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Substance use disorder a bio-directional subset of reward deficiency syndrome

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1. ABSTRACT

This commentary is to inform clinicians challenged with an increase in people seeking treatment for Substance Use Disorder (SUD), that the ninety percent revolving door, is, in part, due to post–withdrawal, untreated neurotoxicity. This impairment attenuates neurotransmitter signaling and compromises resting state functional connectivity, leading to unwanted sequelae including depression, sleep disturbances, sensation seeking, lack of satisfaction and impulsivity. Neuroimaging studies indicate that neurobiological recovery can take years. Like a “double edge sword” SUD has a biological bi –directional (bio-directional) effect on the brain reward circuitry. The acute intake of psychoactive drugs results in heightened dopaminergic activity, while, the opposite, hypodopaminergia occurs following chronic abuse. Individuals with SUD can have a genetic predisposition, compounded by stress and neurotoxically induced, epigenetic insults that impact recovery from protracted abstinence. Follow-up post –short-term recovery usually includes supportive therapies and programs like 12 –steps and other fellowships. However, relapse will usually occur if post –short-term recovery hypodopaminergia is not treated with attempts at epigenetic manipulation of compromised brain neurochemistry using some manner of pro-dopamine regulation.

2. INTRODUCTION

The field of addiction science is rife with controversy, in part, the consequence, of a continued lack of good treatment options. The over-prescription

of powerful painkillers is responsible for a tragic rise an opiate overdose across the United States of America (1). The clinical and addiction science community is faced with a 3,000 percent increase from 2007 to 2016 of people seeking treatment for SUD. In response to this dilemma, the US government has increased the availability of buprenorphine/naloxone combinations by increasing the number of patients that can be treated from 100 to now 275 with the hope that more people can obtain treatment needed for opiate/ opioid dependence. There is a disagreement about the length of time patients should be maintained on buprenorphine/naloxone. In response to this confusion, the Center for Disease Control (CDC) correctly recommended a very short period of use for this powerful combination (2). Unfortunately, 91 to 127 people (young and old) are lost every day to narcotic overdose. In essence, it is uncanny that narcotic addiction is being treated with powerful narcotics (3). The partial mu agonist buprenorphine has been shown in many studies to be beneficial in the short –term (4), however, long –term use requires caution. Most recently, Blum *et al.* (5), questioned the increase in allowance to 275 and suggested stronger guidelines including genetic testing, monitoring blunted response (6) and encouraged addiction specialists to refrain from long-term utilization.

The impetus for this commentary is to inform clinicians challenged with this growing patient cohort that the ninety percent revolving door is, in part, due to post –withdrawal untreated compromised resting state functional connectivity. A consequence of compromised resting state functional connectivity is unbalanced dopaminergic functionality, a concomitant inability to cope with stress and vulnerability to relapse. Reinstatement of substance use can potentially be due to the reward gene polymorphisms or environmentally induced epigenetics and mood changes (7). The underlying etiologies of mood disorders consist of complex interactive operations of genetic and environmental factors. Mood disorders are expressed both genetically and epigenetically and manifest in individuals as co-morbidities, that vary from severe major clinical depression to anxiety. In fact, the majority of research findings suggest that the notion of endophenotypes may facilitate efforts to detect and define disorders. The extreme complexity of the disease states may be elucidated by staging the genetic markers for several inherent predispositions to genetic risk. Several strategies have been developed that can discern essential elements in the etiopathogenesis of the disorders that effect drug efficacy, drug metabolism, and adverse drug effects, for example, with regard to selective serotonin reuptake inhibitors and dopaminergic dynamics. These complex interactions include transporter gene expression, and genes encoding receptor systems, hypothalamic-pituitary-adrenal axis factors, neurotrophic factors, and inflammatory factors affecting neuro-immune function. For a variety of symptoms associated with affective states, genetic biomarker identification facilitates treatment choice, response prediction, and prognosis, thereby optimizing clinical practice procedures. Epigenetic regulation of primary brain signaling, for example, serotonin-dopamine and hypothalamic-pituitary-adrenal function, mesolimbic circuitry and factors governing their metabolism are necessary considerations. The participation of neurotrophic factors remains indispensable to neurogenesis, survival, and functional maintenance of brain systems.

Certainly, the role that epigenetics plays, is important in the overall recovery process, and treatment should be targeted to overcoming the negative epigenetic effects directed at many reward genes. According to Nestler *et al.,* experiences—such as exposure to stress can through heritable epigenetic modifications be passed on to subsequent generations (8). There is growing evidence that supports epigenetic regulation as a key mechanism underlying the lifelong regulation of gene expression that can mediate stress vulnerability. (8). One profound example of this epigenetic modulation was illustrated in a cohort of pathological gamblers. Hillemacher *et al.,* found that deoxyribonucleic acid (DNA)-methylation patterns, in the Dopamine Receptor D2 (*DRD2*) gene, were altered with respect to abstinence. Over a period of twelve to thirty months lack of treatment utilization resulted in higher methylation levels in both non-abstinent participants and participants without treatment-seeking behavior. Methylation of the *DRD2* gene, seen in these results, point towards altered (reduced) *DRD2* expression due to changes in DNA methylation in life –long pathologic gamblers (9). These results may have relevance in determining the pathophysiological negative feedback mechanism that lead to the establishment of behavioral and other addictions in vulnerable people.

