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The Psychoneurosis of Substance Use Disorders: A Biopsychosocial Reconceptualization of Comorbidity, Neurobiological Intersections, and Integrated Treatment Paradigms

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Abstract:
Substance use disorders (SUDs) represent a significant public health challenge, affecting an estimated 275 million people worldwide, with alcohol use disorders alone accounting for 107 million cases and other drug use disorders affecting 71 million individuals (Degenhardt & Hall, 2012; Degenhardt et al., 2018). The clinical complexity of SUDs is substantially amplified by their frequent comorbidity with psychiatric conditions, a phenomenon historically subsumed under the rubric of "psychoneurosis." Contemporary epidemiological research demonstrates that 37% of adults with alcohol use disorders and 53% with drug use disorders meet criteria for co-occurring psychiatric disorders (Regier et al., 1990; Kessler et al., 1996). This paper presents a comprehensive conceptual analysis of the psychoneurosis of SUDs, integrating neurobiological, psychological, psychoneuroimmunological, and treatment dimensions. The researcher proposes that the psychoneurosis of substance use is best understood through a biopsychosocial lens that acknowledges bidirectional causal pathways, shared neurobiological vulnerabilities, and the critical importance of integrated treatment approaches (Engel, 1977; Drake et al., 2004). Drawing on neuroimaging findings, psychoneuroimmunological research, and clinical outcome studies, the researcher argues that the historical concept of psychoneurosis, while outdated in its specific formulations, captures an essential clinical reality: the inextricable entanglement of substance use and psychiatric symptomatology requires reconceptualization within modern dimensional frameworks (Freud, 1894; Insel et al., 2010). The researcher examines the neurobiological intersections of stress and substance use, the limbic system dysregulations underlying comorbidity, the psychoneuroimmunological mechanisms linking substance exposure to psychiatric symptoms, and the emerging evidence base for integrated psychosocial and pharmacological interventions. The paper concludes with recommendations for a reconceptualized approach to assessment, treatment, and research that moves beyond categorical distinctions toward a truly integrated understanding of substance use and mental health.
Keywords: Substance use disorders; comorbidity; psychoneurosis; biopsychosocial; neurobiology; stress; limbic system; psychoneuroimmunology; integrated treatment; dimensional models

1. Introduction

The relationship between substance use and psychiatric symptomatology has occupied a central position in clinical psychiatry since the discipline's inception. The concept of "psychoneurosis", a term largely abandoned in contemporary diagnostic nomenclature, attempted to capture the notion that certain psychiatric symptoms represented maladaptive responses to psychological conflicts rather than organic brain disease (Freud, 1894). While the term has fallen into disuse, the clinical reality it sought to describe remains profoundly relevant: substance use

disorders (SUDs) are rarely isolated phenomena but instead exist in complex, bidirectional relationships with a wide range of psychiatric conditions (Grant et al., 2004; Compton et al., 2007).

Substance use has been intertwined with human history for millennia, with individuals consuming various substances for medicinal, spiritual, and recreational purposes throughout the ages. However, occasional use differs significantly from substance use disorders, which the DSM-5 characterizes as a cluster of cognitive, behavioral, and physiological symptoms indicating continued substance use despite significant substance-related problems (American Psychiatric Association, 2013). The global burden of SUDs is staggering: approximately 275 million people worldwide are affected by substance use, with young adults being the most vulnerable population (Degenhardt & Hall, 2012; Degenhardt et al., 2018).

The Epidemiologic Catchment Area study, a landmark investigation of psychiatric comorbidity in community samples, estimated that 37% of adults with alcohol use disorders and 53% with drug use disorders have co-occurring psychiatric disorders (Regier et al., 1990). More recent data from addiction treatment facilities indicate even higher rates: mood disorders (40-42%), anxiety disorders (24-27%), post-traumatic stress disorder (24-27%), severe mental illness (16-21%), antisocial personality disorder (18-20%), and borderline personality disorder (17-18%) (Kessler et al., 1996; Grant et al., 2015; Hasin et al., 2015). Among adults with schizophrenia in community settings, lifetime SUD rates may approach 50% (Volkow & Morales, 2015; Volkow et al., 2016).

The implications of this comorbidity for clinical outcomes are profound. Individuals with co-occurring SUDs and psychiatric disorders experience more severe symptomatology, poorer treatment outcomes, higher rates of treatment dropout, greater functional impairment, and increased mortality compared to those with either condition alone (Drake et al., 2004). The presence of psychiatric comorbidity complicates treatment planning, contributes to diagnostic overshadowing, and is associated with higher healthcare utilization and costs (Clark et al., 2001). Despite the clinical significance of this comorbidity, the mechanisms underlying the co-occurrence of SUDs and psychiatric disorders remain incompletely understood. Several explanatory models have been proposed (Mueser et al., 1998; Khantzian, 1997). The secondary substance use model posits that having a psychiatric disorder increases susceptibility to addictive behaviors because substances may temporarily reduce symptoms of mental conditions, acting as a negative reinforcer. This model embraces the self-medication hypothesis, in which the constant use of substances to remedy negative affective states leads to an SUD diagnosis (Khantzian, 1985; 1997). The secondary psychopathology model proposes that SUDs may promote vulnerability to psychiatric disorders due to the consequences of chronic drug use or related withdrawal symptoms. The common factor model suggests that shared genetic and environmental factors, such as traumatic or stressful life experiences, may mediate the relationship rather than reflect a direct causal association (Kendler et al., 2003; Koob & Volkow, 2016).

The Research Domain Criteria (RDoC) framework, developed by the National Institute of Mental Health, offers a promising approach for investigating psychiatric comorbidities. The RDoC is a multi-system framework that maps domains of neurobehavioral functioning to mental disorders, emphasizing a multidimensional approach that integrates neurobiological and psychosocial factors (Insel et al., 2010; Cuthbert & Insel, 2013). This framework focuses on common underlying constructs of multiple disorders, such as disruption to positive valence systems as a core feature of both SUDs and anxiety disorders (Koob & Volkow, 2016).

This paper presents a comprehensive conceptual analysis of the psychoneurosis of substance use disorders, integrating findings from neuroimaging, psychoneuroimmunology, and clinical treatment research. The researcher argues that reconceptualizing the relationship between substance use and psychiatric symptomatology within a biopsychosocial framework has critical implications for clinical practice, treatment development, and research.

2. Historical Context: The Evolution of the Psychoneurosis Concept

2.1 Origins of the Psychoneurosis Construct

The term "neurosis" was first introduced by the Scottish physician William Cullen in the 18th century to describe disorders of the nervous system that did not present with obvious organic pathology. Sigmund Freud later refined this concept, distinguishing between neuroses and psychoses, with neuroses characterized by the individual's retention of reality testing despite experiencing distressing symptoms (Freud, 1894). The term "psychoneurosis" emerged to emphasize the psychological origins of these conditions, distinguishing them from "organoneuroses" which were believed to have primarily physical causes (Freud, 1894).

Throughout the early 20th century, the concept of psychoneurosis evolved to encompass a range of conditions including anxiety disorders, depressive disorders, obsessive-compulsive disorder, and dissociative disorders. The psychodynamic understanding of these conditions emphasized unconscious conflicts, defense mechanisms, and the role of early childhood experiences in shaping adult psychopathology (Freud,

1894).

