific literature that clearly meets all the necessary elements to constitute a real disease [42]. Lewis's point that brain changes in addiction is like recurrent, highly motivated goal seeking results in the development of deep habits, Pavlovian learning, and prefrontal disengagement. This analysis relies on concepts of self-organization, neuroplasticity, personality development, and delay discounting. It also highlights neural and behavioral parallels between substance addictions, behavioral addictions, normative compulsive behaviors, and falling in love. While this might be correct and understanding these events as something natural to the homo-sapiens, it does not negate the fact that many mental health issues including schizophrenia bipolar, major depression, ADHD, PTSD, aberrant craving behavior, gambling, anorexia, bulimia, overeating, hypersexuality, hoarding, excessive shopping, etc. are driven by molecular rearrangements as coded by one's DNA denoted by antecedent polymorphism that alter normal neurotransmitter induction. Moreover, the further insult by known biological insults as observed with epigenetics that loads onto augmenting brain dysfunction even prior to any intake of psychoactive drugs, behaviors, and child abuse, certainly adheres to a disease construct [43-45].

Sophisticated neurobiological and genetic research yields thousands of studies that reveals brain reward dysfunctional trait modified by environmental (epigenetic) events inducing either positive (increased acetylation to augment gene expression) or negative (increased methylation to suppress gene expression) histone modifications. It is indeed uncanny that there are scientists suggesting anything other than possible molecular rearrangements responsible for altered neurochemical transduction even at birth. Eliminating the term "addiction" replacing it with "reward dysregulation" with 72,486 PUBMED Listed articles (5-26-23) seems like a smart way to help eliminate the long-standing confusion.

We do not agree with the proposal that having important objective genetic and now even epigenetic information concerned with potential unwanted reward circuitry infractions has negative connotations. One case in point from our laboratory alone, when we used the term "Isoquinolism" instead of "Alcoholism" that we published in Lancet in the 80's resulted in a reduced stigma and patients bonded to that concept with concomitant attenuation of quilt [46]. A frequently raised question relates to what the benefit of GARS testing in known addicts already in treatment programs reveal that is clinically important? Based on an array of previous research, we believe that there are many important reasons for GARS testing in people expressing addictive behaviors of all types. In previous peer reviewed published reports, the benefits of GARS have been carefully denoted and included *overcoming denial and guilt, reducing shame, confirming genograms, resource allocation issues exposed, medication monitoring dosing assistance, overcoming pain requirements and potential opioid addiction liability avoidance and pro-dopamine regulation* [47]. One novel benefit of GARS screening, especially in people suspected of reward dysregulation is the ability to help customize KB220 ingredients for a more personalized approach tailored to the individual transduction needs [48-53].

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. In essence, our proposal relates to the importance of early genetic testing to identify preaddiction or RDS in children. Finally, indeed the "preaddiction construct" is real if one understands it from a neurobiological brain disorder involving both DNA antecedents along with negative epigenetic insults based on excess methylation onto genes (e.g., child abuse). Moreover, we absolutely do not accept the thoughtless idea that genetic addiction testing is like "rolling the dice" and we combat that conceptualization with evidenced based objective genetic and epigenetic investigations published worldwide. A Pubmed search using "psychiatric Genetics" resulted in 29,665 as of 5-28-23.

To assist in further comprehension, we have developed a high-level schematic based on our novel model (Figure 1).

Figure 1

Conclusion

We applaud the scientific retort in terms of questioning the reality of addiction as a brain disease/disorder, including the notion that preaddiction does not exist as well as the non-objectiveness of genetic testing of addiction risk. However, the naysayer's evidence is obscenely pitiful relative to the important exacting science that is now imbedded in the peer-reviewed literature. In our expert opinion, while more high quality research is required "let's not throw away the baby with the bath oil "instead embrace genetic addiction testing to identify "preaddiction" like "prediabetes" and develop safe non-invasive and possibly nonpharmacological positive neuroadaptive clinically important therapeutic advances waiting for novel gene edits to help "cure" mRNA dysfunctional transcriptional misfires.

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