Szutorisz *et al.* (10), reported that a consequence of adolescent germline exposure to Δ(9)-tetrahydrocannabinol (THC) is behavioral and neurobiological abnormalities in the subsequent generation of rats. Specifically, adult F1 offspring that were themselves unexposed to THC displayed increased work effort to self-administer heroin. On the molecular level, changes in the messenger Ribonucleic acid (mRNA) expression of cannabinoid, dopamine, and glutamatergic receptor genes, was associated with parental THC exposure The striatum an important part of the neuronal circuitry mediates compulsive behaviors and reward-sensitivity. As a consequence of parental THC exposure adult offspring had decreased NMDA receptor binding and protein and mRNA levels in the dorsal striatum. Moreover, excitatory synapses of the striatal circuitry, that are known to mediate compulsive and goal-directed behaviors, were altered.

These findings demonstrate that the molecular characteristics of the striatum are efffected by parental history of germline THC exposure (10). Importantly, epigenetics can impact offspring phenotype and could confer enhanced risk for psychiatric disorders in the subsequent generation. The profound therapeutic implications of these findings are that, despite pre-existing genetic risk for vulnerability to all addictive behaviors including SUD (11) epigenetic manipulation could provide a therapeutic advantage if directed towards balancing dopamine function rather than a long-term dopamine blockade.

The idea that D2 receptor stimulation can be accomplished epigenetically via amino acid – enkephalinase therapy to potentially induce dopamine release, causing the induction of D2-directed mRNA and thus the proliferation of D2 receptors is suggested herein. The proliferation of D2receptors can indeed attenuate craving behavior. In fact, Thanos *et al.* (12-14) showed that, a form of gene therapy DNA-directed compensatory overexpression of the dopamine D2 receptors (*DRD2*), resulted in a significant reduction in both cocaine self-administration, and alcohol craving behavior in rodents (13, 15). Moreover, clinicians should also be cognizant that SUD post-recovery often involves co-morbid depression which has been linked to dopamine D1 and D2 function. In fact, Corrales *et al.* (16) proposed that regulatory regions of dopamine receptors could through an imbalance of D1-D2 heteromers effect the level of manifestation of depressive symptoms and modulation of cognitive processes. Their suggestion followed the observation that located upstream of the dopamine D1 receptor (*DRD1*) and the *DRD2* genes respectively, and there is a significant interaction effect, between rs1039089 in conjunction with rs877138 (16). Indeed, using a natural dopaminergic repletion-therapy long-term to promote healthy dopaminergic function will ultimately lead to an accessible, effective and safe modality to treat Reward Deficiency Syndrome (RDS) behaviors (17). Further support for this concept comes from a comprehensive understanding of the role of dopamine has in the nucleus accumbens (NAc) as a “wanting” messenger of the mesolimbic DA system (18). In fact, Robinson *et al.* (2016) suggested that in both gambling disorder and food addiction sensitization of the “wanting” system results in the dissociation of “liking” and “wanting” (18).

3. DEFINING REWARD DEFICIENCY SYNDROME (RDS) AS A PSYCHOLOGICAL CONSTRUCT

Rather than being a separate and distinct mental illness RDS, is related to some mental health disorders (17, 19). The mental illnesses include a wide range of substance and non-substance addictive, compulsive, and impulsive behaviors. Reward Deficiency Syndrome refers dysfunction in the cascade of reward neurotransmission, due to genetic and environmental influences (epigenetic) which result in behavioral problems. RDS is DNA-related, a gene and chromosome type of syndrome, that interferes with the usual achievement of human physiological drives for food, water, and sexual reproduction and well-being.