2.2 The Psychoneurosis Concept and Substance Use

Early psychodynamic theorists recognized the relationship between substance use and psychiatric symptomatology. Freud himself wrote extensively about the role of substances in managing psychological distress, and later psychoanalysts developed theories of addiction as a form of self-medication for underlying psychological conflicts. The self-medication hypothesis, formally articulated by Khantzian (1985), represents the most direct descendant of this psychoneurotic tradition. Khantzian proposed that individuals select specific substances based on their capacity to alleviate particular painful affective states, for example, opiates for aggression and rage, stimulants for depression, and alcohol for anxiety. This hypothesis has received substantial empirical support and remains influential in contemporary addiction research (Khantzian, 1997).

2.3 The Decline and Legacy of the Psychoneurosis Concept

The psychoneurosis concept fell into decline following the publication of DSM-III (American Psychiatric Association, 1980), which abandoned the neurosis-psychosis distinction in favor of a descriptive, atheoretical approach to classification (American Psychiatric Association, 2013). The DSM-III's rejection of psychodynamic terminology was motivated by concerns about reliability and the desire for a more scientifically rigorous approach to diagnosis.

Despite its decline as a formal diagnostic category, the concept of psychoneurosis has left an enduring legacy. The recognition that psychological conflicts, defense mechanisms, and early life experiences contribute to psychiatric symptomatology remains foundational to contemporary psychotherapy. Moreover, the psychoneurosis concept anticipated the current emphasis on dimensional approaches to psychopathology, such as the RDoC framework and the Hierarchical Taxonomy of Psychopathology (HiTOP; Kotov et al., 2017), by recognizing that psychiatric symptoms exist on continua rather than as discrete categories (Krueger & Markon, 2006).

3. Epidemiology of Comorbidity: Substance Use Disorders and Psychiatric Conditions

3.1 Prevalence and Patterns of Comorbidity

The co-occurrence of SUDs and psychiatric disorders is the rule rather than the exception in clinical populations. A substantial body of epidemiological research has documented the high prevalence of this comorbidity across diverse populations and settings (Regier et al., 1990; Kessler et al., 1996; Grant et al., 2004; Compton et al., 2007).

The National Comorbidity Survey (NCS), a representative epidemiological study of the US population, found that 56% of individuals with a lifetime history of substance use disorder had at least one co-occurring psychiatric disorder (Kessler et al., 1996). The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) reported similar findings, with 20% of individuals with alcohol use disorder and 30% of those with drug use disorder meeting criteria for another psychiatric disorder (Grant et al., 2004; Grant et al., 2015).

Specific patterns of comorbidity have been identified. Mood disorders are particularly common, with major depressive disorder occurring in 30-50% of individuals with SUDs (Hasin et al., 2015). Anxiety disorders, including generalized anxiety disorder, panic disorder, and social anxiety disorder, affect 20-40% of individuals with SUDs (Kushner et al., 2000). Post-traumatic stress disorder (PTSD) is present in 25-50% of individuals seeking treatment for SUDs (Najavits et al., 1997; 1998; Jacobsen et al., 2001). Personality disorders, particularly antisocial and borderline types, are diagnosed in 25-50% of individuals with SUDs (Brooner et al., 1997).

3.2 Age and Gender Differences

The relationship between SUDs and psychiatric disorders varies by age and gender. Among adolescents, the prevalence of SUDs is elevated in those with psychiatric disorders, particularly conduct disorder and attention-deficit/hyperactivity disorder. Research suggests that ADHD predates the onset of substance use and is a significant risk factor for the development of SUDs.

Gender differences in comorbidity patterns have also been identified. Women with SUDs are more likely than men to have co-occurring anxiety and mood disorders (Brady & Randall, 1999), while men with SUDs are more likely to have antisocial personality disorder and other externalizing disorders (Compton et al., 2007). Women with SUDs are also more likely to have experienced trauma and to have PTSD (Najavits et al., 1997; Hien et al., 2004).

3.3 Substance-Specific Comorbidity Patterns

The type of substance used is associated with distinct patterns of psychiatric comorbidity. Alcohol use disorder is strongly associated with mood, anxiety, and personality disorders (Hasin et al., 2015; Grant et al., 2015). Cocaine use disorder is associated with mood disorders, particularly bipolar disorder, as well as antisocial personality disorder. Opioid use disorder is associated with mood and anxiety disorders, as well as PTSD (Brooner et al., 1997). Cannabis use disorder is associated with mood and anxiety disorders, as well as psychotic disorders in vulnerable individuals (Boden et al., 2008; Di Forti et al., 2019).

4. Neurobiological Foundations of the Psychoneurosis of SUDs

The neurobiology of addiction has been extensively characterized over the past several decades, revealing a complex interplay of neurotransmitter systems, neural circuits, and neuroadaptive processes that underlie the transition from casual substance use to compulsive drug-seeking behavior (Koob & Le Moal, 2008; Volkow et al., 2016; Kalivas & Volkow, 2005). Substance use disorders are increasingly understood as disorders of brain circuitry, involving dysfunction in three key systems: the mesolimbic dopamine pathway (reward processing), the prefrontal cortex (executive control), and the limbic system (emotion regulation) (Koob & Volkow, 2016; Volkow & Morales, 2015).

4.1 Dopamine Dysregulation and Reward Processing

Central to addiction's pathophysiology is dysfunction in the mesolimbic dopamine pathway involving regions like the ventral tegmental area (VTA), nucleus accumbens (NAc), and prefrontal cortex (PFC), which mediate reward, reinforcement, and motivation. The mesolimbic system includes neurons that originate in the VTA and project upward to the ventral striatum (VS), including the nucleus accumbens. Drug consumption induces rapid "bursts" of dopamine release in the VS (phasic dopamine release), which activate dopamine D1 receptors and are associated with the rewarding experience of feeling "high" or euphoric (Volkow & Morales, 2015). The adjacent nigrostriatal dopamine system originates in the substantia nigra and projects upward to the dorsal striatum (DS). Like in the VS, drug consumption also increases dopamine release in the DS, though to a lesser extent (Everitt & Robbins, 2016).

Chronic substance use triggers neuroadaptive changes, including dopamine receptor downregulation and glutamatergic excitotoxicity, leading to compulsive drug-seeking and impaired impulse control (Kalivas & Volkow, 2005; Volkow et al., 2016). Chronic substance use results in downregulation of dopamine D2 receptors in the VTA and NAc, which weakens the brain's reward system and leads to compulsive substance-seeking behavior (Volkow & Morales, 2015). This disruption is closely associated with glutamatergic dysregulation, contributing to emotional dysregulation and impairments in decision-making (Kalivas & Volkow, 2005).

With long-term drug use, an individual's reward processing distorts to disproportionately favor drug consumption over other rewards. This reflects, in part, long-term potentiation (LTP), one of the mechanisms driving neuroplasticity in the brain triggered by drug-induced signaling. These neuroplastic changes drive incentive salience, heightened or focused attention toward cues linked to rewarding behaviors (Robinson & Berridge, 2008). The mesocortical system originates in the VTA and includes neuronal projections to the medial prefrontal cortex (mPFC). Release of dopamine into the mPFC cues incentive salience, which increases motivation for further drug consumption (Robinson & Berridge, 2008).

The commonalities between SUDs and psychiatric disorders at the neurobiological level are striking. Many psychiatric conditions, particularly mood and anxiety disorders, are also characterized by dysregulation of reward circuitry, altered dopamine signaling, and impaired prefrontal-limbic connectivity. This shared neurobiology provides a foundation for understanding the high rates of comorbidity and suggests that treating one condition may have beneficial effects on the other.

4.2 Prefrontal-Limbic Imbalance and Emotional Dysregulation

A critical finding in addiction neuroscience is the identification of prefrontal-limbic imbalance, characterized by prefrontal cortex hypoactivity and amygdala hyperactivity (Goldstein & Volkow, 2011; Volkow et al., 2016). This imbalance leads to impaired impulse control, difficulty managing emotions, and heightened stress reactivity. The PFC's inability to regulate emotional responses in the limbic system exacerbates relapse vulnerability, particularly during stress.

Brain imaging studies using functional MRI have consistently demonstrated reduced PFC activity and increased limbic hyperactivity in individuals with addiction, indicating a loss of executive control over compulsive behaviors (Goldstein & Volkow, 2011; Volkow & Morales,

2015). This pattern of prefrontal-limbic imbalance is also observed in individuals with anxiety disorders, depression, and PTSD, suggesting that this circuit dysfunction may represent a transdiagnostic vulnerability factor that predisposes individuals to both SUDs and psychiatric disorders (Etkin et al., 2011).

The limbic system, which includes the amygdala, hippocampus, and associated structures, is central to emotional processing, stress responses, and memory formation (Davis, 1992). Dysfunction in these regions has been implicated in the development and maintenance of both SUDs and anxiety disorders (Davis, 1992). Anxiety and substance use play a reciprocal role at each stage of addiction, marked by significant psychosocial impairment and dysregulation in the brain (Koob, 2008; Koob & Volkow, 2016).

4.3 The Role of Stress and the HPA Axis

Exposure to lifetime stressors constitutes a significant risk factor for both psychiatric disorders and SUD development and relapse (Koob, 2015). Indeed, hypothalamic--pituitary--adrenal (HPA) axis modulation, alterations in neuroanatomical and neurotransmitter systems, as well as neuroinflammation are common features of stress-related mood disorders and SUDs (Koob, 2015).

The relationship between stress and substance use is bidirectional and self-reinforcing. Stress can precipitate substance use as a coping mechanism (negative reinforcement), while chronic substance use dysregulates the stress response system, making individuals more vulnerable to stress-induced craving and relapse (Koob & Le Moal, 2001; Koob, 2008). This is particularly relevant to the psychoneurosis of SUDs, as many individuals who develop substance use problems have histories of trauma, adverse childhood experiences, or chronic stress that predates their substance use (Anda et al., 2006; Felitti et al., 1998).

The role of the HPA axis in addiction and psychiatric comorbidity has been extensively investigated. Dysregulation of the HPA axis, characterized by either hypercortisolemia or hypocortisolemia depending on the phase of the disorder, has been consistently observed in individuals with SUDs and co-occurring psychiatric disorders. The interaction between the HPA axis and reward circuits is complex, with glucocorticoid receptors located throughout the mesolimbic dopamine system.

Trauma-focused therapies, such as Eye Movement Desensitization and Reprocessing (EMDR), have been shown to reduce trauma-related cravings and relapse rates in individuals with SUDs and co-occurring trauma. These interventions appear to recalibrate the HPA axis, reduce amygdala hyperactivity, and restore emotional balance, thereby promoting long-term recovery.

4.4 Neurobiological Mechanisms of Comorbidity: Amplification, Attenuation, and Unique Effects

A recent systematic review of neuroimaging studies investigating psychiatric comorbidity in SUDs identified distinct patterns of neurobiological interaction depending on the specific psychiatric condition (Tesselaar et al., 2025). This review hypothesized that co-occurring psychopathology could (1) amplify the neurobiological effects of SUD, (2) attenuate it, (3) have unique neurobiological effects, or (4) have no additional neurobiological effects.

The findings revealed that different co-occurring psychiatric disorders have distinct effects on the neurobiology of SUD (Tesselaar et al., 2025). Specifically:

- **Amplifying effects** were found for co-occurring schizophrenia and personality disorder (Tesselaar et al., 2025). This suggests that these conditions exacerbate the neurobiological disruptions associated with SUD, potentially explaining the particularly poor outcomes observed in these populations.
- **Unique effects** were found for schizophrenia, ADHD, and personality disorder (Tesselaar et al., 2025). This indicates that these conditions contribute neurobiological alterations that are distinct from those associated with SUD alone, suggesting that the combination of SUD and these conditions represents a qualitatively different neurobiological state.
- **Attenuating or no effect** was found for depression on SUD (Tesselaar et al., 2025). This surprising finding suggests that depression may not amplify or significantly alter the neurobiological effects of SUD, though it does not diminish the clinical significance of this comorbidity.
- **Contradictory findings** were reported for PTSD (Tesselaar et al., 2025), indicating that the relationship between PTSD and SUD is complex and may depend on specific factors such as substance type, trauma characteristics, or individual vulnerability.

These findings have important implications for treatment, suggesting that different comorbid conditions may require different therapeutic approaches and that a one-size-fits-all approach to treating comorbid SUDs is unlikely to be optimal (Tesselaar et al., 2025).

5. Psychoneuroimmunological Dimensions of Substance Use Disorders

Psychoneuroimmunology is a specialized field of research that studies the interactions between the nervous and immune systems and the relationships between behavior and health (Ader et al., 1991; Dantzer et al., 2008). This field has particular relevance to understanding the psychoneurosis of SUDs, as substance abuse, and particularly withdrawal from an abused substance, can be significant stressors that result in immunological and neurological changes that negatively impact behavior and health outcomes (Loftis & Hauser, 2013; Dantzer, 2001).

5.1 Neuroimmune Interactions in Substance Use

Both stress and substance abuse have measurable and reciprocal effects on immune system cytokines, which can be influential modulators of neuropsychiatric function (Dantzer et al., 2008). In addition to stress-induced effects on immune function, pre-clinical studies are beginning to link immune factor signaling with neural and behavioral aspects of addiction, such as drug seeking and resilience to relapse (Loftis & Hauser, 2013; Hutchinson et al., 2007).

Communication between the brain and the immune system is bi-directional, and immune-to-brain communication pathways induce a cascade of cellular and molecular events in the central nervous system, which have behavioral consequences (Dantzer et al., 2008). Thus, investigating addiction from a psychoneuroimmunological perspective may provide a more integrated view of the pathophysiological mechanisms associated with SUDs (Loftis & Hauser, 2013; Irwin, 2008).

5.2 Substance-Specific Immune Effects

Research has examined the psychoneuroimmune processes associated with exposure to alcohol, stimulants, and opioids (Loftis & Hauser, 2013; Irwin & Miller, 2007):

Alcohol (Ethanol): Acute behavioral effects of ethanol may be influenced by microglial-dependent central immune signaling. Acute ethanol exposure can trigger mast cell degranulation and asthma-like symptoms in sensitized animals, suggesting that alcohol's immunomodulatory effects extend beyond the central nervous system. Chronic alcohol consumption has been consistently associated with increased pro-inflammatory cytokine levels (IL-6, TNF-α, IL-1β) in both humans and animal models. This chronic inflammation may contribute to neurotoxicity and psychiatric symptoms, including mood disorders and cognitive deficits.

Opioids: Morphine administration has been shown to suppress splenic NK cell activity and impair toll-like receptor expression, rendering peritoneal leukocytes less effective in recognizing antigens (Hutchinson et al., 2007; 2011). Chronic heroin users exhibit significantly increased CD4+CD25 high regulatory T cells compared to patients in opioid maintenance therapy, and the proliferative response of CD4+ T cells upon stimulation was significantly decreased in heroin users. This suggests that opioid use can lead to immunosuppression, potentially increasing vulnerability to infections and other health problems. Opioids also affect microglial activation through Toll-like receptor 4 (TLR4) signaling, with implications for neuroinflammation and psychiatric symptoms (Hutchinson et al., 2007; 2011).

Stimulants: Cocaine and methamphetamine have demonstrated immunomodulatory effects in animal models (Loftis & Hauser, 2013). Methamphetamine administration has been associated with increased expression of pro-inflammatory cytokines in the brain (IL-6, TNF-α, IL-1β), potentially contributing to the neurotoxic and psychiatric effects of the drug (Cadet et al., 2005). Cocaine has been shown to alter the balance between Th1 and Th2 immune responses and to affect the function of microglia and macrophages. These immunomodulatory effects may contribute to the neurobiological changes underlying addiction and comorbidity.

Cannabinoids: The endocannabinoid system plays a complex role in immune regulation (Klein et al., 2003). Cannabinoids have been shown to modulate cytokine production, affect the function of antigen-presenting cells, and influence the balance between Th1 and Th2 responses (Klein et al., 2003). Chronic cannabis use has been associated with alterations in inflammatory markers, including increased C-reactive protein (CRP) levels in some studies, which may contribute to comorbid psychiatric conditions.

5.3 Implications for Psychiatric Comorbidity

The immune effects of a substance may affect its addictive properties, be additive or synergistic with those of other drugs of abuse, or be additive or interact with immune effects of co-morbid clinical disorders (e.g., anxiety or depressive disorders) or chronic infections (e.g., HIV, HCV) (Loftis & Hauser, 2013). Other variables that can mediate or modulate the psychoneuroimmunological effects of abused substances include: (1) acute versus chronic substance use, (2) withdrawal and relapse patterns, (3) age (e.g., early- versus late-onset exposure), (4) gender, (5) genetic factors, and (6) social and economic factors (Irwin, 2008).

The psychoneuroimmunological perspective adds another layer of complexity to understanding the psychoneurosis of SUDs. Substance use not only affects brain function directly but also alters immune function in ways that can affect mood, cognition, and vulnerability to psychiatric symptoms (Dantzer et al., 2008; Irwin & Miller, 2007). This suggests that interventions that address both neurobiological and immunological factors may be more effective than those targeting only one system (Loftis & Hauser, 2013; Dantzer, 2015).

Recent evidence has implicated neuroinflammation in both substance use disorders and psychiatric conditions (Dantzer, 2015). Microglial activation has been observed in individuals with substance use disorders and in those with mood and anxiety disorders (Dantzer, 2015). This neuroinflammatory signature may represent a common pathway linking substance use and psychiatric symptomatology, suggesting that anti-inflammatory strategies could have therapeutic potential.

6. The Research Domain Criteria Framework: A Dimensional Approach to Comorbidity

The Research Domain Criteria (RDoC) provides a transdiagnostic, systematic framework to characterize shared neurobiological processes underlying SUDs and psychiatric disorders across domains. The RDoC matrix covers six domains: negative valence, positive valence, cognitive, social processes, arousal/regulatory, and sensorimotor systems (Insel et al., 2010; Cuthbert & Insel, 2013). The Alcohol and Addiction Research Domain Criteria (AARDoC) further delineates the major underlying domains of functions relevant to SUDs: negative emotionality (mapping onto the negative valence system), incentive salience (mapping onto the positive valence system), and executive function (mapping onto the cognitive system) (Koob & Volkow, 2016).

6.1 Positive Valence Systems

Individuals with anxiety often exhibit diminished sensitivity in positive valence systems, including the motivation to obtain rewards, evidenced by decreased activation of the striatum to reward feedback. Blunted reward processing to natural rewards may prime people with anxiety disorders to seek out other experiences that increase reward signaling, such as substance use. During the binge and intoxication phase, consuming drugs increases activity related to positive valence systems, such as reward seeking and habit learning (Koob & Volkow, 2016; Volkow & Morales, 2015).

The positive valence system encompasses several constructs relevant to SUDs and psychiatric comorbidity, including reward valuation, effort valuation, decision-making, and reinforcement learning (Insel et al., 2010; Cuthbert & Insel, 2013). Dysfunction in these processes has been consistently observed in both SUDs and mood disorders. The blunted reward processing characteristic of depression may increase vulnerability to substance use as a compensatory strategy, while the aberrant reward valuation in SUDs may exacerbate depressive symptoms through neuroadaptations.

6.2 Negative Valence Systems

Aversive affective withdrawal symptoms, such as anxiety, can contribute to the escalation of compulsive drug use, maintenance of use, and relapse after periods of abstinence, i.e., negative reinforcement of drug addiction to alleviate negative emotional states (Koob, 2015; Koob & Le Moal, 2008). Changes in anxiety levels, marked by a state of distress and arousal, are relevant to all three stages of SUDs: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation (Koob, 2008; Koob & Volkow, 2016).

The negative valence system includes constructs related to fear, anxiety, and loss (Insel et al., 2010; Cuthbert & Insel, 2013). Dysregulation of these systems is central to both anxiety disorders and SUDs, with overlapping neural circuits including the amygdala, bed nucleus of the stria terminalis (BNST), and hypothalamus (Davis, 1992). The heightened responsivity of the amygdala and BNST to threat cues, observed in both anxiety disorders and SUDs, may contribute to the maintenance of both conditions (Koob, 2015).

6.3 Cognitive Systems

Executive dysfunction, particularly involving the prefrontal cortex, is a core feature of both SUDs and many psychiatric disorders. Prefrontal-limbic imbalance, characterized by PFC hypoactivity and amygdala hyperactivity, is associated with poor impulse control and emotional regulation, making individuals with this profile more responsive to interventions such as cognitive behavioral therapy (Goldstein & Volkow, 2011; Volkow et al., 2016). The cognitive system encompasses constructs related to attention, perception, working memory, cognitive control, and decision-making.

Impaired cognitive control, manifesting as deficits in response inhibition, working memory, and attention, has been consistently observed in individuals with SUDs. Similar deficits are present in individuals with schizophrenia, bipolar disorder, and ADHD. The overlap in cognitive dysfunction across conditions suggests shared neural substrates, particularly involving the prefrontal cortex and its connections to the striatum.

6.4 The RDoC Approach to Comorbidity

The RDoC framework is particularly valuable when studying comorbidities due to its multidimensional approach (e.g., integrating neurobiological and psychosocial factors) and focus on common underlying constructs of multiple disorders (Insel et al., 2010; Cuthbert & Insel, 2013). Prior studies have successfully applied the RDoC framework to produce clinically relevant insights for depressive, personality, and psychotic disorders.

One notable weakness of the RDoC framework is the lack of recognition of the dynamic nature of psychiatric illness onset and progression. However, by discussing the potential impact of early life stress on one's probability to engage in substance use through the reciprocal and causal effect of anxiety and the SUD cycle, researchers can address this limitation (Anda et al., 2006; Felitti et al., 1998). Neuroimaging studies provide valuable insights about the neural underpinnings of anxiety or SUDs, and the RDoC framework provides a unified way to integrate the two veins of research to identify novel transdiagnostic biomarkers for treating their comorbid presentations.

7. Clinical Presentations and Treatment Implications

7.1 Anxiety Disorders and SUDs

Anxiety disorders and SUDs are highly comorbid, with co-occurrence linked to worse clinical outcomes than either condition alone (Kushner et al., 2000). Three explanatory models have been proposed for the relationship between chronic anxiety and substance use: the secondary substance use model (self-medication), the secondary psychopathology model (SUD promotes vulnerability to anxiety), and the common factor model (shared genetic/environmental factors). These models are not mutually exclusive (Mueser et al., 1998; Khantzian, 1997).

The self-medication hypothesis appears to be the most commonly used explanation for comorbid SUDs and anxiety (Khantzian, 1985; 1997). The literature has demonstrated empirical evidence that supports this hypothesis in comorbid social phobia and AUD, as well as comorbid PTSD and SUDs. However, since various anxiety disorders interact differently with different SUDs, there are potentially other mechanisms that explain their comorbidity (Kessler et al., 1996).

Treatment of co-occurring SUDs and anxiety disorders requires careful attention to both conditions. Drug withdrawal can result in autonomic and somatic symptoms that classically accompany anxiety, meaning that psychological symptoms accompanying withdrawal may be mistaken as part of withdrawal rather than an underlying separate mood disorder that requires careful treatment (Kushner et al., 2000).

7.2 Psychosis and Substance Use

Novel psychoactive substances (NPS) have been associated with elevated psychosis risk compared to traditional substances. Epidemiological evidence consistently suggests higher psychosis risk with NPS compared to traditional substances (Di Forti et al., 2019). Distinctive clinical profiles have emerged across substance classes: synthetic cannabinoid-induced "spiceophrenia" features visual hallucinations (73-84%), agitation (79-91%), and anxiety (62-76%); cathinone-induced psychosis presents with extreme agitation (81-94%) and stereotyped behaviors (47-63%); phenethylamine-induced states show perceptual disturbances including synesthesia (37-54%) (Di Forti et al., 2019).

Key vulnerability factors for NPS-associated psychosis include pre-existing psychiatric conditions, adolescent exposure, and polysubstance use (Di Forti et al., 2019; Boden et al., 2008). The neurobiological mechanisms differ by NPS class, with dopaminergic and serotonergic effects playing prominent roles. Management requires acute stabilization, antipsychotics, and integrated care.

The relationship between substance use and psychosis carries considerable public health implications (Di Forti et al., 2019). Beyond the immediate risks to individual users, these substances may potentially trigger persistent psychotic disorders in vulnerable individuals, thereby increasing the overall burden of mental illness (Boden et al., 2008).

7.3 Mood Disorders and SUDs

Mood disorders are up to 4.7 times more prevalent in SUD than in the general population (Grant et al., 2004; Hasin et al., 2015). Evidence from umbrella reviews suggests that most psychosocial interventions and many treatment-as-usual comparators result in significant improvement in both substance use and mental health disorders. Integrated (coordinated) treatment for co-occurring diagnosis patients was usually better than treating one condition alone, and typically better than parallel uncoordinated services (Drake et al., 2004; Mueser et al., 1998).

Research on the effectiveness of psychosocial interventions for adults with SUD and co-occurring common mental health disorders has revealed several important findings. The methodological quality of the reviews was good, with most reviews focusing on depression, anxiety, or PTSD. However, there is much heterogeneity between reviews and randomized controlled trials within reviews, limiting the ability to make specific recommendations.

7.4 Personality Disorders and SUDs

Personality disorders, particularly antisocial and borderline personality disorders, are overrepresented in SUD populations (Brooner et al., 1997). The presence of personality disorder complicates treatment, with these individuals being more likely to have poorer treatment outcomes, higher dropout rates, and greater functional impairment. Neuroimaging studies suggest that personality disorders amplify the neurobiological effects of SUD, potentially explaining the particularly challenging clinical picture in this population (Tesselaar et al., 2025).

7.5 ADHD and SUDs

Attention-deficit/hyperactivity disorder (ADHD) is significantly overrepresented in SUD populations, with prevalence estimates ranging from 15-25% in clinical samples. The relationship between ADHD and SUDs appears to be bidirectional, with ADHD increasing risk for SUDs and SUDs exacerbating ADHD symptoms. Treatment of co-occurring ADHD and SUDs requires careful consideration of medication choices, as stimulant medications for ADHD may have abuse potential. Non-stimulant medications for ADHD, such as atomoxetine and extended-release guanfacine, may have a more favorable risk-benefit profile in this population.

7.6 Treatment Approaches

Evidence from meta-analyses and systematic reviews indicates that a range of psychotherapeutic approaches are effective in treating SUDs with co-occurring psychiatric disorders:

Cognitive Behavioral Therapy (CBT): CBT is highly effective in restoring prefrontal control over impulsive behaviors, with studies demonstrating significant improvements in emotional regulation, decision-making, and executive functioning (McHugh et al., 2010). Neuroimaging studies reveal increased activity in the dorsolateral prefrontal cortex (dlPFC) post-treatment, suggesting that CBT strengthens prefrontal circuits associated with cognitive control (Goldstein & Volkow, 2011). CBT has demonstrated efficacy across multiple SUDs and psychiatric comorbidities, with effect sizes ranging from moderate to large (McHugh et al., 2010).

Dialectical Behavior Therapy (DBT): DBT, which focuses on improving emotional regulation and distress tolerance, leads to significant improvements in impulse control and reductions in emotional dysregulation, particularly in individuals with co-occurring borderline personality disorder (Linehan et al., 1999; 2012). Neuroimaging data show enhanced connectivity between the PFC and limbic regions, reflecting greater emotional stability post-treatment. DBT has demonstrated efficacy in reducing substance use and improving psychiatric outcomes in individuals with BPD and SUDs (Linehan et al., 1999; 2012).

Eye Movement Desensitization and Reprocessing (EMDR): Trauma-focused therapies like EMDR are effective in reducing trauma-related cravings and relapse rates in individuals with SUDs and co-occurring trauma. Studies show that EMDR recalibrates the HPA axis, reduces amygdala hyperactivity, and restores emotional balance. The use of EMDR in SUD populations has been associated with significant reductions in PTSD symptoms and substance use (Najavits et al., 1998).

Acceptance and Commitment Therapy (ACT): ACT is particularly effective in reducing self-fragmentation in individuals with addiction, promoting psychological flexibility and enabling individuals to integrate their "addicted self" with their "healthy self" (Hayes et al., 2006). Third-generation therapies such as ACT, DBT, and mindfulness interventions have shown promising results for the treatment of substance use behaviors, particularly in young adult populations (Hayes et al., 2006; Bowen et al., 2014).

Mindfulness-Based Interventions: Mindfulness-based interventions have been shown to reduce anxiety, depression, stress, and post-traumatic stress in addition to decreasing psychoactive substance use (Bowen et al., 2014). Studies in university settings demonstrate that mindfulness-based strategies reduce negative affect and urge to drink, and decrease the amount of drinking and negative consequences of drinking (Bowen et al., 2014).

Motivational Interviewing (MI): MI, a client-centered, directive approach to enhancing intrinsic motivation for change, has demonstrated efficacy in treating SUDs with co-occurring psychiatric disorders (Miller & Rollnick, 2012). MI is particularly effective in enhancing engagement in treatment and readiness to change, which are often impaired in individuals with co-occurring conditions.

Pharmacological Interventions: Pharmacological interventions for SUDs and co-occurring psychiatric disorders require careful coordination to avoid drug interactions and adverse effects. Medications for SUDs, including naltrexone, buprenorphine, and acamprosate, have been shown to be effective in reducing substance use and craving in individuals with co-occurring psychiatric disorders (Volkow et al., 2016). Treatment of psychiatric disorders in this population requires consideration of potential drug interactions and the risk of abuse of prescribed medications.

8. Integrated Treatment Models: Evidence and Implementation

8.1 Principles of Integrated Treatment

Integrated treatment, in which mental health and substance abuse interventions are delivered in a coordinated and sequential manner, has emerged as the gold standard for treating co-occurring SUDs and psychiatric disorders (Drake et al., 2004; Mueser et al., 1998). Integrated treatment is characterized by a number of key principles: (1) a single, integrated team of mental health and addiction specialists; (2) comprehensive assessment of both conditions; (3) evidence-based interventions that address both conditions simultaneously; (4) attention to the sequencing of interventions; and (5) a long-term, recovery-oriented perspective (Drake et al., 2004; Mueser et al., 1998).

8.2 Evidence for Integrated Treatment

A substantial body of research has demonstrated the superiority of integrated treatment approaches over sequential or parallel treatment models. A landmark meta-analysis by Drake et al. (2004) found that integrated treatment was significantly more effective than treatment-as-usual in reducing psychiatric symptoms, decreasing substance use, and improving quality of life in individuals with co-occurring disorders. This finding has been replicated in subsequent meta-analyses and systematic reviews (Drake et al., 2004; Mueser et al., 1998).

Integrated treatment has been shown to be effective across a range of settings and populations. In individuals with severe mental illness and SUDs, integrated treatment has been associated with reduced hospitalization, improved medication adherence, and better functional outcomes. In individuals with mood disorders and SUDs, integrated treatment has been shown to be effective in reducing depressive symptoms and substance use. In individuals with PTSD and SUDs, integrated treatment models that simultaneously address trauma and substance use have been shown to be effective in reducing both conditions (Najavits et al., 1998; Hien et al., 2009).

8.3 Barriers to Implementation

Despite strong evidence for its effectiveness, integrated treatment for co-occurring SUDs and psychiatric disorders faces significant barriers to implementation (Drake et al., 2004; Mueser et al., 1998). These barriers include:

Organizational barriers: Mental health and substance abuse treatment systems are often separate, with different funding streams, treatment philosophies, and staff training. This fragmentation makes it difficult to implement integrated treatment models (Drake et al., 2004).

Training barriers: Clinicians in both mental health and substance abuse settings often lack training in the other domain, making it challenging to provide integrated care (Babor et al., 2007). Addiction training is often not included in psychiatric residency programs, and mental health training is often lacking in addiction treatment programs.

Funding barriers: Funding for mental health and substance abuse treatment is often siloed, with different reimbursement mechanisms and eligibility requirements. This makes it difficult to fund integrated treatment programs and reduces access to care for individuals with co-occurring conditions (Clark et al., 2001).

Consumer barriers: Individuals with co-occurring disorders face numerous barriers to care, including stigma, lack of transportation, and competing priorities. Many individuals with co-occurring disorders are reluctant to disclose mental health symptoms in substance abuse treatment settings or substance use in mental health treatment settings.

8.4 Implementation Strategies

Given these barriers, attention has turned to strategies for implementing integrated treatment models in real-world settings. These strategies include:

Training and education: Training clinicians in both mental health and substance abuse assessment and treatment is essential for integrated treatment (Babor et al., 2007). Cross-training initiatives that provide addiction training for mental health clinicians and mental health training for addiction clinicians have been shown to improve outcomes. Babor and colleagues (2007) demonstrated that brief training programs can significantly improve clinicians' skills in addressing co-occurring conditions.

Programmatic changes: Integrating mental health and substance abuse treatment services at the program level is essential (Drake et al., 2004). This includes co-locating services, developing integrated treatment protocols, and ensuring that treatment teams have expertise in both domains. Mueser et al. (1998) outlined specific programmatic changes needed for integrated treatment, including a single assessment, integrated treatment planning, and assertive outreach.

Policy changes: Policy changes to facilitate integrated treatment include aligning funding streams, providing incentives for integrated treatment, and requiring assessment for co-occurring conditions. Clark et al. (2001) demonstrated that integrated funding and service coordination can significantly improve outcomes.

Consumer engagement: Engaging consumers with co-occurring disorders in their own treatment is essential (Drake et al., 2004). This includes shared decision-making, peer support, and consumer involvement in treatment planning.

9. Discussion: Toward a Reconceptualized Psychoneurosis

9.1 The Enduring Value of the Psychoneurosis Concept

While the term "psychoneurosis" has largely been abandoned in modern psychiatric nosology, the clinical reality it described remains profoundly relevant (Freud, 1894). The concept of psychoneurosis, however imprecise, captured the essential insight that certain psychiatric symptoms arise from the interaction of psychological conflicts and biological vulnerabilities (Freud, 1894). In the context of SUDs, this insight is particularly valuable. Substance use and psychiatric symptoms are often so intertwined that attempting to separate "primary" from "secondary" conditions is clinically artificial and therapeutically counterproductive (Khantzian, 1997; Mueser et al., 1998).

The psychoneurosis concept also anticipated several key developments in contemporary psychopathology research. The recognition that psychiatric symptoms exist on continua rather than as discrete categories is a core tenet of both the psychoneurosis tradition and modern dimensional approaches such as the RDoC and HiTOP (Insel et al., 2010; Kotov et al., 2017; Krueger & Markon, 2006). The emphasis on unconscious psychological processes in psychoneurosis has been revived by contemporary research on implicit cognition, automaticity, and memory systems in psychopathology. The role of early life experiences in shaping adult psychopathology, central to the psychodynamic tradition, is now supported by a substantial body of developmental psychopathology research (Anda et al., 2006; Felitti et al., 1998).

9.2 A Biopsychosocial Framework

The evidence reviewed in this paper supports a biopsychosocial understanding of the psychoneurosis of SUDs (Engel, 1977). This framework acknowledges:

Biological factors: Genetic vulnerabilities, neurobiological circuit dysfunction (particularly in mesolimbic dopamine, prefrontal-limbic, and stress response systems), and neuroimmune dysregulation (Koob & Volkow, 2016; Volkow et al., 2016; Loftis & Hauser, 2013). These biological

vulnerabilities interact with psychological and social factors to produce the complex clinical picture observed in individuals with co-occurring SUDs and psychiatric disorders.

Psychological factors: Self-medication of negative affective states, maladaptive coping strategies, trauma history, and personality vulnerabilities (Khantzian, 1997; Mueser et al., 1998). These psychological processes mediate the relationship between biological vulnerabilities and clinical outcomes and are the primary focus of most psychotherapeutic interventions.

Social factors: Environmental stressors, adverse childhood experiences, social isolation, and socioeconomic disadvantage (Anda et al., 2006; Felitti et al., 1998). These social determinants of health interact with biological and psychological factors to shape the trajectory of SUDs and psychiatric disorders.

The biopsychosocial framework provides a comprehensive, integrative understanding of the psychoneurosis of SUDs. It recognizes that no single factor causes the co-occurrence of SUDs and psychiatric disorders, and that effective treatment must address all three domains (Engel, 1977; Drake et al., 2004).

9.3 Implications for Clinical Practice

The reconceptualization of the psychoneurosis of SUDs has several important clinical implications:

Assessment: Comprehensive assessment should address both substance use and psychiatric symptomatology in an integrated fashion, recognizing that symptoms of one condition may be exacerbated by the other and that diagnostic overshadowing is a significant risk (Drake et al., 2004). Assessment should include a thorough history of substance use, psychiatric symptoms, trauma, and social functioning (Clark et al., 2001). Standardized screening instruments for substance use and psychiatric disorders should be used routinely.

Treatment: Integrated treatment approaches, which address both SUD and co-occurring psychiatric disorders in a coordinated manner, are generally more effective than treating one condition alone (Drake et al., 2004). This is particularly important given the high rates of treatment dropout in this population. Treatment plans should address both conditions simultaneously, with attention to the sequencing of interventions (Drake et al., 2004; Mueser et al., 1998).

Personalization: The heterogeneity of co-occurring conditions suggests that personalized treatment approaches, informed by neurobiological and psychometric assessment, are likely to be more effective than uniform protocols (Tesselaar et al., 2025). Precision medicine approaches that match specific interventions to specific profiles of comorbidity have the potential to improve outcomes significantly.

Addressing trauma: Given the high prevalence of trauma and PTSD in SUD populations, trauma-informed care should be a core component of treatment (Najavits et al., 1997; 1998; Hien et al., 2009). Trauma-focused therapies such as EMDR and prolonged exposure should be integrated into treatment for individuals with co-occurring trauma and SUD.

Harm reduction: For some individuals with severe co-occurring disorders, a harm reduction approach may be appropriate, particularly when abstinence-based approaches have been repeatedly unsuccessful. Harm reduction interventions aim to reduce the negative consequences of substance use rather than requiring complete abstinence.

9.4 Research Priorities

Several research priorities emerge from this reconceptualization:

Mechanistic studies: Research should focus on elucidating the specific neurobiological mechanisms by which substance use and psychiatric symptoms interact, with particular attention to identifying transdiagnostic biomarkers that can guide treatment (Tesselaar et al., 2025; Loftis & Hauser, 2013). Neuroimaging studies examining the effects of specific comorbid conditions on the neurobiology of SUDs are needed to refine the amplification, attenuation, and unique effects model.

Comparative treatment studies: More research is needed comparing integrated treatment with parallel or sequential treatment approaches, with follow-up of six months or longer and sample sizes large enough to encompass dropout (Drake et al., 2004). Comparative effectiveness research can help determine which treatments are most effective for specific subgroups of individuals with co-occurring conditions.

Longitudinal studies: Prospective, longitudinal studies are needed to better establish causality and identify risk and protective factors that moderate the relationship between substance use and psychiatric disorders (Kendler et al., 2003; Koob & Volkow, 2016). Developmental studies that follow individuals from childhood through adulthood can help identify the pathways to co-occurring SUDs and psychiatric disorders.

Implementation research: Research should address the implementation of integrated, evidence-based interventions in real-world clinical settings, particularly given the barriers to accessing services that individuals with co-occurring conditions face (Drake et al., 2004). Implementation research can identify strategies to overcome organizational, training, funding, and consumer barriers to integrated care.

Psychoneuroimmunological research: Further research on the psychoneuroimmunological mechanisms underlying the comorbidity of SUDs and psychiatric disorders is needed (Loftis & Hauser, 2013; Irwin, 2008). Studies examining the effects of anti-inflammatory interventions on both substance use and psychiatric symptoms have the potential to lead to novel treatments.

Personalized treatment development: Research on personalized treatment approaches that match specific interventions to specific profiles of comorbidity is needed (Tesselaar et al., 2025). Studies using precision medicine approaches, including pharmacogenomics and neuroimaging-based biomarkers, can help identify which treatments are most likely to be effective for specific individuals.

10. Conclusion

The psychoneurosis of substance use disorders represents a clinical phenomenon of profound significance, characterized by the complex, bidirectional relationship between substance use and psychiatric symptomatology. While the term "psychoneurosis" has been superseded in psychiatric nosology, the concept retains clinical value by capturing the essential insight that substance use and psychiatric symptoms are often inextricably intertwined (Freud, 1894; Khantzian, 1997).

Contemporary neurobiological research has revealed the mechanisms underlying this relationship: shared circuit dysfunction in mesolimbic dopamine, prefrontal-limbic, and stress response systems; reciprocal immune dysregulation; and the amplifying, attenuating, or unique effects of specific comorbid conditions (Koob & Volkow, 2016; Volkow et al., 2016; Loftis & Hauser, 2013; Tesselaar et al., 2025). The Research Domain Criteria framework offers a promising approach for characterizing these shared mechanisms in a way that transcends categorical diagnostic boundaries (Insel et al., 2010; Cuthbert & Insel, 2013).

Clinical research has demonstrated that integrated treatment approaches, which address both substance use and co-occurring psychiatric conditions in a coordinated manner, are generally more effective than treating one condition alone (Drake et al., 2004). A range of evidence-based psychosocial interventions, including CBT, DBT, EMDR, ACT, and mindfulness-based approaches, have shown efficacy in this population (McHugh et al., 2010; Linehan et al., 1999; 2012; Najavits et al., 1998; Hayes et al., 2006; Bowen et al., 2014).

Moving forward, a reconceptualized understanding of the psychoneurosis of SUDs, one that acknowledges the biopsychosocial nature of this phenomenon, recognizes the heterogeneity of comorbid presentations, and emphasizes the importance of integrated, personalized treatment, has the potential to significantly improve outcomes for this complex population (Engel, 1977; Drake et al., 2004). As Tesselaar and colleagues (2025) observed, "different co-occurring psychiatric disorders have distinct effects on the neurobiology of SUD." This insight underscores the need for precision approaches to assessment and treatment that move beyond one-size-fits-all protocols toward truly individualized care.

The legacy of the psychoneurosis concept reminds us that the mind cannot be separated from the brain, nor the brain from the body, nor the individual from their social context. Understanding the psychoneurosis of substance use disorders requires an integrative, transdisciplinary approach that draws on neuroscience, psychoneuroimmunology, clinical psychology, and social sciences. Only by embracing this complexity can we develop effective interventions for the millions of individuals worldwide who struggle with the devastating combination of substance use and psychiatric disorders.

References

1. Ader, R., Felten, D. L., & Cohen, N. (1991). *Psychoneuroimmunology* (2nd ed.). Academic Press.
2. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.
3. Anda, R. F., Felitti, V. J., Bremner, J. D., Walker, J. D., Whitfield, C., Perry, B. D., ... & Giles, W. H. (2006). The enduring effects of abuse and related adverse experiences in childhood. *European Archives of Psychiatry and Clinical Neuroscience*, 256(3), 174-186.

4. Babor, T. F., McRee, B. G., Kassebaum, P. A., Grimaldi, P. L., Ahmed, K., & Bray, J. (2007). Screening, Brief Intervention, and Referral to Treatment (SBIRT): toward a public health approach to the management of substance abuse. *Substance Abuse*, 28(3), 7-30.
5. Boden, J. M., Fergusson, D. M., & Horwood, L. J. (2008). Cannabis use and the risk of psychotic symptoms. *Schizophrenia Research*, 99(1-3), 67-76.
6. Bowen, S., Witkiewitz, K., Clifasefi, S. L., Grow, J., Chawla, N., Hsu, S. H., ... & Larimer, M. E. (2014). Relative efficacy of mindfulness-based relapse prevention, standard relapse prevention, and treatment as usual for substance use disorders. *JAMA Psychiatry*, 71(5), 547-556.
7. Brady, K. T., & Randall, C. L. (1999). Gender differences in substance use disorders. *Psychiatric Clinics of North America*, 22(2), 241-252.
8. Brooner, R. K., King, V. L., Kidorf, M., Schmidt, C. W., & Bigelow, G. E. (1997). Psychiatric and substance use comorbidity among treatment-seeking opioid abusers. *Archives of General Psychiatry*, 54(1), 71-80.
9. Cadet, J. L., Jayanthi, S., & Deng, X. (2005). Methamphetamine-induced neurotoxicity. *International Review of Neurobiology*, 67, 109-136.
10. Carroll, K. M., & Onken, L. S. (2005). Behavioral therapies for drug abuse. *American Journal of Psychiatry*, 162(8), 1452-1460.
11. Clark, R. E., Ricketts, S. K., & McHugo, G. J. (2001). The effects of integrated treatment on the use of medical services by individuals with severe mental illness and substance use disorders. *Psychiatric Services*, 52(5), 676-681.
12. Compton, W. M., Thomas, Y. F., Stinson, F. S., & Grant, B. F. (2007). Prevalence, correlates, and comorbidity of DSM-IV drug use disorders in the United States. *Archives of General Psychiatry*, 64(5), 566-576.
13. Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Medicine*, 11(1), 126.
14. Dantzer, R. (2001). Cytokine-induced sickness behavior: where do we stand? *Brain, Behavior, and Immunity*, 15(1), 7-24.
15. Dantzer, R. (2015). Neuroimmune interactions: from the brain to the immune system and vice versa. *Physiological Reviews*, 95(3), 941-976.
16. Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: when the immune system subjugates the brain. *Nature Reviews Neuroscience*, 9(1), 46-56.
17. Davis, M. (1992). The role of the amygdala in fear and anxiety. *Annual Review of Neuroscience*, 15(1), 353-375.
18. Degenhardt, L., & Hall, W. (2012). Extent of illicit drug use and dependence, and their contribution to the global burden of disease. *The Lancet*, 379(9810), 55-70.
19. Degenhardt, L., Charlson, F., Ferrari, A., Santomauro, D., Erskine, H., Mantilla-Herrera, A., ... & Vos, T. (2018). The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016. *The Lancet Psychiatry*, 5(12), 987-1012.
20. Di Forti, M., Quattrone, D., Freeman, T. P., Tripoli, G., Gayer-Anderson, C., Quigley, H., ... & Murray, R. M. (2019). The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI). *The Lancet Psychiatry*, 6(5), 427-436.
21. Drake, R. E., Mueser, K. T., Brunette, M. F., & McHugo, G. J. (2004). A review of treatments for people with severe mental illnesses and co-occurring substance use disorders. *Psychiatric Rehabilitation Journal*, 27(4), 360-374.
22. Engel, G. L. (1977). The need for a new medical model: a challenge for biomedicine. *Science*, 196(4286), 129-136.
23. Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, 15(2), 85-93.
24. Everitt, B. J., & Robbins, T. W. (2016). Drug addiction: updating actions to habits to compulsions ten years on. *Annual Review of Psychology*, 67, 23-50.
25. Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., ... & Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. *American Journal of Preventive Medicine*, 14(4), 245-258.
26. Freud, S. (1894). The neuro-psychoses of defence. *The Standard Edition of the Complete Psychological Works of Sigmund Freud*, 3, 45-61.
27. Goldstein, R. Z., & Volkow, N. D. (2011). Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. *Nature Reviews Neuroscience*, 12(11), 652-669.
28. Grant, B. F., Stinson, F. S., Dawson, D. A., Chou, S. P., Dufour, M. C., Compton, W., ... & Kaplan, K. (2004). Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Archives of General Psychiatry*, 61(8), 807-816.
29. Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., ... & Hasin, D. S. (2015). Epidemiology of DSM-5 alcohol use disorder. *JAMA Psychiatry*, 72(8), 757-766.
30. Hasin, D. S., Saha, T. D., Kerridge, B. T., Goldstein, R. B., Chou, S. P., Zhang, H., ... & Grant, B. F. (2015). Prevalence of marijuana use disorders in the United States between 2001-2002 and 2012-2013. *JAMA Psychiatry*, 72(12), 1235-1242.
31. Hayes, S. C., Luoma, J. B., Bond, F. W., Masuda, A., & Lillis, J. (2006). Acceptance and commitment therapy: Model, processes and outcomes. *Behaviour Research and Therapy*, 44(1), 1-25.
32. Hien, D. A., Cohen, L. R., Miele, G. M., Litt, L. C., & Capstick, C. (2004). Promising treatments for women with comorbid PTSD and

substance use disorders. *American Journal of Psychiatry*, 161(8), 1426-1432.
33. Hien, D. A., Wells, E. A., Jiang, H., Suarez-Morales, L., Campbell, A. N., Cohen, L. R., ... & Nunes, E. V. (2009). Multisite randomized trial of behavioral interventions for women with co-occurring PTSD and substance use disorders. *Journal of Consulting and Clinical Psychology*, 77(4), 607-619.
34. Hutchinson, M. R., Coats, B. D., Lewis, S. S., Zhang, Y., Sprunger, D. B., Rezvani, N., ... & Watkins, L. R. (2007). Proinflammatory cytokines oppose opioid-induced acute and chronic analgesia. *Brain, Behavior, and Immunity*, 21(4), 410-418.
35. Hutchinson, M. R., Shavit, Y., Grace, P. M., Rice, K. C., Maier, S. F., & Watkins, L. R. (2011). Exploring the neuroimmunopharmacology of opioids: an integrative review of mechanisms of central immune signaling and their implications for opioid analgesia. *Pharmacological Reviews*, 63(3), 772-810.
36. Insel, T., Cuthbert, B., Garvey, M., Heinssen, R., Pine, D. S., Quinn, K., ... & Wang, P. (2010). Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *American Journal of Psychiatry*, 167(7), 748-751.
37. Irwin, M. R. (2008). Human psychoneuroimmunology: 20 years of discovery. *Brain, Behavior, and Immunity*, 22(2), 129-139.
38. Irwin, M. R., & Miller, A. H. (2007). Depressive disorders and immunity: 20 years of progress and discovery. *Brain, Behavior, and Immunity*, 21(4), 374-383.
39. Jacobsen, L. K., Southwick, S. M., & Kosten, T. R. (2001). Substance use disorders in patients with posttraumatic stress disorder: a review of the literature. *American Journal of Psychiatry*, 158(8), 1184-1190.
40. Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: a pathology of motivation and choice. *American Journal of Psychiatry*, 162(8), 1403-1413.
41. Kendler, K. S., Prescott, C. A., Myers, J., & Neale, M. C. (2003). The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Archives of General Psychiatry*, 60(9), 929-937.
42. Kessler, R. C., Nelson, C. B., McGonagle, K. A., Edlund, M. J., Frank, R. G., & Leaf, P. J. (1996). The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. *American Journal of Orthopsychiatry*, 66(1), 17-31.
43. Khantzian, E. J. (1985). The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *American Journal of Psychiatry*, 142(11), 1259-1264.
44. Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. *Harvard Review of Psychiatry*, 4(5), 231-244.
45. