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Reward Deficiency Syndrome (RDS): A Common Neurogenetic Trait/State of All Addictions: Is this the new DSM?

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Abstract: Steven Hyman, former director of the National Institute of Mental Health (2012), argued that neuroscience research in psychiatry frequently inherits the DSM's assumption that disorders are discrete entities, even though empirical boundaries between conditions are often porous. In response, Hyman and colleagues advanced the Research Domain Criteria (RDoC), which organizes psychopathology around core neurobiological domains that cut across diagnoses. In a conceptually similar direction, Blum (1995) introduced Reward Deficiency Syndrome (RDS) as a transdiagnostic construct intended to unify substance-related and behavioral addictions. To date, PubMed includes more than 1,650 reports referencing "reward deficiency" and 281 specifically referencing RDS. Recent genome-wide association and pharmacogenomic findings in very large cohorts (88.8 million subjects) are interpreted as supporting dopaminergic dysregulation as a key phenotype underlying RDS vulnerability. The Genetic Addiction Risk Severity (GARS®) panel was developed to estimate liability for RDS and "preaddiction." Notably, many conditions listed in DSM-5 share overlapping genetic polymorphisms, with frequent

convergence on pathways involved in dopaminergic neurotransmission. Building on this framework, we propose a biphasic prevention and treatment strategy for both substance (e.g., alcohol, nicotine) and non-substance (e.g., highly palatable food/glucose-related) addictive behaviors. In the acute setting, harm-reduction approaches may require targeted modulation of postsynaptic dopamine receptors (D1–D5) within the nucleus accumbens (NAc). Over longer time horizons, however, durable recovery may depend on restoring dopamine signaling—specifically, promoting dopamine activation and release within the NAc to support dopamine homeostasis. Failure to balance short-term and long-term dopaminergic interventions may contribute to affective instability, maladaptive behavior, and, in vulnerable individuals, suicidal ideation. Individuals with serotonergic/dopaminergic receptor deficits and/or high catechol-O-methyltransferase (COMT) activity may be more likely to self-medicate using substances or behaviors that transiently increase dopamine release. A growing body of evidence suggests that increasing D2 receptor expression in genetically vulnerable populations could reduce addictive risk. Although D2 agonists can downregulate receptors in vivo, in vitro work indicates that sustained stimulation may promote receptor proliferation, and gene-transfer studies producing DRD2 overexpression reduce alcohol and cocaine seeking in rodent models. Finally, naturalistic dopaminergic repletion strategies may represent a safer long-term approach to normalize dopaminergic function, support recovery, and improve quality of life across RDS-related behaviors. (WC 286)

Keywords: Dopamine Homeostasis, Precision Addiction Management, GARS, KB220, Reward Deficiency Syndrome (RDS), Neuroimaging

KEY FINDINGS (2025)

51.2%- Over half of people 12 and older have used illicit drugs at least once.

Cost-1.15M

Drug overdoses have killed over 1 million people in the U.S. alone since 1999.

Cost-$44.5B

The federal budget for drug control in 2024 was nearly $45 billion.

INTRODUCTION

Relapse raises a fundamental question: is renewed substance use primarily a matter of choice, or does it reflect a biological process that can overwhelm volition? Closely related is a second debate about sequence and causality. Do individuals initiate drug use because they already carry an underlying vulnerability, or does drug exposure itself create—or meaningfully amplify—that vulnerability (Gold et al., 2020)? These questions motivate the present discussion.

A substantial body of work indicates that repeated exposure to drugs of abuse can produce epigenetic and molecular adaptations that disrupt normal neurotransmitter signaling within reward-related brain circuits. Such adaptations are linked to reduced likelihood of sustained abstinence and to escalation of use through tolerance, withdrawal, and negative reinforcement. Across neuroscience, psychiatry, and neurology, there is broad agreement that environmental pressures can alter gene expression, in part through epigenetic mechanisms that influence transcription and downstream cellular function

(Hamilton PJ & Nestler EJ, 2019). In this context, emerging research has suggested that locus-specific neuro-epigenetic processes may contribute to the persistence of addictive behaviors, and that clarifying these mechanisms could support the development of more targeted interventions.

These scientific perspectives also intersect with how society assigns responsibility for behavior. Modern legal systems largely operate "as if" human actions are undetermined—presuming agency and choice—despite the fact that determinism underlies much of scientific explanation. Yet empirical findings increasingly demonstrate that inherited variation can shape behavioral tendencies across organisms, including humans.

For example, Tikkanen et al. (2010) reported that carriers of the high-activity MAOA-H allele showed greater risk for severe, impulsive, recidivistic violent behavior when heavy drinking occurred in combination with childhood physical abuse (CPA). Such observations have encouraged legal scholars and courts to wrestle with how biological predispositions and environmental exposures might influence culpability.

To maintain coherence between these competing frameworks, courts typically preserve the presumption of responsibility while allowing limited recognition of biological constraint through mitigating doctrines and defenses. In practice, this often appears as efforts to introduce neurogenetic evidence under theories such as insanity or diminished capacity—approaches that implicitly argue compromised self-control. Nonetheless, prevailing standards make these defenses difficult to establish, and successful outcomes remain uncommon. The underlying principle is simple: the insanity defense generally assumes most individuals can choose within moral and legal norms, while creating an exception for those who are unable to do so.

Our group has highlighted a case example in which rehabilitation and treatment monitoring were prioritized over incarceration for a repeat driving-while-intoxicated (DWI) offender, with genetic risk information incorporated into sentencing considerations. In this report, eligibility for an alternative sentencing pathway was evaluated using the Genetic Addiction Risk Severity (GARS) test, described as an early instance in which genetically informed "determinism," rather than a purely "free will" framework, shaped decisions regarding a DWI recidivist (Green, Brewer, Mullin, Floyd, & Blum, 2021).

Historically, the view of alcoholism as a disease has roots in the early twentieth century, including Bill Wilson's framing in The Big Book and later Jellinek's influential typology (Blum, 1991; Jellinek, 1960). Jellinek argued that alcoholism reflected an epigenetic phenomenon and proposed five clinical patterns: Alpha (psychological dependence), Beta (medical complications, including liver and nerve disorders), Gamma (increasing tissue tolerance), Delta (inability to abstain), and Epsilon (binge drinking). Although this framework advanced the field, it left key mechanistic questions unresolved:

(1) what biogenetic processes drive alcoholism,

(2) how stress and social context alter cellular function in ways that contribute to alcoholism, and

(3) whether chronic excessive drinking produces enduring cellular changes that reinforce alcoholism.

By foregrounding epigenetics, Jellinek's model helped set the stage for molecular neurobiological research designed to address these unanswered questions.

Meaning Check (What I Preserved from Your Original)

- The relapse/free will vs physiology framing and the "predisposition vs induced vulnerability" question (Gold et al., 2020).
- Drug-induced epigenetic adaptations disrupting reward circuitry; tolerance/withdrawal escalation; call for mechanistic precision (Hamilton PJ & Nestler EJ, 2019).
- The legal "as if" framework; determinism vs free will; MAOA-H + heavy drinking + CPA and severe impulsive violence (Tikkanen et al., 2010).
- Courts' limited receptivity; insanity/diminished capacity logic; rarity of success.
- The DWI case example using GARS in alternative sentencing (Green et al., 2021).
- Disease model lineage: Bill Wilson/Big Book → Jellinek (Blum, 1991; Jellinek, 1960) + the five types + the 3 unresolved questions.

BACKGROUND AND STATS: THE DISEASE MODEL AS OVERLAPPING ADDICTIONS FROM BIRTH TO ADULTHOOD

Shifts in addiction terminology increasingly require a broader clinical lens—one that treats **non-substance, impulsive, and compulsive behaviors** as legitimate addictive conditions rather than peripheral "habits." A consistent theme across contemporary research is that many addictive behaviors co-occur and likely share overlapping psychological drivers, genetic liabilities, and neurobiological circuitry. In other words, the boundaries between "chemical" and "behavioral" addictions may be less distinct than traditional classification systems imply.

Epidemiologic findings support this overlap. In a study of 3,003 adolescents and young adults (42.6% male; mean age 21 years), Kotyuk et al. (2020) reported patterned co-occurrences between substance use and other potentially addictive behaviors. Specifically, smoking was associated with problematic Internet use, excessive exercise, eating-disorder pathology, and gambling; alcohol use correlated with problematic Internet use, online gaming, gambling, and eating-disorder pathology; and cannabis use showed links with problematic online gaming together with gambling. Collectively, these observations reinforce models that conceptualize addictions as sharing common etiologic pathways—consistent with Reward Deficiency Syndrome and related component models that emphasize transdiagnostic vulnerability rather than isolated disorders.

From a public health perspective, both substance-related and behavioral addictions remain highly prevalent and impose major societal costs. Dependence involving alcohol, psychostimulants, and benzodiazepines continues to represent a substantial burden [Seth et al., 2018; Gressler et al., 2018]. Chronic pain care alone is frequently cited as costing U.S. taxpayers hundreds of billions of dollars annually, and the clinical response—particularly the expansion of opioid prescribing—contributed to an iatrogenic pathway into opioid misuse. In

parallel with rising prescription volume, opioid-involved overdose deaths increased sharply between 1999 and 2010 [Pergolizzi et al., 2018]. Current estimates suggest that approximately 2 million Americans experience opioid addiction associated with prescription exposure, with large annual economic costs [Florence et al., 2016]. In 2015, opioid-related overdoses accounted for 33,091 deaths, with roughly half involving prescription opioids [Rudd et al., 2016], and aggregate economic losses have been estimated to exceed one trillion dollars.

Importantly, evidence supports non-opioid strategies for chronic pain management [Amie et al., 2018], yet scaling these approaches remains difficult [Blum et al., 2018b; Salling & Martinez, 2016]. Clinical practice often lags behind the research base, and opioid-centered models still dominate many care pathways despite data suggesting that non-opioid treatments—such as NSAIDs—can outperform opioids for chronic pain outcomes [Savannah et al., 2016; Krebs et al., 2018]. This gap underscores the need for treatment systems that reduce reliance on potentially addictive pharmacotherapies and instead integrate risk-informed, mechanism-oriented strategies. In that spirit, the development of "Reward Deficiency Solution Systems" (RDSS) and Precision Addiction Medicine/Management (PAM) has been proposed as a pathway to modify prescribing behaviors and reduce opioid-related morbidity and mortality [Blum et al. 2015a; Blum et al. 2018a].

The neurobiology of pain and addiction further supports an integrated view. Reward circuitry is not only central to reinforcement and motivation; it also modulates nociception and the affective experience of pain. Changes within dopaminergic pathways can alter sensory and emotional components of pain processing and may contribute to chronic pain syndromes [Chen et al., 2009]. Within this framework, analgesic tolerance should not automatically be equated with addiction; the distinction becomes clinically meaningful when patterns of maladaptive behavior emerge—such as illicit drug seeking or "doctor shopping"—that reflect compulsive acquisition beyond medical need.

Reward Deficiency Syndrome (RDS) itself was introduced in a general scientific venue and has since been discussed across a large body of literature, including PubMed-indexed work on RDS and on dopamine dysregulation. RDS is referenced in the SAGE Encyclopedia of Abnormal Psychology and Mental Illness and has been described in standard software definitions (MS-Word, 2017).

A central premise of RDS is that dopamine signaling shapes psychological constructs tied to reinforcement—often described as "wanting" and "liking"—and that disturbances in these processes can help explain why diverse addictive behaviors cluster under a common biological vulnerability.

The RDS framework has also been linked to evolving professional definitions of addiction. The ASAM definition of addiction (2011) incorporated genetic and neurochemical considerations (Smith et al., 2012), strengthening the argument that addiction reflects physiological mechanisms rather than moral failure. Accordingly, addiction treatment and pain management now sit at a potential inflection point: a shift toward **Precision Addiction Management** that aims to reduce guesswork in identifying risk and to center care on restoring "dopamine homeostasis" as a clinical objective (Baron et al., 2018; Blum et al., 2018a).

WHAT ARE THE UNDERLYING BIOGENETIC MECHANISMS THAT CAUSE ADDICTIVE BEHAVIORS?

RDS – Overview (Rewritten)

A central premise of Reward Deficiency Syndrome (RDS) is that many addictive, impulsive, and compulsive disorders arise from a shared neurobiological vulnerability. In this framework, diverse clinical presentations—whether driven by substances or behaviors—reflect common genetic variants and environmentally shaped (epigenetic) adaptations that weaken the brain's capacity to generate normal reward, pleasure, and satisfaction. RDS therefore functions as an umbrella construct linking multiple conditions in abnormal psychology and neuropsychiatry, including chemical and behavioral addictions, certain personality-related compulsive traits, autism spectrum disorders, and post-traumatic stress disorder (PTSD), among others.

Reward Signaling and the Drive to "Self-Correct" Reward Tone

Subjective pleasure and reinforcement depend on coordinated signaling across multiple neurotransmitter systems. These systems interact at synapses in ways that ultimately regulate dopaminergic output within core reward circuitry—particularly mesolimbic pathways and the nucleus accumbens. When ordinary reward signaling is blunted, individuals may experience reduced hedonic tone or diminished satisfaction from natural reinforcers. The RDS model proposes that, in response, some individuals seek to "normalize" internal reward tone by engaging in high-risk behaviors or consuming substances that transiently increase dopamine release, producing short-term relief, stress reduction, or a sense of well-being that feels otherwise unattainable. Over time, these compensatory behaviors can become repetitive, escalating, and difficult to control.

Genetic Variation and Association Logic

Genetic association is inferred when specific variants occur at higher frequency in affected groups than in appropriately matched controls. Genes—DNA sequences encoding functional proteins—shape the synthesis, release, receptor binding, and clearance of neurotransmitters. Polymorphisms (genetic variants) can modify these functions, altering receptor density, transporter activity, enzymatic degradation, or downstream signaling. Within the RDS model, such variants collectively influence how reward circuitry responds to both natural reinforcers and drug- or behavior-induced stimulation.

Historical Research Foundations: DRD2 and Related Reward Gene Findings

During the 1990s, multiple groups reported associations between severe alcoholism and the A1 allele of the dopamine D2 receptor gene (DRD2). Subsequent work extended this association to a wider range of compulsive and impulsive addictive behaviors. In parallel, receptor binding and availability studies suggested that individuals carrying the A1 allele exhibit reduced dopamine receptor availability in brain regions essential for reward processing. These findings are often interpreted as indicating a biologically mediated

reduction in reward sensitivity, which may increase vulnerability to craving and reinforcement-driven behavior.