Reward Deficiency Syndrome behaviors include substance and non-substance addictions, attention deficit hyperactivity disorder (ADHD), obesity, personality and autism spectrum disorders; the name was coined by Blum *et al.* in 1996. Currently, RDS has been selected to be included in SAGE Encyclopedia of Abnormal Psychology (2017) and a word search “Reward Deficiency Syndrome” results in over 100 Pubmed listed articles (8-1-2016) and a word search “Reward Deficiency” results in over 565 Pubmed listed articles (8-1-2016). The concept arose from associations of human genetic units DRD2 and the A1 allele and many psychiatric disorders (20). The conditions were linked to hypodopaminergic trait and include ADHD and Tourette’s syndrome, conduct disorder, obesity, gambling, internet gaming, post-traumatic stress disorder (PTSD), and premenstrual syndrome (PMS) (21). This group of behaviors has been associated with *genetic* variants and *epigenetic* (environmental) changes that lead to an inadequacy in the neurotransmission of reward or pleasure (22). The RDS concept included here was developed based on animal and human research that explored the molecular biology of *neurotransmission*, and behavioral genetics. Understanding this concept, explained in the following paragraphs, is central to treating the abnormal psychology of personality and *autistic spectrum disorders*, as well as, *substance* and *non-substance behavioral* (process) *addictions*.

For one to feel ordinary pleasure, complex interactions of neurotransmitters ultimately regulate the dopaminergic activity of the brain in the reward center -the mesolimbic system, and particularly in the nucleus accumbens. Individuals, who suffer from a lack of ordinary pleasure in their lives, are predisposed to use substances or behaviors, to activate dopamine release, relieve stress and feel pleasure. These behaviors include sensation seeking (novelty seeking) and impulsivity.

3.1. The research

Genetic associations are made when the incidence of a genetic variant, is found to be significantly higher in a group of *unrelated people with the condition*, than in controls *people without the condition*. In RDS, the conditions are behavioral disorders. Genes are DNA that directs the functional properties of proteins like neurotransmitters. Genetic alleles are unusual versions of a gene that can change genetic function;

they are called polymorphisms or variants. Early in the 1990's when the statistically significant association of severe alcoholism with a variant of the *DRD2* gene, the A1 allele was discovered (20) Nobel *et al*. did a binding study using the same brain tissue. They found that the presence of the A1 allele resulted in lower dopamine receptor availability in the parts of the brain known to effect reward (23). The A1, a minor allele of the *DRD2* gene, as well as polymorphisms in other reward genes, have been shown to be associated with alcoholism, particularly its severe form, as well as with smoking, obesity, and other addictive behaviors, like pathological gambling, internet addiction, and compulsive sexual behaviors.

Earlier studies had explored the role of neurotransmitters in pleasure. In the limbic neural circuitry serotonin, enkephalin, GABA, and dopamine work together in a complex cascade of activation and inhibition that result in the release of dopamine. Dopamine was identified as one of the most powerful neurotransmitters that control feelings of well-being and reward. Negative emotions and craving are the results of disruption of the intercellular reward cascade that leads to reduced dopamine availability (24).

Addiction is a brain disorder related to neurotransmitter dysregulation, notably of, dopamine and serotonin, that causes and cravings and the compulsive continued use of substances regardless of negative consequences. Addiction, along with compulsion emanate from parts of the brain that produce pleasure. The biological basis of these behaviors makes them chronic and prone to relapse. Addiction/Compulsion causes loss of control over substance use, and other addictive behaviors so that uncontrollable behaviors escalate as addiction progresses.

3.2. Hypodopaminergic function

The hypodopaminergic trait is itself polygenetic (involves many genes) and may result from variations in a number of reward genes. Reward genes and, many second messengers, like enzymes and (epigenetic) mRNA, govern neurotransmitter function in the dopaminergic, serotonergic, endorphinergic, opioidergic, GABAergic, adrenergic, and cholinergic pathways. Many associations with other genes and these behaviors have also been identified (25).

Numerous genes that are involved in the function of the reward neurotransmitters in the brain have variations that result in a hypodopaminergic function. For example, the Monoamine Oxidase (MOA) gene is involved in reward brain function. Individuals may have high MOA activity, an increased rate of mitochondrial dopamine catabolism, due to the effect of an allele. Other examples are reduced numbers of serotonergic receptors, due to polymorphisms of the 5-HT (2A) receptor gene (-1438A/G). Serotonin transporter gene 5-HTTLPR polymorphisms also reduce synaptic serotonin levels, due to the biallelic (short and long alleles) and triallelic polymorphisms (including rs25531 A/G a single nucleotide variation) (26). Also, the availability of dopamine in the synapse may be further reduced due to environmental factors. Prolonged stress and long –term substance abuse also, result in reduced cascade function and decreased dopamine release (27).

Animal and human neuroimaging studies found that drugs like alcohol, opiates, psychostimulants and nicotine, glucose, and process addictions, like excessive internet gaming, hypersexuality, and gambling activate dopamine release. Substances and behaviors that cause the release of dopamine into the brains' pleasure centers are initiated and maintained, to alleviate craving or stress and restore feelings of well-being by restoring *dopamine homeostasis* (28). Recently neuroimaging studies have shown that the brain regions involved in reward circuitry are effected by anticipated behaviors such as sex and gaming and palatable foods in addition to alcohol and drugs of abuse (26, 29).

3.3. RDS conceptualization

The biological processes of reward that underlie addiction to substances and all addictive, compulsive and impulsive behaviors are the basis of the RDS conceptualization. RDS then is a deficiency, a hypodopaminergic state that results from some combination of genetic variations, environmental stressors, and adverse molecular effects or blunting due to prolonged substance use or behavioral habituation.

3.4. RDS behaviors

RDS refers to an insufficiency of usual feelings of satisfaction and represents a failure of the system that normally confers satisfaction. Intercellular disruption of the reward cascade results in aberrant behaviors. Numerous disorders share the genetic hypodopaminergic trait and, for this reason, the RDS designation. Addictive, compulsive and impulsive behaviors such as overeating, drug and alcohol abuse, pathological gambling, hyperactivity, spectrum disorders, risk-taking and personality disorders all come under the RDS rubric, see Figure 1. (30, 31).

In summary, a number of psychological factors that include sensation seeking, satisfaction, motivation, and impulsivity make up RDS behaviors. The possibility that RDS is involved with anhedonia and anti-reward mechanisms is being explored (32, 33). In fact, Gardner's' group from NIDA most recently

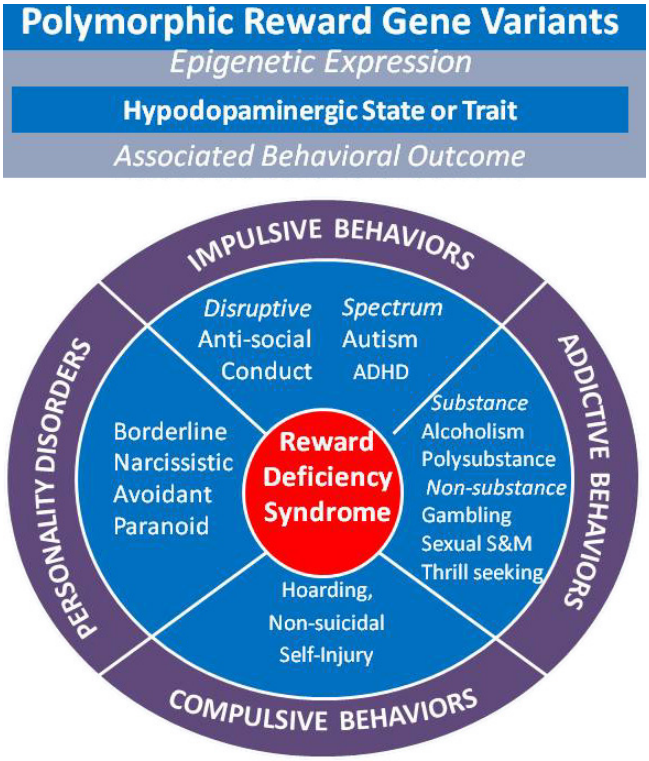

Figure 1. Reward deficiency syndrome behaviors (RDS) reproduced with permission from (17). The Figure illustrates examples of various linked RDS behaviors.

suggested that the D2 receptor and not the D3 receptor is crucial for a reward cue to maintain either its incentive or predictive qualities (34).

While RDS includes a remarkable list of behaviors, there is indeed a common psychological thread which has been uncovered in unpublished work involving over 1700 individuals from Demetrovics and associates in Hungary. Based on the original construct developed by Blum's group involving over 200 items, post analysis resulted in 29 items having significant predictive RDS value. Factor analysis revealed four important clusters: *the lack of satisfaction; the need for being in action; risk-seeking behaviors; search for overstimulation* linking to a generalized reward deficiency trait. While this is a work in progress, a general reward deficiency factor has been associated with gender, sensation seeking, and impulsivity. Females show a higher degree of reward deficiency trait, and higher sensation seeking and higher impulsivity predict a greater level of reward deficiency.

4. THE EPIGENETICS OF PROLONGED EXPOSURE AND STRESS

Individual neurons in the reward cascade are catalyzed by some specific neurotransmitters, which bind to certain receptor types that serve a particular function. In the research literature both animal and human neuroimaging studies have established that, for example, gene variants of both serotonin and dopamine can result in significantly lower than normal receptor densities. Microdialysis studies have shown that the Val158Me5t gene variant of the Catechol-O-Methyltransferase Gene (COMT) increases synaptic dopamine clearance (catabolism), subsequently reducing dopamine function (35). These are examples of the impact on the brain reward cascade that one or more reward gene variant can have on predisposing individuals to RDS behaviors.

Elevated stress levels, together with neurotransmitter genetic variants, may have a cumulative epigenetic effect on vulnerability to addiction and other RDS behaviors. Drugs of abuse enhance dopamine signaling and sensitize dynamic mesolimbic mechanisms that evolved to provide motivation for survival behaviors (36). Reward deficiency behaviors have in common, that they stimulate the functioning of brain reward circuitry, are voluntarily self-administered, and enhance dopaminergic synaptic function in the nucleus accumbens either directly or indirectly. Reward deficiency behaviors can progress from occasional recreational use to impulsive use then habitual, compulsive use. Also, hypodopaminergic function, caused by genetic variations impacted by epigenetics, can induce impairments in the pre-frontal cortex – cingulated gyrus, which in turn leads to poor judgment

and potential habit reinstatement and relapse (37). For example, re-exposure to addictive drugs is one of the triggers for craving.

Clinicians have observed that after prolonged abstinence from drugs of choice, individuals will experience a euphoric high with reinstatement. This "super sensitivity" which can lead to relapse and overdose might point toward the existence of genetic dopaminergic polymorphisms (38). Blunting is another harmful molecular effect that occurss due to prolonged substance use. The repeated release of high amounts of dopamine into the synaptic cleft induces prolonged, heightened postsynaptic receptor activity, resulting in receptor down-regulation and, for this reason, further decreases dopamine function. Receptor down-regulation has been reported, in both obese rats and drug-addicted humans. Receptor down-regulation is why habituated addicts require ever increasing substance or behavior to maintain the rewarding effect of the habit. However after prolonged abstinence dopamine receptor supersensitivity, an enhanced biochemical response develops, and reinstatement at the previous level of habituation in the case of substance abuse may lead to fatalities (38, 39).

Environmentally induced epigenetic effects on the chromatin structure of the DNA due to stress or triggered by cues can increase craving. Stress-triggered craving involves the neurotransmitters corticotrophin-releasing factor and norepinephrine. These neurotransmitters necessitate the abundant release of dopamine (100 times resting state) and subsequently temporary hypodopaminergic functioning. Repeated, or prolonged stress can induce a chronic hypodopaminergic state (40). Cue-triggered craving involves the basolateral nucleus of the amygdala, the hippocampus, and through glutaminergic activation causes an enhanced release of dopamine that if chronic ultimately leads to a hypodopaminergic state. Due to this hypodopaminergic trait (genetic) or state (environment), drug intake or aberrant behaviors will escalate (41).

5. TYPOLOGY OF SUBSTANCE USE DISORDER (SUD): NEUROBIOLOGICAL CONSTRUCT

In the late 1980's Cloninger's group (42) developed a typology of alcoholism based on an investigation involving 862 men and 913 women adopted by non-relatives. Both male and female adoptees were at greater risk to develop alcohol abuse if their biological, but not their adoptive, parents were alcoholic. Three types of families with alcoholism were identified they included differing frequency of alcohol abuse, somatoform disorders in women and antisocial behavior in male adoptees. The combination of both genetic and environmental risk factors was necessary for the most common, milieu-limited type development of alcoholism. Alcohol abuse in families with the less common, male-limited, type of vulnerability was highly heritable in men, but women instead had multiple somatic complaints and seldom abuse. The common vulnerability in the third type of family was expressed as antisocial behavior with violent criminality and recurrent alcohol abuse in males, and as high-frequency somatization in female relatives. However, approximately one decade earlier instead of classifying alcoholism or other reward-seeking behavior in terms of neurochemistry Blum (24) and Blum *et al.* (43) also described three types of alcoholics. The theory was called "*The Psychogenetic Theory of Alcoholism."* The equations were:

- Type 1. Alchohol-craving Behavior (ACB) = Generic deficiency of internal opioids (GDIO) + environment (E), the born alcoholic
- Type 2. ACB = Norman genetics of internal opioids (NGIO) + stress-induced deficiency of internal opioids (SED), the stress-related alcoholic
- Type 3. ACB = NG + alcohol toxicity- induced deficiency of internal opioids (TEDIO), the chronic alcoholic

While these earlier theories have stood the test of time, many in-depth genetic, epigenetic and neuroimaging studies are unraveling an increasingly multifaceted understanding of both psychological and neurobiological mechanisms of reward-seeking behaviors. This conceptualization of the typology of alcoholism identified internal opioids (enkephalins) as a key neurotransmitter and its deficiency as an agency of induction of alcohol seeking behaviors, in 1980. Today, however, the formula would identify a dopamine deficiency as a leading cause of alcoholism and possibly most, if not all, RDS behaviors.

6. SUBSTANCE USE DISORDER (SUD) AND RDS: A BIOLOGICAL BI-DIRECTIONAL (BIO-DIRECTIONAL) PHENOMENON

Drugs of abuse have a bio-directional effect on mesolimbic brain reward circuitry. Substance use disorder is a "double-edged sword" having a bio-directional effect on neurotransmitter function, whereby, acute intake of psychoactive drugs results in heightened dopaminergic activity, while the opposite, a hypodopaminergic effect occurs following chronic abuse. Psychoactive drugs induce multi-phasic effects on the integrity of neurochemistry that alter the functionality of neurotransmission and second messengers. These effects result initially in ever-increasing tolerance, withdrawal and continued drug seeking, while, withdrawal from opiates and alcohol, for example, can also lead to a hyperdopaminergic state (44). Chronic use of these substances including cocaine also induces a hypodopaminergic state

leading to tolerance (45-47). Specifically, Siciliano *et al.*, (46) found that there was an attenuation of baseline dopamine synthesis in the ventral striatum after two cycles of chronic intermittent ethanol (CIE). They also found that low dopaminergic activity was positively correlated with drinking as indicated by high dopamine/metabolite ratios. The authors suggested that decreased dopaminergic activity is associated with excessive drinking. Tacelosky *et al.*, (47) found reduced expression of the D2R in the nucleus accumbens and hippocampus following chronic heroin intake. Reduced D2R expression was correlated with greater motivation for seeking behavior. Holroyd *et al.*, (45) show that *in vitro* selective loss of D2 autoreceptors amplifies the effect of cocaine on dopamine transmission and impairs the feedback inhibition of dopamine release in the NAC. In fact, mice lacking D2 autoreceptors acquire a cued-operant self-administration task for cocaine faster than littermate control mice although both groups acquire normal reward similarly. They also show that mice lacking D2 autoreceptors exhibited perseverative responding when cocaine-paired cues were present, although they were able to extinguish cocaine self-administration in the absence of cocaine and paired cues. The authors suggest that this enhanced cue reactivity was selective for cocaine and absent during extinction of sucrose self-administration. Their conclusion was that low levels of D2 autoreceptors could contribute the salience cocaine-paired cues to vulnerability for cocaine use and relapse. So, SUD and possibly non-substance related behaviors, represent a bio-directional phenomenon leading to post –recovery depression, sleep disturbances, sensation seeking, lack of satisfaction, reduced motivation, and even impulsivity.

Most recently, Colon-Perez *et al.* (48) found that the active ingredient in bath salts 3,4-methylenedioxypyrovalerone (MDPV), caused widespread disruption of brain functional connectivity. A reduction of connectivity between frontal cortical and striatal areas was revealed by a detailed analysis of its effects. The prelimbic prefrontal cortex and other regions of the frontal and insular cortex with hypothalamic, ventral, and dorsal striatal areas showed decreased connectivity. Although widespread, the reduced connectivity between these regions and the somatosensory cortex was effected less severely. Blockade of the dopamine receptor did not prevent the MDPV-induced decrease in functional connectivity. Interestingly, reduced brain functional connectivity has been linked to cognitive dysfunction, audiovisual hallucinations, and negative affective states like those reported for MDPV-induced intoxication and reported in patients suffering from psychosis.

Individuals with hypodopaminergic trait due to the presence of certain reward gene polymorphisms are potentially at high risk for the subsequent development of RDS behaviors like SUD. In unpublished work, a number of candidate reward genes that included the *DRD 2*, *3*, *4*; *MOA-A*; *COMT*; *DAT1*; *5HTTLLR*; *OPRM1*; and *GABRA3* genes were studied to explore the potential for correlation with the Addiction Severity Index (ASI) to predict SUD severity. The preliminary statistical analysis reveals that there was a trend whereby allelic risk above the means score, associated significantly, with the ASI Alcohol Risk Severity and Drug Severity Scores. If this finding is supported in larger populations, it will demonstrate that objective genetic polymorphisms can predict clinical outcomes. The next steps, identifying candidate gene polymorphic associations with RDS as the phenotype, requires that epigenetic effects such as subsequent methylation or deacetylation of the chromatin markers attached to DNA, that alter gene expression and the effects of miRNA, must be carefully dissected.

Work from Thanos *et al.* (49) compared male and female wild-type (Drd2 +/+), heterozygous ($Drd2^{+/-}$) and knockout (Drd2 -/-) mice reared post-weaning in either an enriched environment (EE) or a deprived environment (DE). In mice with normal or decreased *D2* gene expression longer lifespan was found to correlate with EE. The dopamine receptor D2 +/+ EE mice lived almost16% longer than their DE counterparts. Dopamine receptor D2 +/+ lived 22% and Drd2 +/- EE mice 21% longer than Drd2 -/- EE mice. Moreover, environmental factors like body weight and locomotor activity were moderated; compared to DE mice; EE mice show greater behavioral variability between genotypes.

Regarding the “double edge sword” concept, it is important to realize that based on certain reward gene polymorphisms, individuals have a high-risk for all RDS behaviors, that can be compounded by environmentally induced, epigenetic insults that ultimately influence post –recovery protracted abstinence. These effects on the integrity of dopamineric neurochemistry and functional conectivity, can continue for years (50).The consequence of substances withdrawal is a neurotoxic issue. Ultimately, impairment of brain reward circuitry and attenuation of neurotransmitter signaling lead to unwanted associated sequelae that include depression, sleep disturbances, sensation seeking, lack of satisfaction and impulsivity. Post –short-term recovery usually includes supportive therapies and programs, and attending 12 –steps and other fellowship programs. If post- withdrawal, clinicians fail to attempt to manipulate compromised brain neurochemistry epigenetically potentially through pro-dopamine regulation, and the neurological impairment is left untreated, relapse will usually follow.

7. CRITICAL ISSUES

The literature is rife with studies that support reward deficiency and hypodopaminergic state as

being an important feature of SUD. Cui *et al.* (51) used a new conditional bacterial artificial chromosome rescue strategy in mice that targeted MOR expression. A subpopulation of striatal direct pathway neurons enriched in the striosome and nucleus accumbens, in an otherwise MOR-null background mice, restores opiate reward, opiate-induced striatal dopamine release and partially restores motivation to self-administer an opiate.

However, reward deficiency may not induce SUD in adolescence. In fact, the opposite may be true. The prefrontal cortex (PFC) continues to develop until people reach their 20s (52) and there is increasing concern among addiction specialists about the involvement of teenagers and young adults in substance abuse. It is well known that in this population, appropriate decision-making is problematic due to PFC immaturity. Doremus-Fitzwater and Spear (53) following a review of the literature suggest "that adolescents are uniquely poised to seek out hedonic stimuli, experience greater "pleasure" from rewards, and consume rewarding stimuli in excess." Yokum *et al.* (54) in support of this notion, through genotyping of dopaminergic genes in adolescents, found that a genetic propensity for greater dopamine signaling capacity increases the risk for future weight gain. They suggested that theoretically, a more reliable method of modeling genetic risk associated with future weight gain might involve combining alleles that have a similar function. Taken together, this would indicate that instead of the hypodopaminergic trait being a vulnerability marker for subsequent RDS behaviors, in fact, the hyperdopaminergic trait is the culprit, a marker for adolescence having a under-developed PFC, particularly in the cingulate gyrus. The question remains unresolved and requires an in-depth review of the risk alleles that were chosen in the Yokum *et al.* (54) experiment, which may not entirely represent appropriate genotyping. An example is the utilization of the DAT 10R instead of 9R; the 9R is four times stronger than 10R in clearing dopamine from the synapse.

The turbulence of the underdeveloped adolescent PFC provides impetus to not only continue relevant neuroimaging studies in both animal and human models but to encourage the preventive measures embraced by governmental and social media outlets.

8. FUTURE PERSPECTIVE: PRO-DOPAMINE REGULATION

This commentary regarding dopamine agonistic therapy for reward dependence was written following a non-systematic review, of some relevant databases. PubMed Central Clinical Queries and PubMed/MEDLINE, as well as, author searches based on knowledge of the field, was carried out, for the results see Table1.

Chronic or long-term therapy with D2 agonists results in a proliferation of D2 receptors *in vitro* (55). One example is KB220, a dopamine agonistic agent that activates the release of brain dopamine at the reward site, induces enhanced resting state functional connectivity and reduces extreme craving behaviors (56). KB220 was developed to follow the "brain reward cascade." After serotonin release stimulates enkephalin, the hypothalamic release of enkephalin, in turn, inhibits GABA in the substantia nigra. The reward cascade ends in the NAc with the modulation of dopamine release by GABA (28, 52, 57). Synaptic release of dopamine stimulates the D1-D5receptors causing reduced stress and increased feelings of well-being (19). Under normal conditions dopamine in the NAc, controls and maintains and our drives relating to pleasure. With chronic SUD motivational drives revert to "wanting" not "liking" (18). When compared to non-dependent individuals substantially decreased levels of dopamine D2 receptors are seen in alcohol and drug dependent subjects using Positron emission tomography (PET) (58). As mentioned earlier, in animals, overexpression of the dopamine D2 receptor gene via vector delivery resulted in a notable reduction of alcohol and cocaine consumption (13-15, 59).

Dopamine release is effected, in the right direction (increased synaptic dopamine), by compounds that are enkephalinase inhibitors, for example, S-nitroso-N-acetylpenicillamine (SNAP) the decomposition product of sodium nitroprusside an enkephalinase inhibitor, induced dopamine increase in the striatum dialysates of rats (60). Sodium nitroprusside has not yet been studied as an anti-craving substance. However, Bromocriptine a dopaminergic agonist has been investigated. Boundry (55) found that chronic or long-term therapy with D2 agonists results in a proliferation of D2 receptors *in vitro*, *in vivo* studies show the opposite-a downregulation of D2 receptors after bromocriptine administration (61). Noble *et al*. found increased reward activity in individuals who carry the DRD2 A1 allele (23). Compared to A2 carriers, A1 carriers have a low DR2 density that paradoxically corresponds to greater reward sensitivity to bromocriptine (62, 63). Knowing that the A1 allele is associated with the striatal activity that L-amino acid decarboxylase undergoes, during dopamine synthesis may explain the paradox and the importance of utilizing amino-acid therapy.

Specifically, Laakso *et al.* reported that in healthy Finnish subjects those with the A1 allele had increased activity of striatal L-amino acid decarboxylase. They found that Heterozygous carriers of the A1 allele (A1/A2; 10 subjects) (18F)-FDOPA uptake in the putamen was (18%) significantly higher than

Table 1. Data base search results

DATABASES	SEARCH PHRASE				
	Dopamine agonistic therapy for addiction	*Dopamine agonist for addiction*	*Dopamine agonistic therapy for reward dependence*	*Dopamine agonist for reward dependence*	*Dopamine antagonistic therapy for addiction*
Cochrane Systematic Reviews	0	21	3	0	13
DARE	0	3	0	0	0
PubMed Central Clinical Queries	41	574	54	337	474
National Guideline Clearinghouse	18	5	0	0	5
PsychINFO	13	15	0	1	7
ACP PIER	83	1	0	0	0
PsychSage	15	15	0	0	0
PubMed/MEDLINE	612	11930	75	633	120

Modified from Blum *et al*., (31)

homozygous A2 allele carriers (A2/A2; 23 subjects). L-amino acid decarboxylase is a rate-limiting enzyme for trace amine synthesis and is present in the final step of dopamine synthesis. That subjects with the A1 allele have lower D2 receptor expression and decreased autoreceptor function, is supported by a higher trace amine synthesis rate in A1 allele carriers, which may explain a risk for all addictive behaviors (64). The importance of utilizing amino-acid therapy for carriers of the DRD2 A1 allele is that their higher trace amine synthesis rate may mean that the supply of amino-acids like L-phenylalanine and L-tyrosine might satisfy the need of the rate-limiting step in the synthesis of dopamine suggesting a bulit –in protective mechanism.

Both genetic and epigenetic effects may continue for future generations and could explain our clinical finding of better compliance with amino-acid therapy in carriers of the D2 receptor-deficient, A1 allele, possible due to the release of neuronal doapmine following epigentic acetylation effecting the glutaminergic drive (65). Pro-dopamine regulation therapy, such as KB220 variants, may enhance DRD2 expression by reduced methylation and increased acetylation, in DRD2 A1 allele carriers and others who have dopamine deficiency (66). Increased dopamine function should then lead to a reduction of drug and non-drug seeking behaviors and mortality (67).

Finally, Badgaiyan *et al.* (68) provided clear evidence that in human ADHD subjects either at rest or during activation, the status of brain dopamine varies. Based on diverse sets of data, studies have reached contradictory conclusions the presence of a hyperactive or hypoactive dopamine system or a disturbed glutamatergic disorder (69). Since secondary approaches were used in previous studies, Badgaiyan *et al.* (68) measured the tonic and phasic dopamine release directly in ADHD subjects. A single scan dynamic molecular imaging technique was used to measure and matched the tonic release of dopamine in both ADHD and healthy control subjects were measured. The phasic release during the presentation of Eriksen's flanker task was measured in the two groups of subjects. A dopamine receptor ligand 11C-raclopride was administered intravenously to subjects while they were under a positron emission tomography (PET) camera. PET data was then obtained, while subjects either completed the flanker task (phasic release experiments) or rested (tonic release experiments). Ligand binding potential (BP) variations and other receptor kinetic parameters were analyzed. During task performance, drastically lowered ligand BP, in the right caudate of ADHD subjects, representing increased phasic release while, at rest, the ligand BP was considerably greater in the right caudate, implying decreased tonic release. This outcome clarifies prior findings of decreased or augmented dopaminergic activity. Understanding dopamine tone in ADHD is relevant to SUD and RDS behaviors in general as being hypodopaminergic (68). The take home message here is that since ADHD is a subset of RDS, these data reveal that there is lower dopamine at rest, which suggests a hypodopaminergic trait supporting our original hypothesis related to RDS and neurotransmission (70).

9. CONCLUSION

Post –recovery SUD should be considered as a neurotoxic condition, and clinicians need to treat this unwanted condition with the development of agents that induce "dopamine homeostasis." It is well –known that protracted abstinence is accompanied by abnormal neurochemical correlates and impaired resting state functional connectivity (71, 72). Ignoring this phenomenon will only exacerbate relapse. Clinicians should carefully review the work of Gold and others (73-84). While self-help groups are beneficial (57, 85), the laudable goal of restoring normal psychological

behavior requires concomitant treatment of the addicted brain, by way of neurochemical manipulation with the objective of establishing “dopamine homeostasis.”

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