The Brain Reward Cascade: Multi-Neurotransmitter Control of Dopamine Output

RDS is not framed as a "dopamine-only" phenomenon. Rather, dopamine is treated as the final common pathway modulated by a broader set of interacting systems—serotonergic, endorphinergic/opioidergic, GABAergic, glutamatergic, adrenergic, and cholinergic signaling—whose integrated effects help determine net dopamine release in the nucleus accumbens. Disruptions anywhere along this interconnected cascade can reduce dopaminergic tone, which the RDS model links to heightened craving, dysphoria, irritability, and negative affective states that promote further substance use or behavioral reinforcement seeking.

Hypodopaminergic Function as a Polygenic Trait/State

Hypodopaminergia is described as a polygenic liability that may emerge when multiple reward-related variants collectively reduce dopamine availability or signaling efficiency. Beyond dopamine receptor variants, polymorphisms affecting neurotransmitter synthesis, receptor expression, transporter function, and enzymatic catabolism can shift reward tone. For example, high monoamine oxidase (MAO) activity can increase dopamine breakdown, reducing dopaminergic signaling at key receptor sites. Similarly, certain serotonin-related variants may reduce receptor expression (e.g., 5-HT2A receptor gene -1438A/G) or lower synaptic serotonin availability (e.g., serotonin transporter variants including 5-HTTLPR, with biallelic and triallelic forms such as rs25531 A/G). In combination, such variants may diminish the modulatory support normally provided by serotonergic signaling within reward circuitry.

Environment and Epigenetics: Stress, Repeated Exposure, and "Blunting" of Reward

Genetic predisposition is amplified by environmental factors that reshape the reward system across time. Chronic stress and repeated exposure to substances of abuse can impair reward cascade function and reduce dopamine release. Animal models and human neuroimaging studies indicate that dopamine release can be triggered not only by drugs (e.g., alcohol, opiates, psychostimulants, nicotine) but also by a range of behaviors and cues (e.g., gaming, gambling, hypersexuality, and consumption of highly palatable foods). These effects are reinforced because they can temporarily relieve stress or craving and produce a compensatory rise in reward signaling.

With prolonged repetition, however, supraphysiologic dopamine surges can drive maladaptive neuroadaptations. Sustained activation of postsynaptic receptors may contribute to receptor downregulation and diminished reward responsiveness—often described as "blunting." This mechanism provides a biological explanation for escalation: progressively higher doses or more intense behaviors may be required to achieve the same effect. The model further notes a paradox observed after extended abstinence: receptor supersensitivity may emerge, such that returning to prior doses—especially in substance

use—can become dangerous and, in some settings, lethal through excessive receptor activation.

Craving as a Biologically Driven State: Stress- and Cue-Mediated Pathways

RDS conceptualizes craving as a state shaped by both reward and stress systems. Stress-induced craving can alter chromatin structure and engage stress mediators such as corticotropin-releasing factor and norepinephrine, producing sharp fluctuations in dopamine signaling that may culminate in transient hypodopaminergia. When stress is chronic or repeatedly experienced, this pattern may consolidate into a more enduring hypodopaminergic state. In parallel, cue-induced craving—through activation of memory- and salience-related structures such as the basolateral amygdala and hippocampus—can be associated with glutamatergic dysregulation and dopaminergic perturbations. Over time, these mechanisms may help explain relapse vulnerability even after periods of abstinence.

RDS Behaviors as a Spectrum

Within this framework, RDS is associated with reduced satisfaction and diminished reinforcement from ordinary life experiences, paired with increased drive to seek stronger reinforcers. Consequently, a broad set of behaviors—alcohol misuse, overeating, substance dependence, pathological gambling, hyperactivity, autism spectrum disorders, elevated risk-taking, hypersexuality, and certain personality-related compulsive traits—have been described as part of the RDS behavioral spectrum (Blum, Cull, Braverman, & Comings, 1996). The unifying feature is not the specific substance or activity, but the shared vulnerability: impaired reward processing that promotes repeated, escalating reinforcement seeking.

ANALYTICS OF GENETIC ADDICTION RISK SEVERITY (GARS) (REWRITTEN; LOW-SIMILARITY)

Genetic Addiction Risk Severity (GARS) is presented as a practical way to translate reward-circuit genetics into a clinically interpretable profile. In this model, a patient's allele pattern is treated as a neurogenetic "map" that may inform prevention—especially when risk is identified early—by anticipating vulnerability to substance misuse, compulsive behaviors, and related phenotypes grouped under Reward Deficiency Syndrome (RDS). The underlying rationale is that individual differences in reward-circuit function are partly traceable to common polymorphisms across genes that regulate neurotransmission and neuromodulation.

Figure 1 summarizes the conceptual basis for this approach by depicting the Brain Reward Cascade (BRC), the multi-system signaling network proposed to shape dopamine output in reward circuitry.

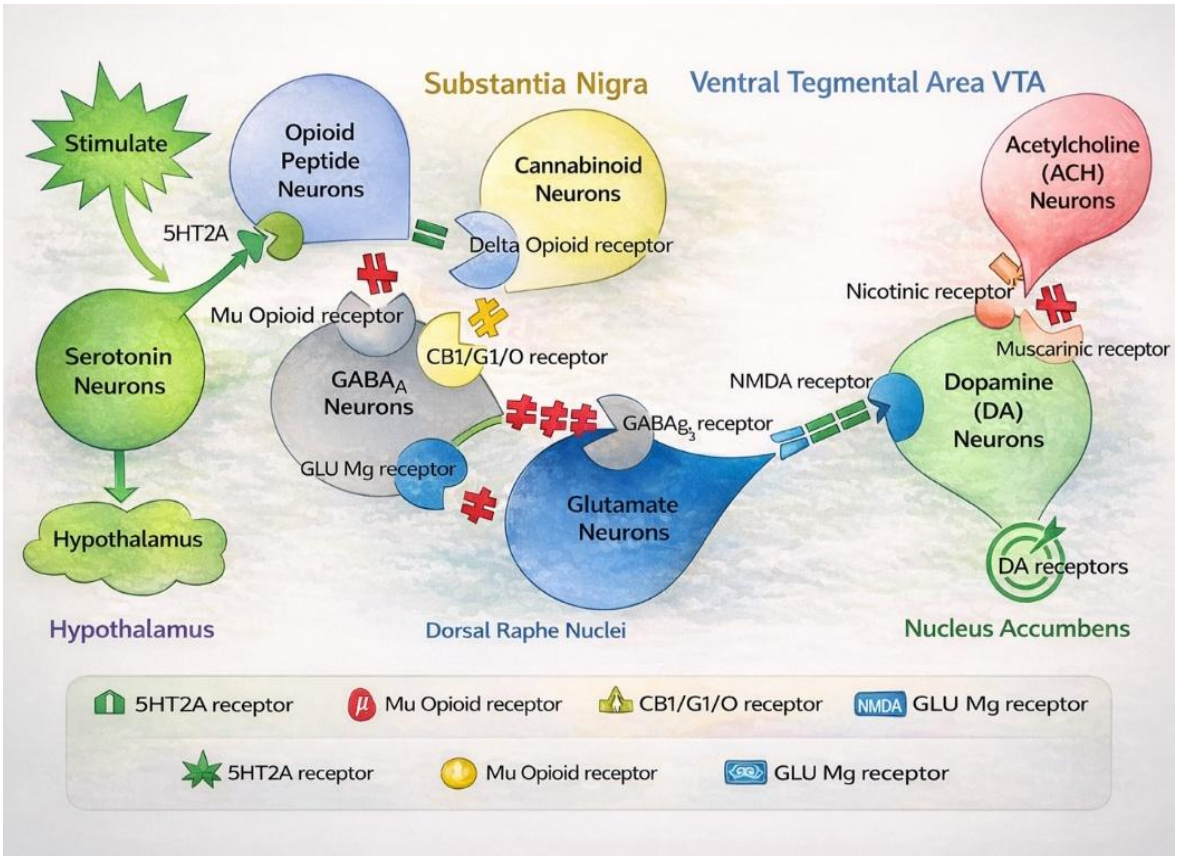

Figure 1: The brain reward cascade.

Figure 1 illustrates interactions among at least seven major neurotransmitter pathways involved in the Brain Reward Cascade (BRC). Environmental stimuli initiate serotonergic signaling in the hypothalamus. Serotonin activity—via receptors such as 5-HT2A—facilitates release of opioid peptides from hypothalamic opioid neurons. These peptides are proposed to exert two major downstream effects through distinct opioid receptor mechanisms: (i) an inhibitory influence (possibly via enkephalin and μ-opioid receptor signaling) projecting to GABAA neurons in the substantia nigra, and (ii) a stimulatory influence on cannabinoid-related signaling (e.g., anandamide and 2-arachidonoylglycerol) through ß-endorphin-linked δ-receptor pathways. Cannabinoid signaling (notably 2-arachidonoylglycerol) can indirectly reduce inhibitory GABAA tone by acting on Gi/o-coupled CB1 receptors in the substantia nigra. Additional modulation may occur through glutamatergic inputs involving the dorsal raphe nuclei, which can further disinhibit substantia nigra GABAA neurons via glutamate receptor mechanisms (e.g., GLU M3). When engaged, GABAA neurons can powerfully inhibit ventral tegmental area (VTA) glutamatergic drive through GABAB-related mechanisms. Cholinergic influences within the nucleus accumbens may also modulate signaling through muscarinic (inhibitory) and nicotinic (excitatory) receptor actions. Ultimately, glutamatergic projections within the VTA stimulate dopamine neurons through NMDA receptors, promoting dopamine release in the nucleus accumbens (NAc). The NAc “bullseye” represents the downstream experience of incentive salience or euphoria—the “wanting” response (Blum et al., 2020).

From Cascade Variation to Measurable Risk

Within this framework, inherited or acquired perturbations anywhere along the BRC can alter reward responsiveness and, by extension, vulnerability to compulsive reinforcement seeking. The manuscript argues that such variation—whether driven by polymorphisms or epigenetic modification—may also influence pain sensitivity and pain tolerance. Consistent with this premise, GARS is described as a test designed to estimate susceptibility across a cluster of phenotypes that include addiction risk, pain vulnerability, and other compulsive behaviors defined within the RDS construct (Blum et al., 2018d). Parallel lines of work emphasize that dopaminergic tone contributes to pain processing and that reward circuitry participates in the modulation of nociception, creating potential overlap between pathways implicated in chronic pain and those implicated in addiction vulnerability (Chen et al., 2008; Taylor et al., 2016; Upadhyay et al., 2010). These intersections have been used to justify a precision approach in which identifying reward-system risk could support both addiction prevention and safer pain-management strategies.

At the same time, the manuscript acknowledges a central methodological challenge: "true" non-RDS control groups are difficult to define and operationalize. Because subclinical or unreported RDS-related behaviors can contaminate controls, simply counting risk alleles in unscreened comparison samples may inflate noise and distort associations (Chen et al., 2005). Follow-up work using more rigorously screened controls—excluding addictive, compulsive, or impulsive behaviors not only in participants but also within family histories—was reported to strengthen associations between dopaminergic variants and RDS phenotypes. As an illustrative example, the DRD2 A1 allele is described as being linked to an estimated 30–40% reduction in receptor density. In general (unscreened) samples, the A1 allele has been reported at roughly one-third prevalence (Noble et al., 1991). In contrast, in a highly screened "non-RDS" control sample, only one of 30 controls carried A1 (3.3%) (Chen et al., 2005, 2012), a contrast used to argue that careful control selection is essential for valid association inference.

This point is further emphasized by referencing contested findings in the literature. The text notes a JAMA report that did not detect an association between DRD2 and alcoholism (Gelernter et al., 1991) and argues that control selection may have contributed to discrepant outcomes. In support of the broader DRD2/ANKK1 risk narrative, the manuscript points to an extensive literature linking DRD2 A1 and related loci (including ANKK1) with alcoholism and other reward-related behaviors (Neville et al., 2004).

Figure 2-Prevalence of DRD2 A1 allele in unscreened and RDS Free controls

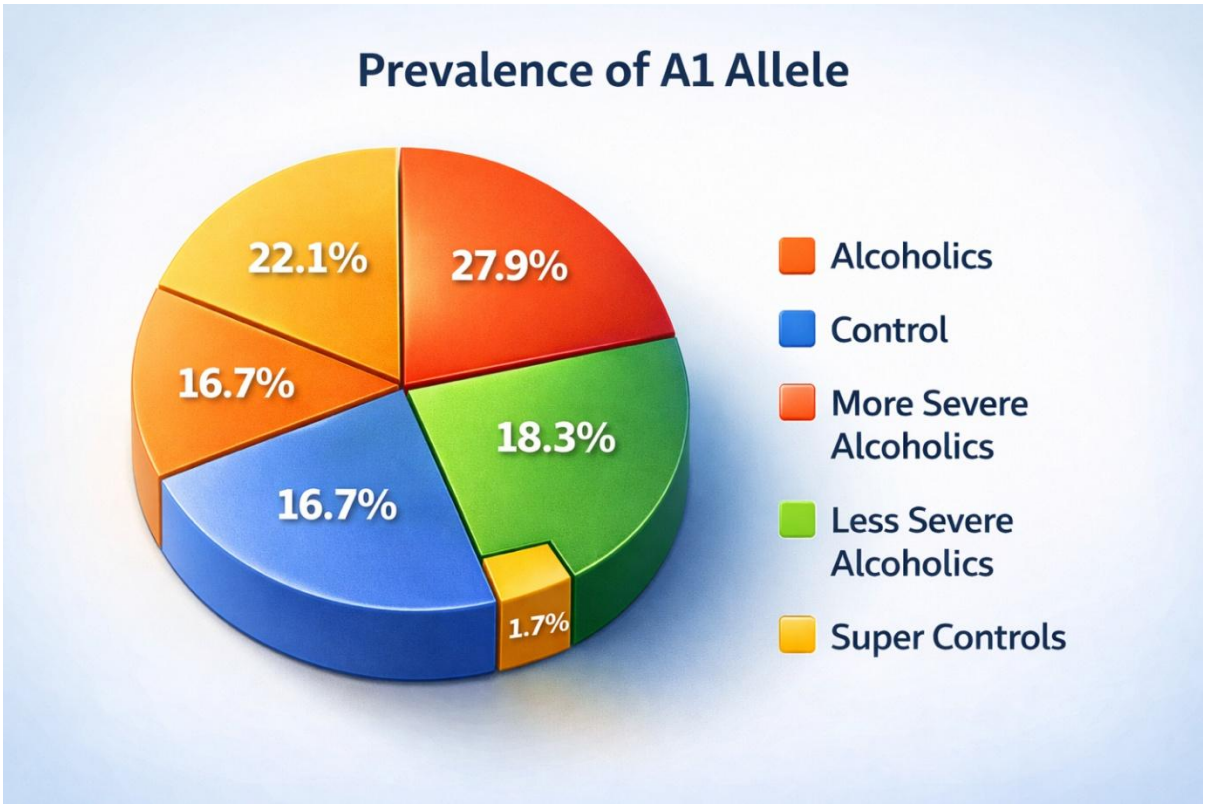

Figure 2: Reframing Reward Deficiency Syndrome (RDS) as the primary underlying phenotype—rather than emphasizing narrower categories such as Substance Use Disorder (SUD) or Behavioral Addictions (BA), which may introduce more measurement noise—could meaningfully shift how addiction risk and recovery are approached. In this view, many maladaptive patterns linked to dopaminergic polymorphisms can be understood as attempts to compensate for chronically reduced reward tone, expressed clinically as diminished satisfaction that is central to the RDS construct.

RDS as Endophenotype (Alternate Rewrite; Lower Similarity)

Reward Deficiency Syndrome (RDS) is presented as an endophenotype arising when the Brain Reward Cascade (Figure 1) is perturbed—a distributed signaling system in reward circuitry with especially important contributions from dopaminergic and opioidergic pathways (Blum et al., 2016a). From this perspective, a family history of alcoholism or other addictions may indicate an inherited shortfall in reward-neurotransmitter production or signaling efficiency. Subsequent environmental exposures can amplify that baseline liability: chronic stress and repeated intake of alcohol or other drugs may further impair cascade function, including through reduced endorphinergic synthesis (Blum et al., 1982).

As one approach to testing the genetics of this broad reward phenotype, Blum et al. (2011) assessed four dopaminergic loci frequently implicated in RDS—dopamine D1 receptor (DRD1), dopamine D2 receptor (DRD2), dopamine transporter (DAT1), and dopamine beta-hydroxylase (DBH). The analysis drew on 55 genotyped participants representing up to five generations from two independent families with multiple affected members, and compared allele frequencies with carefully screened controls (including N = 30 “super controls” for

DRD2 polymorphisms). Behavioral histories relevant to RDS were also compiled for 13 deceased relatives.

In the family cohort, DRD2 Taq1 and DAT1 10/10 were overrepresented relative to controls ($p < 0.015$). The TaqA1 allele, in particular, was detected in 100% of Family A (N = 32) and in 47.8% of Family B (11/23). No statistically significant group differences emerged for the remaining variants examined (see Figure 3).

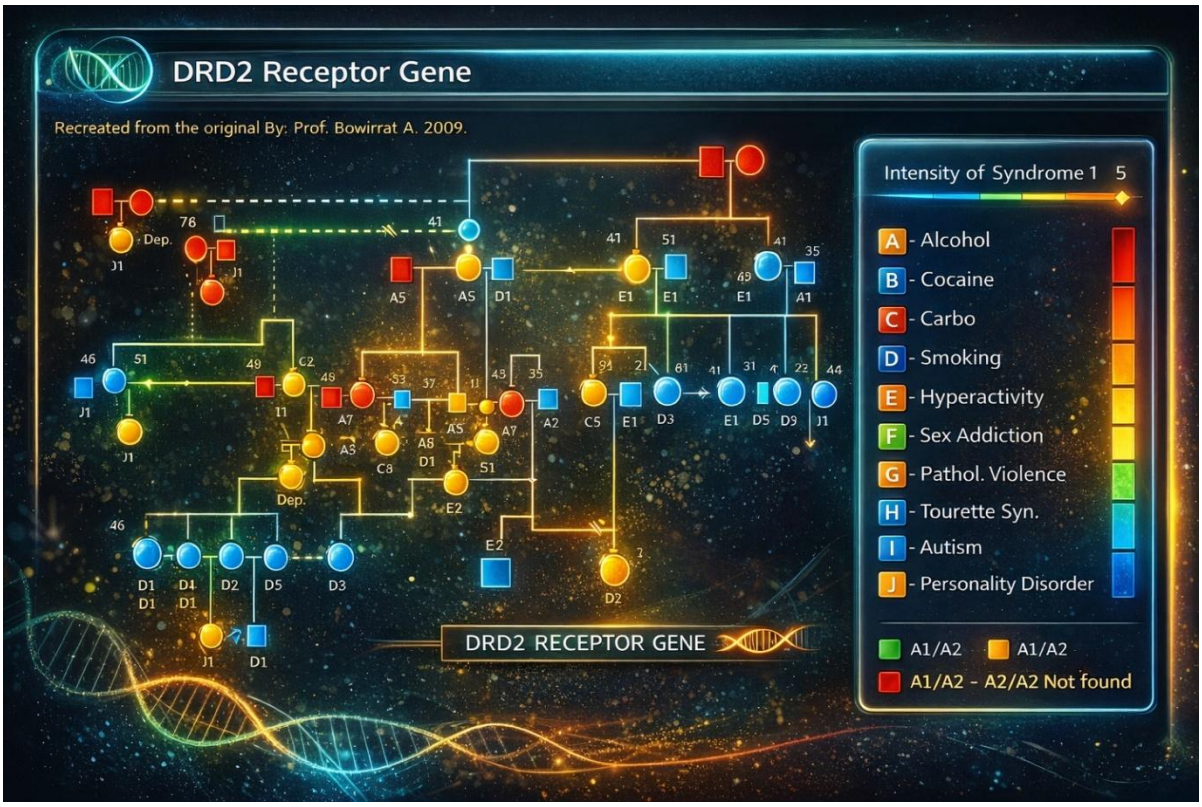

Figure 3: DRD2 polymorphism genotyping in Family A (n = 32), a pedigree characterized by multiple Reward Deficiency Syndrome (RDS) behaviors (Blum et al., 20111).

Despite the small cohort and the need to rely on linkage-based methods, the results are interpreted as consistent with a contribution of dopaminergic variants to RDS-related behavioral expression. More broadly, the work argues for treating RDS as a transdiagnostic endophenotype: analyses that isolate single addictive or compulsive manifestations may increase measurement error and yield misleading associations. In contrast, defining cases using a more inclusive "reward" phenotype could improve signal detection and guide future association and linkage studies across dopaminergic and other neurotransmitter gene candidates.

Bayes Theorem and at Birth Predictability to RDS

Bayes' Theorem is a core result in probability and statistics that updates the likelihood of an outcome in light of prior information and new evidence. The approach is attributed to

Reverend Thomas Bayes (1701–1761), whose work on conditional probability was published after his death in *An Essay towards solving a Problem in the Doctrine of Chances*(1763). Bayes' reasoning was later extended and formalized by Pierre–Simon Laplace (beginning in 1774 and further developed in *Théorie analytique des probabilités*, 1812). Sir Harold Jeffreys subsequently placed Bayesian inference on an axiomatic footing and famously compared its importance in probability theory to the Pythagorean theorem in geometry. In the present context, we used this Bayesian framework to estimate predictive value (PV) for Reward Deficiency Syndrome (RDS) behaviors among individuals carrying the DRD2 A1 allele—treating genotype as prior information relevant to later-life risk for both drug-related and non-drug addictive phenotypes.

Dopaminergic signaling—particularly via the dopamine D2 receptor—plays a central role in reward processing within mesolimbic circuitry. Impaired D2 receptor function has been linked to dysregulated reinforcement seeking spanning alcohol, drugs, nicotine/tobacco, and food-related behaviors. A large literature indicates that inherited factors substantially contribute to vulnerability for severe, compulsive substance-seeking. On this basis, Blum et al. (1995a) and Archer et al. (2012) argued that DRD2 variants represent key contributors to predicting compulsive disease. Applying a Bayesian model, Blum et al. (1995b) reported that when multiple RDS-related behaviors were aggregated, predictive value reached 74.4%. Interpreted clinically, this estimate implies that a child born with the DRD2 A1 allele (relative to the more common A2 allele) would have approximately a 74% probability of developing RDS behaviors and potentially an addiction disorder over the lifespan. Although Bayes' Theorem has not yet been applied to the complete GARS panel, we hypothesize that a multi-locus score would yield even stronger predictive performance.

Understanding GARS

A substantial body of work from Blum's group and others has examined the neurogenetics of reward circuitry, with particular emphasis on dopaminergic pathways (Barh et al., 2017; Blum et al., 2014b, 2012a). In the mid-1990s, Blum introduced the term Reward Deficiency Syndrome (RDS) to capture a cluster of behaviors associated with genetically influenced hypodopaminergic function (Blum et al., 2017b). Since then, RDS has been used across studies of addiction as well as obsessive-compulsive and impulsive phenotypes. As one illustrative report, Blum's group described a case in which lifetime RDS behaviors in a 17-year sober recovering addict were characterized without prior behavioral disclosure, using only the individual's Genetic Addiction Risk Score (GARS) profile (Blum et al., 2013a). This type of finding has been used to support the broader prevention hypothesis: that early genetic risk identification could reduce progression toward pathological substance use and behavioral reinforcement seeking (Loth et al., 2011), thereby reinforcing a disease-model approach.

In the sections that follow, we emphasize selected genes, their polymorphisms, and the RDS-related risks attributed to them. Genome-wide association studies (GWAS) have been interpreted as showing convergence between candidate "reward genes" and broader polygenic signals (Olfson & Bierut, 2012). Collectively, these data are framed as a potential "brain-print"—genetic information that might inform individualized treatment selection, improve recovery trajectories, and reduce relapse risk (Haile et al., 2012). Within this

model, the core liability is a hypodopaminergic trait that can be shifted by epigenetic state, including transgenerational influences such as maternal depression and addiction (Han & Nestler, 2017). As Smith (2017) argues, this perspective reflects a broader movement in addiction medicine toward recognizing reward-circuit pathology and incorporating earlier, biologically grounded risk detection alongside evidence-based care.

From a pharmacogenomic standpoint, evaluating candidate loci across multiple neurotransmitter systems—dopaminergic, endorphinergic, cannabinoidergic, glutaminergic, and GABAergic receptors, as well as serotonergic and dopamine transporters, MAO-A, and COMT—may be clinically useful, although the approach remains debated (Samek et al., 2016). In support of multi-pathway genetic involvement, work from Koob's group at NIAAA has highlighted numerous reward-gene associations related to alcohol use disorder (Reilly et al., 2017; Figure 4).

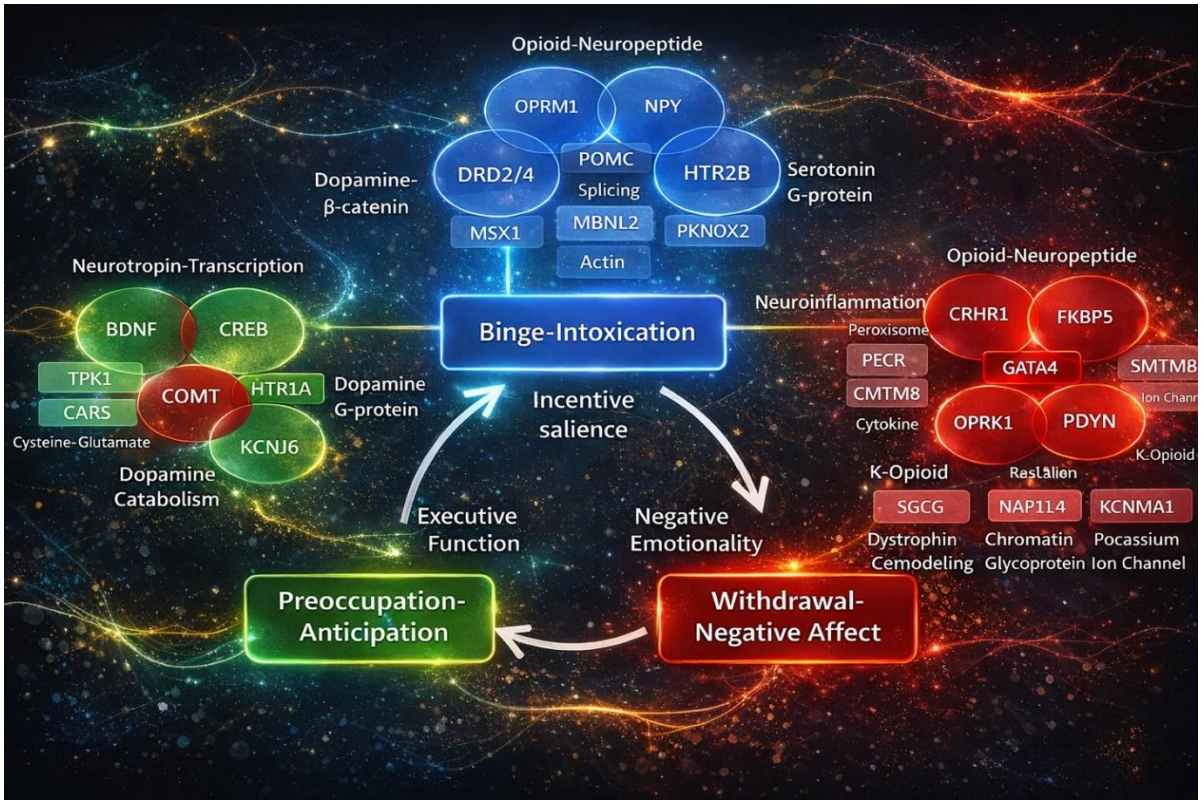

Figure 4: Alcohol-dependence genes in this model are organized according to the addiction-cycle framework. The diagram divides the cycle into three phases—(1) binge/intoxication (blue), (2) withdrawal/negative affect (red), and (3) preoccupation/anticipation (green)—and pairs each phase with a corresponding behavioral domain: incentive salience, negative emotionality, and executive function, respectively. Putative functional candidates derived from non-GWASevidence are depicted as ovals, color-matched to the phase in which each gene is hypothesized to exert its primary influence, whereas GWAS-implicated loci are shown as rectangles and similarly color-coded by stage. Each gene's broad biological role is indicated in black text. Putative relationships among non-GWAS functional candidates are represented by overlapping ovals, and proposed connections between non-GWAS candidates and GWAS hits are illustrated by overlaps between ovals and rectangles. Where feasible,

GWAS loci within a given phase are clustered by shared or related biological functions. The figure also highlights pleiotropy within the preoccupation/anticipation phase: BDNF–COMT functional variants are depicted as influencing both preoccupation/anticipation and withdrawal/negative affect, indicated by dual-color shading that spans the two stages (with Permission Reilly et al. 2017).

A working grasp of these mechanisms supports **precision pharmacogenomic** decision-making and may translate into better clinical results. From a prevention standpoint, genetically stratifying RDS vulnerability—particularly in groups with disproportionate exposure to social or economic risk (e.g., African Americans and economically disadvantaged populations)—could help target screening, triage resources, and tailor early intervention strategies (Levran et al., 2015). In this context, the Genetic Addiction Risk Severity (GARS) test is presented as a high-risk indicator for RDS-related behaviors that track with Addiction Severity Index (ASI) measures, using a multi-variant panel intended to predict drug- and alcohol-severity outcomes (Vitali et al., 2016). Because GARS is inherently multi-locus, standard single-marker performance frameworks (including classic ROC approaches) are described as imperfect fits for evaluation.

Blum's group, working with Geneus Health and the University of Colorado, assessed GARS in a longitudinal 5-year effort designed to quantify hypodopaminergic liability and its association with RDS-linked substance misuse. The study enrolled 393 poly-drug–using patients from eight U.S. treatment centers. Clinical severity was captured using the ASI-MV, and genotyping data were available for 273 individuals. Participants averaged 35.3 years of age (SD = 13.1; range 18–70); 57.8% were male, and 88.1% self-identified as White. Severity stratification placed 17.6% in the low range, 80.7% in the moderate range, and 1.5% in the high range. Across the genotyped subset, the mean GARS risk-allele count was 7.97 (SD = 2.34), spanning 3 to 17 alleles, with genotype distributions reported to be in Hardy–Weinberg Equilibrium.

Using Fisher's Exact Test, preliminary analyses identified a statistically significant association between the GARS panel and the ASI Alcohol Risk Severity Score ($X^2 = 8.84$, df = 1, p = 0.004, 2-tailed), which remained significant after adjustment for age ($p < 0.01$). The relationship with the ASI Drug Severity Risk Score was described as weaker but suggestive (chi-square p = 0.05; linear regression b = -0.122, t = -1.91, p = 0.10, 2-tailed; corrected p = 0.05, 1-tailed). The manuscript emphasizes the clinical utility of objective genotyping given that self-reported psychoactive use may be minimized or omitted. As one example of phenotype linkage, DRD2 A1 carriers have been reported to score higher on the Defense Style Questionnaire than non-carriers (Comings et al., 1995).

Within this dataset, drug-severity prediction was reported when any combination of four GARS risk alleles was present ($p < 0.05$), whereas alcohol-severity prediction required any combination of seven alleles ($p < 0.004$). Every participant carried at least one risk allele, and predictive strength increased with higher allele counts. Significant relationships were also noted for psychological, medical, and family-problem domains. A key methodological caution is highlighted: altering a single SNP or changing allele counts could remove statistical significance, underscoring the importance of careful variant selection and well-defined non-RDS control groups (Blum et al., 2011a). Finally, the rationale for the

specific genes included in GARS is described as being supported by extensive case–control association literature indexed in PubMed (as of 8-16-25) (Figure 5).

Figure 5 Genetic Association Studies of the GARS PANEL

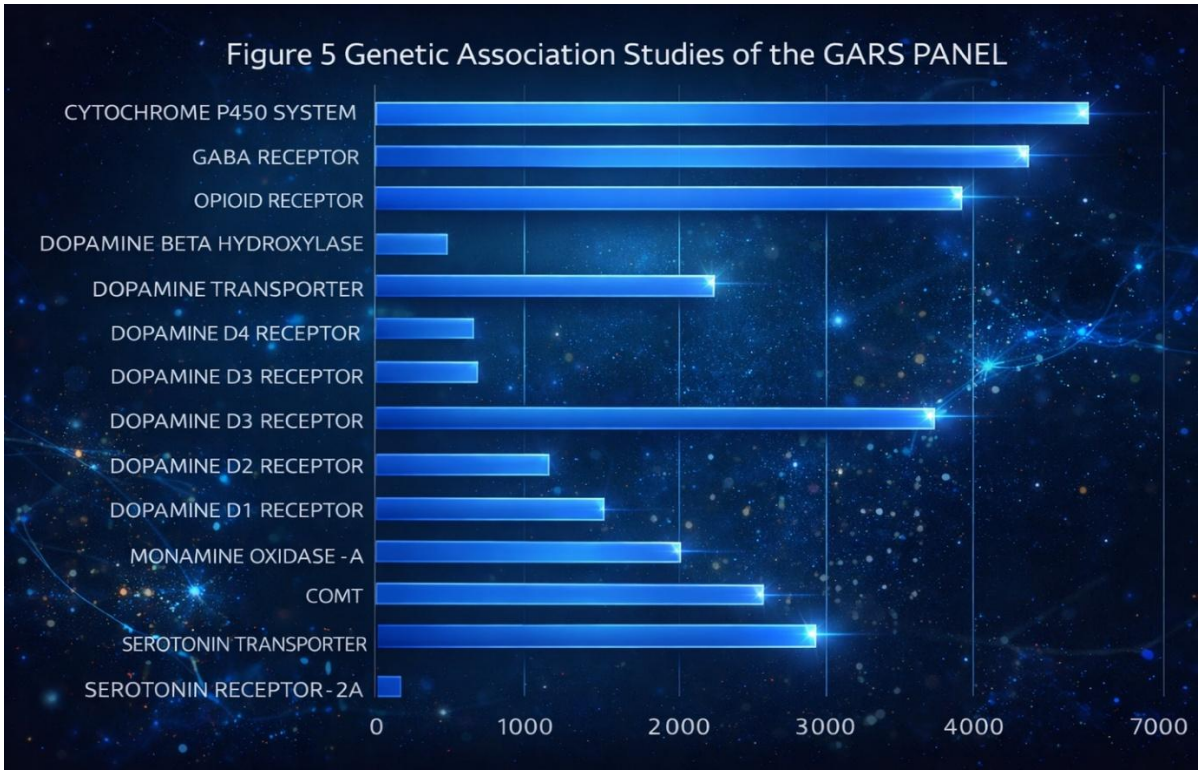

Figure 5: Cytochrome p450 system 5,805 ; GABA receptor- 5,302 ; opioid receptor- 4,911; dopamine-beta hydroxylase – 683; dopamine transporter- 3,140; dopamine d4 receptor – 946; dopamine d3 receptor-1,035; dopamine d2 receptor-4,984; dopamine d1 receptor-1,694; monoamine oxidase -a-2,406; comt- 2,827 ; serotonin transporter- 3,981;serotonin receptor -2a – 124

Transdiagnostic Prediction, Dopamine Constructs, and Anti-Reward

GARS is described as a severity estimator across the broader RDS spectrum, rather than a tool aimed at forecasting dependence on any single substance. In this framing, the score is intended to index vulnerability across multiple compulsive or reinforcement-driven behaviors—such as overeating, gambling, gaming, problematic internet use, shopping, hoarding, and hypersexual/sex-addiction phenotypes. The organizing idea is that RDS represents a shared genetic architecture that biases individuals toward hypodopaminergic states and thereby shapes both hedonic response ("liking") and incentive drive ("wanting") (Blum et al., 2012a).

To specify dopamine's functional role, three major interpretations are commonly discussed: dopamine as a mediator of "liking" (hedonic pleasure), "learning" (reward prediction and updating), or "wanting" (incentive salience). The manuscript argues that available data align most strongly with the incentive-salience ("wanting") model. Consistent with this, neuroimaging work indicates that drugs, highly palatable foods, and anticipatory

cues for activities such as sex or gaming can modulate reward circuitry in complex, sometimes bidirectional ways (Blum et al., 2021). Drugs of abuse, in particular, are described as amplifying dopaminergic signaling and sensitizing mesolimbic pathways, which intensifies reward-circuit responsivity and contributes to the subjective "high." Importantly, these networks are presented as encoding more than pleasure alone; they also support attention allocation, expectancy, and motivational salience.

Within the RDS framework, vulnerability is not purely genetic: elevated stress interacting with dopaminergic and other neurotransmitter variants is proposed to incrementally raise addiction risk. A key pathophysiologic claim is that diminished dopamine release in the nucleus accumbens is a central mechanism linking diverse chemical and behavioral addictions. In turn, multiple lines of work associated with NIDA and NIAAA are cited in support of dopamine homeostasis as a therapeutic endpoint shaped by both inherited factors and epigenetic state (Blum et al., 2017a; Febo et al., 2017).

ANTI-REWARD SYMPTOMOLOGY

Converging evidence suggests that both chronic pain processes and compulsive drug seeking are influenced by allostatic adaptations across reward and stress circuitry. In this model, reward deficiency (RD) is framed as an intra-system adaptation: persistent activation of reward pathways during prolonged drug seeking culminates in a depletion-like hypodopaminergic condition, clinically expressed as anhedonia and reduced motivation for natural reinforcers. By contrast, anti-reward (AR) is described as an inter-system adaptation driven by excessive recruitment of limbic and stress-related structures—including the basolateral and central amygdala, noradrenergic nuclei in the brainstem (lateral tegmental region), the bed nucleus of the stria terminalis, hippocampus, and habenula. This overactivation is linked to high output of stress neurochemicals (e.g., norepinephrine, corticotropin-releasing factor, vasopressin, hypocretin, and substance P), producing aversive affective states such as anxiety, fear, and depression.

Borsook et al. (2016) integrated these processes into the Combined Reward Deficiency and Anti-reward Model (CReAM), proposing that biological, psychological, and social influences on reward, motivation, and stress systems can interact as a self-reinforcing "downward spiral." In this view, the same interacting variables can worsen chronic pain persistence (pain chronification) and intensify both drug-seeking and non-drug reinforcement seeking.

Twin and longitudinal evidence is cited to support an approximately even contribution of inherited factors and environment/epigenetics to human behavioral outcomes—often summarized as ~50% genetic and ~50% epigenetic influence—particularly in alcohol use disorder (Verhulst et al., 2015; Long et al., 2017). Consequently, molecular genetic approaches, including DNA testing, are positioned as relevant tools for connecting maladaptive behavior patterns to individual neurobiological liability. Blum et al. (2012a) further proposed that disruption at any point along the Brain Reward Cascade—whether due to polymorphisms, environmental exposures, or their interaction—can manifest as a spectrum of RDS-linked behaviors.

Although large-scale efforts using dense SNP arrays have sometimes produced weakly replicable single-gene findings, newer analyses suggest that a meaningful fraction of

variance in generalized vulnerability to substance dependence may be attributable to common SNP effects—estimated at roughly 25–36%—with additive contributions that overlap across comorbid conditions (Palmer et al., 2015). The manuscript also emphasizes the forward-looking value of certain variants for risk estimation. Using a Bayesian framework, Blum's laboratory (1995a) reported a Positive Predictive Value (PPV) of 74% for the DRD2 A1 allele with respect to later addictive behaviors, indicating a substantially elevated lifetime risk among carriers. Since the initial 1990 report linking DRD2 TaqA1 to severe alcoholism, multiple groups—including investigators affiliated with NIDA and NIAAA—have replicated and expanded the broader reward-gene landscape, identifying additional candidate loci and second-messenger genes relevant to addiction biology (Reilly et al., 2017). More recently, GWAS work from Gentner's group on suicidal thoughts and behaviors (SITB) highlighted cross-ancestry candidate genes that include ESR1, DRD2, TRAF3, and DCC (Kimbrel et al., 2023).

CURRENT SUBSTANCE USE DISORDER (SUD) STATISTICS

In 2023, an estimated 47.7 million Americans aged 12 years and older were current illegal drug users (use within the prior 30 days). Additional reported indicators include:

- 16.8% of individuals aged 12+ used drugs in the past month (a 1.9% year-over-year increase).
- 70.5 million people (24.9% of those aged 12+) used illicit drugs or misused prescription drugs within the past year.
- 145.1 million individuals aged 12+ reported lifetime illicit drug use.
- Overall use among those aged 12+ increased by 0.3% year-over-year.
- 134.7 million Americans aged 12+ consumed alcohol in the past month.
- 28.9 million people (21.5% of past-month drinkers) met criteria for an alcohol use disorder.
- 64.4 million used tobacco products or nicotine vaping products in the past month.
- 38.6% of illegal drug users had a drug disorder.
- 21.6% of those with drug disorders had an opioid disorder (including prescription pain relievers and heroin).

Substance Usage Rates per Age Group in 2023		
Prescription stimulants	0.9%	1.4%
LSD	1.0%	11.6%
Cocaine	0.2%	1.9%
Prescription sedatives	0.3%	0.4%
Methamphetamines	0.2%	1.0%
Heroin	0.1%	2.4%

Drug Abuse Demographics

Population-level patterns indicate that substance misuse and substance use disorders disproportionately affect younger males. Reported past-month use of illegal drugs or misuse of prescription drugs averages 19.1% in males versus 14.6% in females. Geographic differences are also noted: 22.4% of individuals in non-metropolitan (rural) countiesreported use compared with 25.3% in larger metropolitan counties. By age, prevalence is highest in 18–25-year-olds (39%), while those 26 and older report lower rates (23.9%). Early initiation is highlighted as a major risk amplifier: individuals who first try an illegal drug before age 15 are reported to be 6.5 times more likely to develop a substance use disorder than those who delay until age 21 or later. Adolescent exposure is also substantial—36.8% report illegal drug use by 12th grade—with past-30-day use estimates of 5.4% in 8th graders, 10.0% in 10th graders, and 16.5%in 12th graders.

Opioid Abuse

The Centers for Medicare & Medicaid Services (CMS) expanded Medicare coverage to include opioid treatment programs providing medication-assisted treatment (MAT), with implementation effective January 1, 2020. In terms of prevalence, 8.9 million Americans aged 12+ (3.4%) are reported to misuse opioids at least once within a 12-month period. Misuse rates are described as relatively stable from 2021–2023, at roughly 3.2% among those aged 12+. Approximately 5.9 million individuals (2.1% of those 12+) meet criteria for an opioid use disorder. Most opioid misuse involves prescription products: 5.3 million people (90.0% of opioid misusers) use prescription pain relievers. Heroin involvement is reported in 660,000 individuals (7.4% of opioid misusers), while 336,000 (3.8%) use both heroin and prescription opioids. Hydrocodone is identified as the most commonly misused prescription opioid, with 3.6 millionmisusers.

Duration of exposure is emphasized as a key risk factor: using opioids longer than 3 months is stated to increase addiction risk 15-fold, while most acute pain situations are described as requiring roughly 7 days of medication. Prescribing trends are summarized as follows: opioid dispensing peaked in 2012 at >255 million prescriptions (about 81.3 prescriptions per 100 persons). In 2015, prescribing volume is characterized as high enough that it would equate to dosing every American “around the clock” (e.g., 5 mg hydrocodone every 4 hours) for 3 weeks. By 2018, the national rate declined to 51.4 prescriptions per 100 persons. Even so, 3.6% of U.S. counties are reported to still dispense enough opioid prescriptions for every resident to receive one.Sources of nonmedical opioids are also noted: in 2023, 39.1% of Americans reportedly obtained illegal pain medication from a friend or relative. Global production figures are included as contextual risk indicators: between 2016 and 2017, global opium production reportedly increased 65% to 10,500 tons; in Afghanistan, output reached 9,000 tons/year (87% increase), and >75% of global opium poppy cultivation is stated to occur there.

Poison control data are cited to reflect exposure burden. In 2018, the most frequently reported substance exposure category is described as illegal or misused prescription opioids, totaling nearly 284,000 exposure cases. Of these, 44% involved children under age 5. The report also notes 5,300 cases involving heroin and fentanyl exposures. Additional trends include a 148% increase (over 7 years) in marijuana exposures among children under 5, and a 93%annual increase (over 9 years) in prescription-opioid exposures.

SUMMARY

Reward Deficiency Syndrome (RDS) is framed as a unifying construct spanning both substance-related and behavioral addictions, yet the manuscript highlights the U.S. opioid crisis as an especially urgent manifestation of this broader vulnerability. The argument is that positioning opioids as third-line or tertiary solutions—without parallel strategies aimed at restoring neurochemical balance—creates conditions for recurring relapse and repeated treatment failure. From this viewpoint, critiques of the addiction disease model are considered incomplete because they focus narrowly on specific disorders (e.g., opioid use disorder) rather than addressing shared neurobiological drivers across addictions, including non-substance behavioral forms. RDS is presented as a scientific basis for developing non-addictive interventions tailored to genetic susceptibility, with dopamine homeostasis as a primary therapeutic goal. Although opioids receive disproportionate policy attention, the manuscript emphasizes that cross-addiction risk is high; therefore, earlier identification of addiction vulnerability across behaviors is portrayed as essential for reducing long-term population burden.

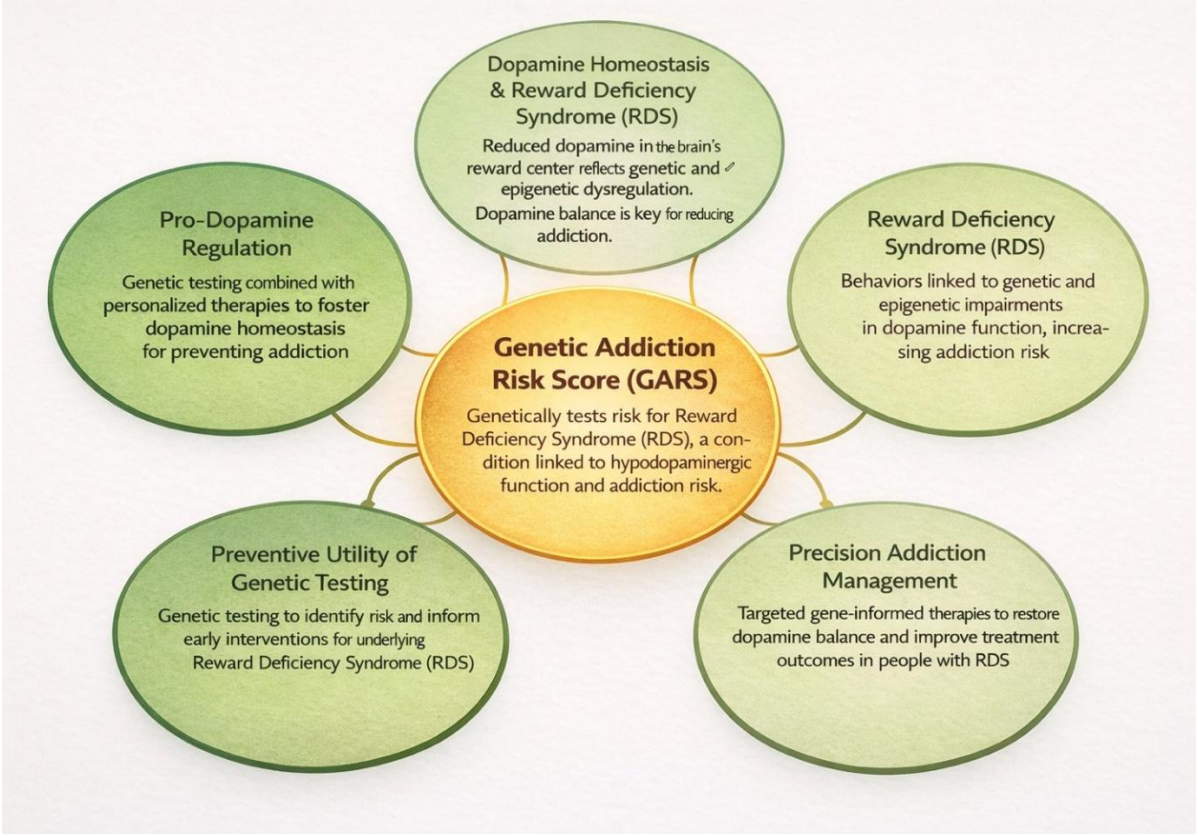

Figure 6: Conceptual framework linking Genetic Addiction Risk Score (GARS), Reward Deficiency Syndrome (RDS), and Precision Addiction Management. This schematic illustrates GARS as the central genomic tool for identifying inherited vulnerability to Reward Deficiency Syndrome (RDS), a hypodopaminergic condition arising from genetic and epigenetic dysregulation within the brain's reward circuitry. Reduced dopamine signaling in the reward center is shown as a core biological substrate underlying increased risk for addictive, compulsive, and impulsive behaviors. Surrounding domains highlight the translational applications of this framework, including (i) the

preventive utility of genetic testing for early risk stratification, (ii) pro-dopamine regulation strategies designed to restore dopamine homeostasis, and (iii) precision addiction management approaches that integrate gene-informed interventions to improve clinical outcomes. Together, the figure emphasizes dopamine homeostasis as a unifying therapeutic target and positions GARS-guided strategies as a foundation for early detection, prevention, and personalized treatment of RDS-related behaviors.

Finally, the manuscript argues that systematic early risk stratification has historically been limited, and proposes Precision Behavioral Management (PBM) / Precision Addiction Management (PAM) as a framework that integrates genetic testing with pro-dopamine regulation as a frontline, gene-guided approach for early detection of RDS behaviors. The authors contend that overlooking brain circuitry—particularly net dopamine output in reward centers—undermines public health goals aimed at reducing addiction-related harm (Mathews et al., 2017). The following disease model of both drug and non-drug behaviors supported by a plethora of thousands of peer review studies is represented in Figure 6

In addition, the manuscript argues that several psychiatric and cardiometabolic problems—such as overeating, obesity, type 2 diabetes, and metabolic syndrome—overlap at the level of reward biology, with dopaminergic polymorphisms frequently implicated. This convergence is used to position **food reward** as an important dimension of RDS. Individuals with reduced serotonergic and/or dopaminergic receptor function, or with comparatively high COMT activity, are described as being more likely to "self-correct" low reward tone not only through substances but also through highly palatable foods rich in refined carbohydrates and fats. From this standpoint, interventions that re-establish hedonostatic balance by improving dopaminergic signaling could plausibly support both sustained addiction recovery and better metabolic outcomes.

Finally, while DSM-5 and ICD-11 maintain a categorical split between substance-related disorders and behavioral addictions, the manuscript emphasizes that convergent neurogenetic and neuroimaging findings are more consistent with a shared hypodopaminergic substrate. RDS is offered as an integrative construct that prioritizes earlier identification of risk, preventive strategies, and restoration of dopamine homeostasis using precision approaches. Although RDS is not a formal diagnostic category, it is portrayed as compatible with dimensional frameworks such as RDoC and HiTOP and as a translational bridge that could inform future nosology, clinical pathways, and policy. In this sense, RDS is positioned less as a standalone diagnosis and more as a practical framework that moves beyond DSM-style boundaries toward early detection, prevention, and dopamine homeostasis.

POLICY STATEMENT AND IMPLICATIONS: TOWARD A BIOLOGICALLY INFORMED FRAMEWORK FOR ADDICTION VULNERABILITY

Current diagnostic and treatment paradigms for addiction remain largely reactive, substance-specific, and behaviorally descriptive. While these approaches have supported standardization of care and reimbursement, they are limited in their capacity to predict vulnerability, guide prevention, or account for the convergent neurobiological mechanisms shared across substance-related and behavioral addictions. Continued reliance on

categorical distinctions that separate substance use disorders from behavioral addictions is increasingly discordant with evidence from neurogenetics, neuroimaging, pharmacogenomics, and systems neuroscience demonstrating a common disruption of reward circuitry—most consistently characterized by hypodopaminergic signaling—across compulsive, impulsive, and addictive phenotypes.

Reward Deficiency Syndrome (RDS) offers a biologically grounded, unifying construct that aligns with contemporary dimensional models of psychopathology, including RDoC and HiTOP. Rather than proposing a replacement for existing diagnostic categories, RDS conceptualizes addiction vulnerability as an upstream neurobiological state that may precede, coexist with, and shape the expression and clinical trajectory of multiple downstream diagnoses. In this framework, observed addictive or compulsive behaviors represent phenotypic manifestations of a shared reward-system liability, modulated by genetic variation, epigenetic state, and environmental stressors.

From a policy perspective, this reconceptualization supports a shift toward earlier identification of vulnerability, prevention-oriented strategies, and precision-guided intervention. Integration of validated genetic and psychosocial risk-stratification tools—such as the Genetic Addiction Risk Severity (GARS) test—into clinical, public-health, and, where appropriate, rehabilitative or judicial contexts may help inform individualized care planning and longitudinal monitoring. These tools are not proposed as diagnostic determinants, but as adjunctive instruments that support prevention, risk mitigation, and treatment personalization within precision-medicine paradigms.

Health systems and payers should recognize that addiction risk is not solely a function of substance exposure, availability, or behavioral choice, but reflects a dynamic interaction between inherited neurobiological traits and environmental, social, and psychosocial stressors. Policies that focus exclusively on downstream harm reduction or symptom suppression—without addressing underlying reward-circuit dysregulation—risk perpetuating cycles of relapse, cross-addiction, treatment failure, and escalating healthcare utilization. In contrast, mechanism-informed approaches aimed at restoring reward-system balance and functional regulation offer a rational pathway to improving long-term outcomes and reducing population-level burden.

At a regulatory and public-health level, the continued separation of behavioral addictions from substance use disorders in coverage determinations, treatment authorization, research prioritization, and prevention policy is increasingly difficult to justify. A biologically informed RDS framework supports parity across addictive and compulsive phenotypes—including alcohol, opioids, stimulants, gambling, overeating, and digitally mediated behaviors—particularly with respect to screening, early intervention, and prevention-focused care.

Importantly, the policy relevance of RDS does not depend on the immediate creation of a new psychiatric diagnosis. The International Classification of Diseases (ICD) already provides mechanisms for documenting risk states, susceptibility conditions, and factors influencing health. From a systems perspective, the absence of a standardized method to document reward-system vulnerability represents a meaningful gap. Clinicians frequently encounter individuals whose clinical trajectories are shaped by impaired reward signaling, yet lack a consistent, non-stigmatizing means of capturing this vulnerability without forcing categorical psychiatric labels or duplicating existing diagnoses.

Accordingly, consideration of ICD-concordant documentation pathways—analogous to existing codes used to capture risk conditions or health-influencing factors—may provide a pragmatic entry point for policy implementation. Standardized documentation of reward-dysregulation vulnerability would facilitate population-level surveillance, cross-national research harmonization, outcomes analysis, and prevention-focused policy development across addiction, mental health, pain, and behavioral health domains. In this respect, ICD-aligned approaches offer a practical bridge between neuroscience, clinical practice, and public-health governance, enabling engagement by national and international health authorities without premature nosological revision. Taken together, these considerations support policies that:

1. promote early identification of neurobiological and genetic vulnerability factors;
2. prioritize research, reimbursement, and regulatory models that emphasize restoration of reward-system balance and functional regulation;
3. integrate addiction biology into rehabilitative, social, and judicial frameworks where appropriate; and
4. align diagnostic and public-health strategies with dimensional, mechanism-based models of addiction vulnerability consistent with contemporary international health policy trends.

Reward Deficiency Syndrome is not advanced as a formal diagnostic replacement, but as a translational scaffold capable of informing prevention strategies, precision-based interventions, and future refinement of classification systems. Positioned between neuroscience and policy, RDS provides a biologically coherent framework that extends beyond the constraints of current categorical models and supports a more predictive, preventive, and personalized approach to addiction and behavioral health.

CONCLUSION

Alcohol use disorder and other substance-related conditions often appear alongside additional RDS-spectrum behaviors, consistent with a shared substrate of diminished dopamine signaling within reward circuitry. In this view, Reward Deficiency Syndrome (RDS) functions as an integrative model that links addiction with compulsive, obsessive, and impulsive behavioral patterns through common neurobiology. The manuscript highlights the scale of the U.S. opioid problem, noting that more than 2 million people have opioid use disorder associated with prescription opioids and that the combined financial impact of licit and illicit opioids exceeds $1 trillion. Although opioid replacement therapy is the most widely used treatment, persistent relapse can lead to repeated cycles of the same interventions rather than durable recovery. The authors further argue that non-opioid strategies can outperform long-term opioid use in relevant chronic-pain contexts. They also cite evidence indicating that alcohol or drug involvement is present in more than half of suicide deaths.

To strengthen recovery, the manuscript emphasizes adjunctive supports—such as fellowship participation, spiritually oriented resources, and nutrigenomic approaches including KB220Z—proposed to influence gene expression, recalibrate neurotransmitter

balance, and improve functional connectivity within dopaminergic networks. KB220Z is described as enhancing connectivity among key reward-related regions, attenuating RDS-associated behaviors, and lowering relapse rates in DUI offender populations. Finally, combining Genetic Addiction Risk Severity (GARS) assessment with semi-customized KB220Z supplementation is presented as a practical method for promoting dopamine homeostasis. On this basis, the authors argue that RDS may provide a more biologically coherent framework than DSM-5 categories for explaining how the brain governs addictive, compulsive, and impulsive behaviors.

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Conflict of Interest

KB owns patents linked to both gars and KB220Z

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Author Contribution

KB developed the initial manuscript followed by editions by KUL,MPL,MSG, AB. The second draft of the manuscript was edited by KM, AS, PKT, RDB, AB EJM. The reference section was developed by SM and YM. The entire manuscript was checked for similarity to other reports in the literature CAD, AKR, DES, DB,SLS, RKAF. The entire manuscript was vetted by ML, AD,RD,JPB,APLL. All authors approved the final manuscript.

REFERENCES

Alonso SJ, Navarro E, Rodriguez M. Permanent dopaminergic alterations in the n. accumbens after prenatal stress. Pharmacol Biochem Behav. 1994 Oct; 49(2):353-8.

Amie L. Severino, Arash Shadfar, Joshua K. Hakimian, Oliver Crane, Ganeev Singh, Keith Heinzerling, Wendy M. Walwyn. Pain Therapy Guided by Purpose and Perspective in Light of the Opioid Epidemic Front Psychiatry. 2018; 9: 119. Published online 2018 Apr 23. doi: 10.3389/fpsyt.2018.00119

Anna M.W. Taylor, Susanne Becker, Petra Schweinhardt, Catherine Cahill. Mesolimbic dopamine signaling in acute and chronic pain: implications for motivation, analgesia, and addiction Pain. 2016 Jun; 157(6): 1194–1198. Published online 2016 Jan 19. doi: 10.1097/j.pain.0000000000000494PMC486658

Archer T, Marlene Oscar-Berman, Kenneth Blum, Mark Gold Neurogenetics and Epigenetics in Impulsive Behaviour: Impact on Reward CircuitryJ Genet Syndr Gene Ther. Author manuscript; available in PMC 2012 Dec 19.Published in final edited form as: J Genet Syndr Gene Ther. 2012 May 30; 3(3): 1000115. Published online 2012 May 30. doi: 10.4172/2157-7412.1000115

Barh,D María E. García-Solano, Sandeep Tiwari, Antaripa Bhattacharya, Neha Jain, Daniel Torres-Moreno, Belén Ferri, Artur Silva, Vasco Azevedo, Preetam Ghosh, Kenneth Blum, Pablo Conesa-

Zamora, George Perry BARHL1 Is Downregulated in Alzheimer's Disease and May Regulate Cognitive Functions through ESR1 and Multiple Pathways Genes (Basel) 2017 Oct; 8(10): 245. Published online 2017 Sep 28. doi: 10.3390/genes8100245

Baron D, Blum K, Chen A, Gold M, Badgaiyan RD. Conceptualizing Addiction From an Osteopathic Perspective: Dopamine Homeostasis. J Am Osteopath Assoc. 2018 Feb 1;118(2):115-118. doi: 10.7556/jaoa.2018.026.

Belcher AM, Volkow ND, Moeller FG, Ferré S. Personality traits and vulnerability or resilience to substance use disorders. Trends Cogn Sci. 2014;18(4):211–217. [PMC free article] [PubMed] [Google Scholar]

Blum K (with James Payne) "Alcohol & the Addictive Brain" (1991) The Free Press, New York, NY.

Blum K, Braverman ER, Sharafshah A, Elman I, Lewandrowski KU, Bowirrat A, Pinhasov A, Thanos PK, Gold MS, Dennen CA, Modestino EJ, Badgaiyan RD, Baron D, Fuehrlein B, Sipple D, Ashford JW, Sunder K, Makale M, Murphy K, Jafari N, Zeine F, Pollack AR, Lewandrowski APL, Khalsa J. Exploring dopamine as the master regulator of brain circuitry and mental health genome. Gene Protein Dis. 2025 Jun 3;5:10.36922/gpd.6557. doi: 10.36922/gpd.6557. PMID: 40746483; PMCID: PMC12311831

Blum K, Briggs AH, DeLallo L, Elston SF, Ochoa R. Whole brain methionine-enkephalin of ethanol-avoiding and ethanol-preferring c57BL mice. Experentia, 1982 Dec 15; 38(12):1469-70.

Blum K, Briggs AH, Elston SF, DeLallo L, Sheridan PJ, Sar M. Reduced leucine-enkephalin--like immunoreactive substance in hamster basal ganglia after long-term ethanol exposure. Science. 1982 Jun 25;216(4553):1425-7. doi: 10.1126/science.7089531. PMID: 7089531.

Blum K, Briggs AH, Elston SF, DeLallo L, Sheridan PJ, Sar M. Reduced leucine-enkephalin--like immunoreactive substance in hamster basal ganglia after long-term ethanol exposure. Science. 1982;216:1425–1427. [PubMed] [Google Scholar]

Blum K, Briggs AH, Elston SF, DeLallo L, Sheridan PJ, Sar M. Reduced leucine-enkephalin--like immunoreactive substance in hamster basal ganglia after long-term ethanol exposure. Science. 1982 Jun 25;216(4553):1425-7. doi:

Blum K, Briggs AH, Trachtenberg MC, Delallo L, Wallace JE, Enkephalinase inhibition: regulation of ethanol intake in genetically predisposed mice. Alcohol. 1987 Nov-Dec;4(6):449-56.).

Blum K, Chen AL, Oscar-Berman M, Chen TJ, Lubar J, White N, Lubar J, Bowirrat A, Braverman E, Schoolfield J, Waite RL, Downs BW, Madigan M, Comings DE, Davis C, Kerner MM, Knopf J, Palomo T, Giordano JJ, Morse SA, Fornari F, Barh D, Femino J, Bailey JA. Generational association studies of dopaminergic genes in reward deficiency syndrome (RDS) subjects: selecting appropriate phenotypes for reward dependence behaviors. *Int J Environ Res Public Health*. 2011a Dec;8(12):4425-59. doi: 10.3390/ijerph8124425. Epub 2011 Nov 29. PubMed PMID: 22408582; PubMed Central PMCID: PMC3290972.

Blum K, Chen ALC, Thanos PK, Febo M, Demetrovics Z, Dushaj K, Kovoor A, Baron D, Smith DE, Roy AK III, Fried L, Chen TJH, Chapman E Sr, Modestino EJ, Steinberg B, Badgaiyan RD. Genetic addiction risk score (GARS) ™, a predictor of vulnerability to opioid dependence. Front Biosci (Elite Ed). 2018c Jan 1;10:175-196. Review. PMID: 28930612

Blum K, Elston SF, DeLallo L, Briggs AH, Wallace JE. Ethanol acceptance as a function of genotype amounts of brain [Met]enkephalin. Proc Natl Acad Sci U S A. 1983 Nov;80(21):6510-2.

Blum K, Gardner E, Oscar-Berman M, Gold M. "Liking" and "wanting" linked to Reward Deficiency Syndrome (RDS): hypothesizing differential responsivity in brain reward circuitry. *Curr Pharm Des*. 2012b;18(1):113-8. PubMed PMID: 22236117; PubMed Central PMCID: PMC3651846.

Blum K, Gold M, Demetrovics Z, Archer T, Thanos PK, Baron D, Badgaiyan RD. Substance use disorder a bio-directional subset of reward deficiency syndrome. Front Biosci (Landmark Ed). 2017 Jun 1;22:1534-1548. doi: 10.2741/4557. PMID: 28410131.

Blum, K., Khalsa, J., Cadet, J. L., Baron, D., Bowirrat, A., Boyett, B., ... & Gold, M. S. (2021). Cannabis-induced hypodopaminergic anhedonia and cognitive decline in humans: embracing putative induction of dopamine homeostasis. Frontiers in Psychiatry, 12, 623403.

Blum K, Lott L, Baron D, Smith DE, Badgaiyan RD, Gold MS. Improving naltrexone compliance and outcomes with putative pro- dopamine regulator KB220, compared to treatment as usual. J Syst Integr Neurosci. 2020 May 30;7:10.15761/JSIN.1000229. doi: 10.15761/JSIN.1000229. PMID: 32934823; PMCID: PMC7489288.

Blum K, Marcelo Febo, Lyle Fried, Mona Li, Kristina Dushaj, Eric R. Braverman, Thomas McLaughlin, Bruce Steinberg, Rajendra D. Badgaiyan. Hypothesizing That Neuropharmacological and Neuroimaging Studies of Glutaminergic-Dopaminergic Optimization Complex (KB220Z) Are Associated With “Dopamine Homeostasis” in Reward Deficiency Syndrome (RDS) Subst Use Misuse. 2017b Mar 21; 52(4): 535–547. Published online 2016 Dec 29. doi: 10.1080/10826084.2016.1244551 PMC5589271

Blum K, Marcelo Febo, Rajendra D. Badgaiyan, Zsolt Demetrovics, Thomas Simpatico, Claudia Fahlke, Oscar-Berman M, Mona Li, Kristina Dushaj, Mark S. Gold. Common Neurogenetic Diagnosis and Meso-Limbic Manipulation of Hypodopaminergic Function in Reward Deficiency Syndrome (RDS): Changing the Recovery Landscape. Curr Neuropharmacol. 2017a Jan; 15(1): 184–194. Published online 2017 Jan. doi: 10.2174/1570159X13666160512150918

Blum K, Marlene Oscar-Berman, Abdalla Bowirrat, John Giordano, Margaret Madigan, Eric R. Braverman, Debmayla Barh, Mary Hauser, Joan Borsten, Thomas Simpatico. Neuropsychiatric Genetics of Happiness, Friendships, and Politics: Hypothesizing Homophily (“Birds of a Feather Flock Together”) as a Function of Reward Gene Polymorphisms J Genet Syndr Gene Ther. Author manuscript; available in PMC 2013 Jan 17.

Blum K, Marlene Oscar-Berman, Zsolt Demetrovics, Debmalya Barh, Mark S. Gold. Genetic Addiction Risk Score (GARS): Molecular Neurogenetic Evidence for Predisposition to Reward Deficiency Syndrome (RDS)Mol Neurobiol. 2014a; 50(3): 765–796. Published online 2014 May 31. doi: 10.1007/s12035-014-8726-5 PMC4225054

Blum K, Merritt JH, Reiter RJ, Wallace JE. A possible relationship between the pineal gland and ethanol preference in the rat. Curr Ther Res Clin Exp. 1973 Jan;15(1):25-30. PMID: 4631379.

Blum K, Noble EP, Sheridan PJ, Montgomery A, Ritchie T, Jagadeeswaran P, Nogami H, Briggs AH, Cohn JB. Allelic association of human dopamine D2 receptor gene in alcoholism. JAMA. 1990 Apr 18;263(15):2055-60. PMID: 1969501.

Blum K, Thompson B, Demotrovics Z, Femino J, Giordano J, Oscar-Berman M, Teitelbaum S, Smith DE, Roy AK, Agan G, Fratantonio J, Badgaiyan RD, Gold MS. The Molecular Neurobiology of Twelve Steps Program & Fellowship: Connecting the Dots for Recovery. J Reward Defic Syndr. 2015;1(1):46-64. doi: 10.17756/jrds.2015-008. PMID: 26306329; PMCID: PMC4545669.

Blum K, Topel H. Opioid peptides and alcoholism: genetic deficiency and chemical management. Funct Neurol. 1986 Jan-Mar;1(1):71-83. PMID: 2956168.

Blum K, Trachtenberg MC, Elliott CE, Dingler ML, Sexton RL, Samuels AI, Cataldie L. Enkephalinase inhibition and precursor amino acid loading improves inpatient treatment of alcohol and polydrug abusers: double-blind placebo-controlled study of the nutritional adjunct SAAVE. Alcohol. 1988 Nov-Dec;5(6):481-93. doi: 10.1016/0741-8329(88)90087-0. PMID: 3072969.

Blum K, Wallace JE, Briggs AH, Trachtenberg MC. Evidence for the importance of the "genotype" theory in alcohol seeking behavior: a commentary. Alcohol Drug Res. 1985-1986;6(6):455-61.

Blum K, Han D, Hauser M, Downs BW, Giordano J, Borsten J, Winchell E, Simpatico T, Madigan MA, Barh D. [2013a]. Neurogenetic Impairments of Brain Reward Circuitry Links to Reward Deficiency Syndrome (RDS) as evidenced by Genetic Addiction Risk Score (GARS): A case study. The IIOAB Journal. 4 (1): 4-9.

Blum, K Edward J Modestino, Jennifer Neary, Marjorie C Gondré-Lewis, David Siwicki, Mark Moran, Mary Hauser, Eric R Braverman, David Baron, Bruce Steinberg, Thomas Mc Laughlin, Rajendra D Badgaiyan Promoting Precision Addiction Management (PAM) to Combat the Global Opioid Crisis. Biomed J Sci Tech Res. 2018a Jan 7; 2(2): 1–4. doi: 10.26717/BJSTR.2018.02.000738

Blum, K Marcelo Febo, Panayotis K. Thanos, David Baron, James Fratantonio, Mark Gold Clinically Combating Reward Deficiency Syndrome (RDS) with Dopamine Agonist Therapy as a Paradigm Shift: Dopamine for Dinner? Mol Neurobiol. 2015a; 52(3): 1862–1869. Published online 2015 Mar 10. doi: 10.1007/s12035-015-9110-9

Blum, K W. Jacobs, E.J. Modestino, N. DiNubile, D. Baron, T. McLaughlin, D. Siwicki, I. Elman, M. Moran, E. R. Braverman, P. K. Thanos, R. D. Badgaiyan. Insurance Companies Fighting the Peer Review Empire without any Validity: the Case for Addiction and Pain Modalities in the face of an American Drug Epidemic SEJ Surg Pain. 2018b Oct 4; 1(1): 1–11. PMC5998670

Blum, K., Febo, M., & Badgaiyan, R. D. (2016a). Fifty Years in the Development of a Glutaminergic-Dopaminergic Optimization Complex (KB220) to Balance Brain Reward Circuitry in Reward Deficiency Syndrome: A Pictorial. *Austin addiction sciences*, *1*(2), 1006.

Blum, K., Febo, M., McLaughlin, T., Cronjé, F. J., Han, D., & Gold, S. M. (2014a). Hatching the behavioral addiction egg: Reward Deficiency Solution System (RDSS)™ as a function of dopaminergic neurogenetics and brain functional connectivity linking all addictions under a common rubric. *Journal of behavioral addictions*, *3*(3), 149–156. doi:10.1556/JBA.3.2014.019

Blum, K., Modestino, E. J., Gondre-Lewis, M., Chapman, E. J., Neary, J., Siwicki, D., … Badgaiyan, R. D. (2018d). The Benefits of Genetic Addiction Risk Score (GARS™) Testing in Substance Use Disorder (SUD). *International journal of genomics and data mining*, *2018* (1), 115. doi:10.29014/IJGD-115.000015

Blum, K., Sheridan. P.J., Wood, R.C., Braverman, E.R., Chen, T.J.H.and Comings, D.E. Dopamine D_2 receptor gene variants: association and linkage studies in impulsive-addictive-compulsive behavior. Pharmacogenetics 5:121-141, 1995a

Blum, K., Wood, R.C., Braverman, E.P., Chen, T.J.H. and Sheridan, P.J. D2 dopamine receptor gene as a predictor of compulsive disease: Bayes' theorem. Functional Neurology: 10(1):37-44, 1995b.

Borg J, Andrée B, Soderstrom H, Farde L. The serotonin system and spiritual experiences. Am J Psychiatry. 2003;160(11):1965–1969. [PubMed] [Google Scholar]

Borsook D, Linnman C, Faria V, Strassman AM, Becerra L, Elman I. Reward deficiency and anti-reward in pain chronification. Neurosci Biobehav Rev. 2016 Sep;68:282-297. doi: 10.1016/j.neubiorev.2016.05.033. Epub 2016 May 28. PMID: 27246519.

Boundy VA, Pacheco MA, Guan W, Molinoff PB. Agonists and antagonists differentially regulate the high affinity state of the D2L receptor in human embryonic kidney 293 cells. Mol Pharmacol. 1995 Nov;48(5):956-64. PMID: 7476927

Brefczynski-Lewis JA, Lutz A, Schaefer HS, Levinson DB, Davidson RJ. Neural correlates of attentional expertise in long-term meditation practitioners. Proc Natl Acad Sci U S A. 2007;104(27):11483–11488. [PMC free article] [PubMed] [Google Scholar]

Campbell JC, Szumlinski KK, Kippin TE. Contribution of early environmental stress to alcoholism vulnerability. Alcohol. 2009 Nov;43(7):547-54..)

Chafetz M Alcoholism report draws overreaction. Rochester Democrat and Chronicle, Sunday, August, 15, 1986

Chen AL, Blum K, Chen TJ, Giordano J, Downs BW, Han D, Barh D, Braverman ER. Correlation of the Taq1 dopamine D2 receptor gene and percent body fat in obese and screened control subjects: a preliminary report. Food Funct. 2012 Jan;3(1):40-8. doi: 10.1039/c1fo10089k. Epub 2011 Nov 3.

Chen TJ, Blum K, Mathews D, Fisher L, Schnautz N, Braverman ER, Schoolfield J, Downs BW, Comings DE. Are dopaminergic genes involved in a predisposition to pathological aggression? Hypothesizing the importance of "super normal controls" in psychiatricgenetic research of complex behavioral disorders. Med Hypotheses. 2005;65(4):703-7.

Chen, A. L., Chen, T. J., Waite, R. L., Reinking, J., Tung, H. L., Rhoades, P., … Blum, K. (2009). Hypothesizing that brain reward circuitry genes are genetic antecedents of pain sensitivity and critical diagnostic and pharmacogenomic treatment targets for chronic pain conditions. *Medical hypotheses*, *72*(1), 14–22. doi:10.1016/j.mehy.2008.07.059

Comings DE, MacMurray J, Johnson P, Dietz G, Muhleman D. Dopamine D2 receptor gene (DRD2) haplotypes and the defense style questionnaire in substance abuse, Tourette syndrome, and controls. Biol Psychiatry. 1995 Jun 1;37(11):798-805.

Davies DL. Normal drinking in recovered alcohol addicts. Q J Stud Alcohol. 1962 Mar; 23:94-104. PMID: 13883819.

Diagnostic and statistical manual of mental disorders: DSM-5 (5 ed.). Washington, DC: American Psychiatric Association. 2013. pp. 490–97. ISBN 978-0-89042-554-1.

Diamond I, Nagy L, Mochly-Rosen D, Gordon A. The role of adenosine and adenosine transport in ethanol-induced cellular tolerance and dependence. Possible biologic and genetic markers of alcoholism. Ann N Y Acad Sci. 1991;625:473-87. doi: 10.1111/j.1749-6632.1991.tb33878.x. PMID: 2058901.

Edwards G. D.L. Davies and 'Normal drinking in recovered alcohol addicts': the genesis of a paper. Drug Alcohol Depend. 1994 Jun;35(3):249-59. doi: 10.1016/0376-8716(94)90082-5. PMID: 7956756.

Elston SF, Blum K, DeLallo L, Briggs AH. Ethanol intoxication as a function of genotype dependent responses in three inbred mice strains. Pharmacol Biochem Behav. 1982 Jan;16(1):13-5. doi: 10.1016/0091-3057(82)90005-3. PMID: 7199182.

Erol A, Karpyak VM. Sex and gender-related differences in alcohol use and its consequences: Contemporary knowledge and future research considerations. Drug Alcohol Depend. 2015 Nov 1;156:1-13. doi: 10.1016/j.drugalcdep.2015.08.023. Epub 2015 Sep 5. PMID: 26371405.

Febo M, Blum K, Badgaiyan RD, Baron D, Thanos PK, Colon-Perez LM, Demortrovics Z, Gold MS. Dopamine homeostasis: brain functional connectivity in reward deficiency syndrome. Front Biosci (Landmark Ed). 2017a Jan 1;22:669-691. doi: 10.2741/4509. PMID: 27814639.

Febo M, Blum K, Badgaiyan RD, Perez PD, Colon-Perez LM, Thanos PK, Ferris CF, Kulkarni P, Giordano J, Baron D, Gold MS. Enhanced functional connectivity and volume between cognitive and reward centers of naïve rodent brain produced by pro-dopaminergic agent KB220Z. PLoS One. 2017b Apr 26;12(4):e0174774. doi: 10.1371/journal.pone.0174774. PMID: 28445527; PMCID: PMC5405923.

Febo M, Blum K, Badgaiyan RD, Baron D, Thanos PK, Colon-Perez LM, Demortrovics Z, Gold MS (2017), Dopamine homeostasis: brain functional connectivity in reward deficiency syndrome. Front Biosci (Landmark Ed). 2017 Jan 1; 22:669-691.

Fingarette H. Alcoholism: the mythical disease. Public Interest. 1988;(91):3-22. PMID: 11617979.

Florence, C. S., Zhou, C., Luo, F., & Xu, L. (2016). The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013. *Medical care*, *54*(10), 901–906. doi:10.1097/MLR.0000000000000625

Fried L, Modestino EJ, Siwicki D, et al. Hypodopaminergia and "Precision Behavioral Management" (PBM): It is a Generational Family Affair. *Curr Pharm Biotechnol*. 2020;21(6):528-541. doi:10.2174/1389201021666191210112108

Gelernter J, O'Malley S, Risch N, Kranzler HR, Krystal J, Merikangas K, Kennedy JL, Kidd KK. No association between an allele at the D2 dopamine receptor gene (DRD2) and alcoholism. JAMA. 1991 Oct 2;266(13):1801-7.

Geller I. Ethanol preference in the rat as a function of photoperiod. Science. 1971 Jul 30;173(3995):456-9. doi: 10.1126/science.173.3995.456. PMID: 5557325.

Gold MS. The Role of Alcohol, Drugs, and Deaths of Despair in the U.S.'s Falling Life Expectancy. Mo Med. 2020 Mar-Apr;117(2):99-101. PMID: 32308224; PMCID: PMC7144704.

Gold MS, Blum K, Febo M, Baron D, Modestino EJ, Elman I, Badgaiyan RD. Molecular role of dopamine in anhedonia linked to reward deficiency syndrome (RDS) and anti- reward systems. Front Biosci (Schol Ed). 2018 Mar 1;10:309-325. doi: 10.2741/s518. PMID: 29293435.

Green R, Brewer R, Mullan, P., Floyd JB, Blum K. Genetic addiction tests convert Prison to treatment & rehabilitation: New hope for DWI offenders. SOBERWORD, 2021

Gressler LE, Martin BC, Hudson TJ, Painter JT. Relationship between concomitant benzodiazepine-opioid use and adverse outcomes among US veterans. Pain. 2018 Mar;159(3):451-459. doi: 10.1097/j.pain.0000000000001111.

Hack SP, Christie MJ. Adaptations in adenosine signaling in drug dependence: therapeutic implications. Crit Rev Neurobiol. 2003;15(3-4):235-74. doi: 10.1615/critrevneurobiol.v15.i34.30. PMID: 15248812.

Haile CN, Kosten TA, Kosten TR. Pharmacogenetic treatments for drug addiction: alcohol and opiates. Am J Drug Alcohol Abuse. 2008;34(4):355-81. doi: 10.1080/00952990802122564. Review. PMID: 18584566

Hamilton PJ, Nestler EJ. Epigenetics and addiction. Curr Opin Neurobiol. 2019 Dec;59:128-136. doi: 10.1016/j.conb.2019.05.005. Epub 2019 Jun 27. PMID: 31255844; PMCID: PMC6889055.

Han MH, Nestler EJ. Neural Substrates of Depression and Resilience. Neurotherapeutics. 2017 Jul;14(3):677-686. doi: 10.1007/s13311-017-0527-x. Review.

Heroux NA, Robinson-Drummer PA, Kawan M, Rosen JB, Stanton ME. Neonatal ethanol exposure impairs long-term context memory formation and prefrontal immediate early gene expression in adolescent rats. Behav Brain Res. 2019 Feb 1;359:386-395. doi: 10.1016/j.bbr.2018.11.018. Epub 2018 Nov 14. PMID: 30447241; PMCID: PMC6314039.

Higgins-Biddle JC, Babor TF (2018). "A review of the Alcohol Use Disorders Identification Test (AUDIT), AUDIT-C, and USAUDIT for screening in the United States: Past issues and future directions". The American Journal of Drug and Alcohol Abuse. 44 (6): 57 586. doi:10.1080/00952990.2018.1456545. PMC 6217805. PMID 29723083.

Höllt V, Haarmann I, Herz A. Long-term treatment of rats with morphine reduces the activity of messenger ribonucleic acid coding for the beta-endorphin/ACTH precursor in the intermediate pituitary. J Neurochem. 1981 Sep;37(3):619-26. doi: 10.1111/j.1471-4159. 1982 . tb12532.x. PMID: 6268751.

Hayek El. S, Allouch F, Razafsha M, Talih F, Gold MS, Wang KK, Kobeissy F. Traumatic brain injury and methamphetamine: A double-hit neurological insult. J Neurol Sci. 2020 Apr 15;411:116711. doi: 10.1016/j.jns.2020.116711. Epub 2020 Jan 30. PMID: 32035311.

Jellinek EM. Alcoholism, a genus and some of its species. Can Med Assoc J. 1960 dec 24;83(26):1341-5.

Kandel D, Kandel E. The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. Acta Paediatr. 2015 Feb;104(2):130-7. doi: 10.1111/apa.12851. Epub 2014 Dec 2. Review. PMID: 25377988

Karlsson H, Hirvonen J, Salminen JK, Hietala J. No association between serotonin 5-HT 1A receptors and spirituality among patients with major depressive disorders or healthy volunteers. Mol Psychiatry. 2011;16(3):282–285. [PubMed] [Google Scholar]

Kelly JF, Humphreys K, Ferri M. Alcoholics Anonymous and other 12-step programs for alcohol use disorder. Cochrane Database Syst Rev. 2020 Mar 11;3(3):CD012880. doi: 10.1002/14651858.CD012880.pub2. PMID: 32159228; PMCID: PMC7065341.

Kimbrel NA, Ashley-Koch AE, Qin XJ, Lindquist JH, Garrett ME, Dennis MF, Hair LP, Huffman JE, Jacobson DA, Madduri RK, Trafton JA, Coon H, Docherty AR, Mullins N, Ruderfer DM, Harvey PD, McMahon BH, Oslin DW, Beckham JC, Hauser ER, Hauser MA; Million Veteran Program Suicide Exemplar Workgroup, the International Suicide Genetics Consortium, the Veterans Affairs Mid-Atlantic Mental Illness Research, Education, and Clinical Center Workgroup, and the Veterans Affairs Million Veteran Program. Identification of Novel, Replicable Genetic Risk Loci for Suicidal Thoughts and Behaviors Among US Military Veterans. JAMA Psychiatry. 2023 Feb 1;80(2):135-145. doi: 10.1001/jamapsychiatry.2022.3896. PMID: 36515925; PMCID: PMC9857322

Kotyuk E, Magi A, Eisinger A, Király O, Vereczkei A, Barta C, Griffiths MD, Székely A, Kökönyei G, Farkas J, Kun B, Badgaiyan RD, Urbán R, Blum K, Demetrovics Z. Co-occurrences of substance use and other potentially addictive behaviors: Epidemiological results from the Psychological and Genetic Factors of the Addictive Behaviors (PGA) Study. J Behav Addict. 2020 Jun 26;9(2):272-288. doi: 10.1556/2006.2020.00033. PMID: 32609628

Kozasa EH, Sato JR, Lacerda SS, Barreiros MA, Radvany J, et al. Meditation training increases brain efficiency in an attention task. Neuroimage. 2012;59(1):745–749. [PubMed] [Google Scholar]

Krebs EE, Gravely A, Nugent S, et al. Effect of Opioid vs Nonopioid Medications on Pain-Related Function in Patients With Chronic Back Pain or Hip or Knee Osteoarthritis Pain: The SPACE Randomized Clinical Trial. *JAMA*. 2018;319(9):872–882. doi:10.1001/jama.2018.0899

Le Berre AP. Emotional processing and social cognition in alcohol use disorder. Neuropsychology. 2019 Sep;33(6):808-821. doi: 10.1037/neu0000572. PMID: 31448948; PMCID: PMC6711390.

Levran O, Matthew Randesi, Joel Correa da Rosa, Jurg Ott, John Rotrosen, Miriam Adelson, Mary Jeanne Kreek Overlapping Dopaminergic Pathway Genetic Susceptibility for Heroin and Cocaine Addictions in African Americans Ann Hum Genet. Author manuscript; available in PMC 2016 May 1.

Littrell J (2014). Understanding and Treating Alcoholism Volume I: An Empirically Based Clinician's Handbook for the Treatment of Alcoholism: Volume II: Biological, Psychological, and Social Aspects of Alcohol Consumption and Abuse. Hoboken: Taylor and Francis. p. 55. ISBN 978-1-317-78314-5. Archived from the original on 20 July 2017. The World Health Organization defines alcoholism as any drinking which results in problems

Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C, Costafreda SG, Dias A, Fox N, Gitlin LN, Howard R, Kales HC, Kivimäki M, Larson EB, Ogunniyi A, Orgeta V, Ritchie K, Rockwood K, Sampson EL, Samus Q, Schneider LS, Selbæk G, Teri L, Mukadam N. Dementia prevention, intervention, and care: 2020 report of the

Lancet Commission. Lancet. 2020 Aug 8;396(10248):413-446. doi: 10.1016/S0140-6736(20)30367-6. Epub 2020 Jul 30. PMID: 32738937; PMCID: PMC7392084.

Long EC, Verhulst B, Aggen SH, Kendler KS, Gillespie NA. Contributions of Genes and Environment to Developmental Change in Alcohol Use. Behav Genet. 2017 Sep;47(5):498-506. doi: 10.1007/s10519-017-9858-y. Epub 2017 Jul 17. PMID: 28714051.

Loth E, Carvalho F, Schumann G. The contribution of imaging genetics to the development of predictive markers for addictions. Trends Cogn Sci. 2011 Sep;15(9):436-46. doi: 10.1016/j.tics.2011.07.008. Epub 2011 Aug 15. Review. PMID: 21840243

Madigan MA, Badgaiyan RD, Baron D, Blum K. Precision Behavioral Management (PBM) A Novel Approach to Combat Post-Traumatic Stress Disorder (PTSD). SOJ Psychol. 2018;5(2):10.15226/2374-6874/5/2/00148. doi: 10.15226/2374-6874/5/2/00148. Epub 2018 Aug 6. PMID: 31440582; PMCID: PMC6706091.

Marlatt GA. The controlled-drinking controversy. A commentary. Am Psychol. 1983 Oct;38(10):1097-110. doi: 10.1037//0003-066x.38.10.1097. PMID: 6357011.

Mathews S Dwyer R, Snoek A. Stigma and Self-Stigma in Addiction. J Bioeth Inq. 2017; 14(2): 275–286. Published online 2017 May 3. doi: 10.1007/s11673-017-9784-y PMC5527047

McBride WJ, Li TK. Animal models of alcoholism: neurobiology of high alcohol-drinking behavior in rodents. Crit Rev Neurobiol. 1998;12 (4):339-69.

Messiha FS, Hartman T, Geller I. Darkness-induced alterations in alcohol dehydrogenase activity in specific brain regions of the rat. Res Commun Chem Pathol Pharmacol. 1975 Feb;10(2):399-402. PMID: 1153841.

MMWR Morb Mortal Wkly Rep. 2016 Dec 30;65(50-51):1445-1452. doi: 10.15585/mmwr.mm655051e1.

MMWR Morb Mortal Wkly Rep. 2018 Mar 30;67(12):349-358. doi: 10.15585/mmwr.mm6712a1.

Moeller SJ, Parvaz MA, Shumay E, Beebe-Wang N, Konova AB, Alia-Klein N, Volkow ND, Goldstein RZ. Gene x abstinence effects on drug cue reactivity in addiction: multimodal evidence. J Neurosci. 2013 Jun 12;33(24):10027-36. doi: 10.1523/JNEUROSCI.0695-13.2013.

Murano T, Koshimizu H, Hagihara H, Miyakawa T. Transcriptomic immaturity of the hippocampus and prefrontal cortex in patients with alcoholism. Sci Rep. 2017 Mar 15;7:44531. doi: 10.1038/srep44531. PMID: 28295046; PMCID: PMC5353747.

McLellan T. What is recovery? Revisiting the Betty Ford Institute Consensus Panel definition: The Betty Ford Consensus Panel and Consultants. J Subst Abuse Treat. 2010 Mar;38(2):200-1. doi: 10.1016/j.jsat.2009.11.002. Epub 2009 Dec 16. PMID: 20005668.

Neville MJ, Johnstone EC, Walton RT. Identification and characterization of ANKK1: a novel kinase gene closely linked to DRD2 on chromosome band 11q23.1. Hum Mutat. 2004 Jun;23(6):540-5. doi: 10.1002/humu.20039. PMID: 15146457.

Nilsson KW, Damberg M, Ohrvik J, Leppert J, Lindström L, et al. Genes encoding for AP-2beta and the Serotonin Transporter are associated with the Personality Character Spiritual Acceptance. Neurosci Lett. 2007;411(3):233–237. [PubMed] [Google Scholar]

Noble EP. “Announcement of the Rand Report”, HEW NEWS, Washington, June 23. 1978, EP. Alcoholic fathers and their sons: neuropsychological, electro psychological, personality and family correlates, in C. R. Cloninger and H. Begleiter eds., *Banbury Report 33: Molecular* Genetics *and*

O'Connor R, Sheehy N (29 January 2000). Understanding suicidal behaviour. *Leicester: BPS Books. pp. 33–37.* ISBN 978-1-85433-290-5.

Olfson E, Bierut LJ. Convergence of genome-wide association and candidate gene studies for alcoholism. Alcohol Clin Exp Res. 2012 Dec;36(12):2086-94. doi: 10.1111/j.1530-0277.2012.01843.x. Epub 2012 Sep 14. PMID: 22978509; PMCID: PMC3521088.

Orford J. The future of alcoholism: a commentary on the Rand Report. Psychol Med. 1978 Feb;8(1):5-8. doi: 10.1017/s0033291700006589. PMID: 635070.

Patterson Silver Wolf DA, Gold M. Treatment resistant opioid use disorder (TROUD): Definition, rationale, and recommendations. J Neurol Sci. 2020 Apr 15;411:116718. doi: 10.1016/j.jns.2020.116718. Epub 2020 Feb 5. PMID: 32078842.

Peele, S Ain't misbehavin': addiction has become an all-purpose excuse, *The* Sciences 29(4) (1989): 14-21.

Pendery ML, Maltzman IM, West LJ. Controlled drinking by alcoholics? New findings and a reevaluation of a major affirmative study. Science. 1982 Jul 9;217(4555):169-75. doi: 10.1126/science.7089552. PMID: 7089552.

Pergolizzi JV Jr, LeQuang JA, Taylor R Jr, Raffa RB; NEMA Research Group. Going beyond prescription pain relievers to understand the opioid epidemic: the role of illicit fentanyl, new psychoactive substances, and street heroin. Postgrad Med. 2018 Jan;130(1):1-8. doi: 10.1080/00325481.2018.1407618. Epub 2017 Nov 30. Review.

Reilly MT, Noronha A, Goldman D, Koob GF. Genetic studies of alcohol dependence in the context of the addiction cycle. *Neuropharmacology*. 2017 Aug 1;122:3-21. doi: 10.1016/j.neuropharm.2017.01.017. Epub 2017 Jan 22. PubMed PMID: 28118990; PubMed Central PMCID: PMC6233301.

Reiter RJ, Blum K, Wallace JE, Merritt JH. Pineal gland: evidence for an influence on ethanol preference in male Syrian hamsters. Comp Biochem Physiol A Comp Physiol. 1974 Jan;47(1):11-6. doi: 10.1016/0300-9629(74)90045-0. PMID: 4148997.

Romeo J, Wärnberg J, Nova E, Díaz LE, Gómez-Martinez S, Marcos A (October 2007). "Moderate alcohol consumption and the immune system: a review". The British Journal of Nutrition. 98 Suppl 1: S111-5. doi:10.1017/S0007114507838049. PMID 17922947.

Rudd RA, Seth P, David F, Scholl L. Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015.

Salling MC, Martinez D. Brain Stimulation in Addiction Neuropsychopharmacology. 2016 Nov; 41(12): 2798–2809. Pre-published online 2016 May 31. Published online 2016 Aug 17. doi: 10.1038/npp.2016.80 PMC5061891

Samek DR, Bailey J, Hill KG, Wilson S, Lee S, Keyes MA, Epstein M, Smolen A, Miller M, Winters KC, Hawkins JD, Catalano RF, Iacono WG, McGue M. A Test-Replicate Approach to Candidate Gene Research on Addiction and Externalizing Disorders: A Collaboration Across Five Longitudinal Studies. Behav Genet. 2016 Sep;46(5):608-626. doi: 10.1007/s10519-016-9800-8. Epub 2016 Jul 21.

Savannah R. Smith, Bhushan R. Deshpande, Jamie E. Collins, Jeffrey N. Katz, Elena Losina

Schoenthaler SJ, Blum K, Braverman ER, Giordano J, Thompson B, et al. NIDA-Drug Addiction Treatment Outcome Study (DATOS) Relapse as a Function of Spirituality. J Reward Defic Syndr. 2015;1(1) [PMC free article] [PubMed] [Google Scholar]

Schuckit MA. Ethanol-induced changes in body sway in men at high alcoholism risk. Arch Gen Psychiatry. 1985 Apr;42(4):375-9. doi: 10.1001/archpsyc.1985.01790270065007. PMID: 3977555...

Seth P, Scholl L, Rudd RA, Bacon S. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016.

Smith DE. Medicalizing the Opioid Epidemic in the U.S. in the Era of Health Care Reform. J Psychoactive Drugs. 2017 Apr-Jun;49(2):95-101. doi: 10.1080/02791072.2017.1295334. Epub 2017 Mar 15.

Smith DE. The process addictions and the new ASAM definition of addiction. J Psychoactive Drugs. 2012 Jan-Mar;44(1):1-4. doi: 10.1080/02791072.2012.662105. PMID: 22641960.

Sobell MB, Sobell LC. Alcoholics treated by individualized behavior therapy: one year treatment outcome. Behav Res Ther. 1973 Nov;11(4):599-618. doi: 10.1016/0005-7967(73)90118-6. PMID: 4777652.

Sobell MB, Sobell LC. Individualized Behavior Therapy for Alcoholics - Republished Article. Behav Ther. 2016 Nov;47(6):937-949. doi: 10.1016/j.beth.2016.11.008. Epub 2016 Nov 10. PMID: 27993342.

Solanki N, Abijo T, Galvao C, Darius P, Blum K, Gondré-Lewis MC. Administration of a putative pro-dopamine regulator, a neuronutrient, mitigates alcohol intake in alcohol-preferring rats. Behav Brain Res. 2020 May 15;385:112563. doi: 10.1016/j.bbr.2020.112563. Epub 2020 Feb 15. PMID: 32070691; PMCID: PMC7244251.

Stacey D, Bilbao A, Maroteaux M, et al. RASGRF2 regulates alcohol-induced reinforcement by influencing mesolimbic dopamine neuron activity and dopamine release. Proc Natl Acad Sci U S A. 2012;109:21128–33. [PMC free article] [PubMed] [Google Scholar

Strong C, Juon HS, Ensminger ME. Effect of Adolescent Cigarette Smoking on Adulthood Substance Use and Abuse: The Mediating Role of Educational Attainment. Subst Use Misuse. 2016 Jan 28;51(2):141-54. doi: 10.3109/10826084.2015.1073323. Epub 2016 Jan 19. PMID: 26787191

Thanos PK, Michaelides M, Umegaki H, Volkow ND. D2R DNA transfer into the nucleus accumbens attenuates cocaine self-administration in rats. Synapse. 2008 Jul;62(7):481-6. doi: 10.1002/syn.20523. PMID: 18418874; PMCID: PMC2659016.

Thanos PK, Rivera SN, Weaver K, Grandy DK, Rubinstein M, Umegaki H, Wang GJ, Hitzemann R, Volkow ND. Dopamine D2R DNA transfer in dopamine D2 receptor-deficient mice: effects on ethanol drinking. Life Sci. 2005 May 27;77(2):130-9. doi: 10.1016/j.lfs.2004.10.061. Epub 2005 Feb 9. PMID: 15862598.

Thanos PK, Volkow ND, Freimuth P, Umegaki H, Ikari H, Roth G, Ingram DK, Hitzemann R. Overexpression of dopamine D2 receptors reduces alcohol self-administration. J Neurochem. 2001 Sep;78(5):1094-103. doi: 10.1046/j.1471-4159.2001.00492.x. PMID: 11553683.

Tikkanen R, Ducci F, Goldman D, Holi M, Lindberg N, Tiihonen J, Virkkunen M. MAOA alters the effects of heavy drinking and childhood physical abuse on risk for severe impulsive acts of violence among alcoholic violent offenders. Alcohol Clin Exp Res. 2010 May;34(5):853-60. doi: 10.1111/j.1530-0277.2010.01157.x. Epub 2010 Mar 1. PMID: 20201935; PMCID: PMC3195419.

Upadhyay, J., Maleki, N., Potter, J., Elman, I., Rudrauf, D., Knudsen, J., … Borsook, D. (2010). Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain : a journal of neurology*, *133*(Pt 7), 2098–2114. doi:10.1093/brain/awq138

Vaillant GE (August 2003). "A 60-year follow-up of alcoholic men". *Addiction*. 98 (8): 1043–51. doi:10.1046/j.1360-0443.2003.00422.x. PMID 12873238. S2CID 12835128

Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med. 2015 Apr;45(5):1061-72. doi: 10.1017/S0033291714002165. Epub 2014 Aug 29.

Vitali M, Carmen Napolitano, Marlene Oscar Berman, Simona Flamminii Minuto, Gemma Battagliese, Maria Luisa Attilia, Eric R Braverman, Marina Romeo, Kenneth Blum, Mauro Ceccanti.

Neurophysiological Measures and Alcohol Use Disorder (AUD): Hypothesizing Links between Clinical Severity Index and Molecular Neurobiological Patterns J Addict Res Ther. 2016 Apr; 5(2): 182. Published online 2016 Apr 26. doi: 10.4172/2155-6105.1000181 PMC5231399

Volkow ND, Wise RA, Baler R. The dopamine motive system: implications for drug and food addiction. Nat Rev Neurosci. 2017 Nov 16;18(12):741-752. doi: 10.1038/nrn.2017.130.

Wallace J. Waging the war for wellness, part 2, *Professional Counselor* 1 (1987): 21-27.

Wallace J., Addict and institution, *The Sciences* 30(1) (1990): 11-12.

You C, Savarese A, Vandegrift BJ, et al. Ethanol acts on KCNK13 potassium channels in the ventral tegmental area to increase firing rate and modulate binge-like drinking. *Neuropharmacology*. 2019;144:29-36. doi:10.1016/j.neuropharm.2018.10.008

Zygo M, Pawłowska B, Potembska E, Dreher P, Kapka-Skrzypczak L. Prevalence and selected risk factors of suicidal ideation, suicidal tendencies and suicide attempts in young people aged 13-19 years. Ann Agric Environ Med. 2019 Jun 17;26(2):329-336. doi: 10.26 444/aaem/93817. Epub 2018 Aug 24. PMID: 31232067.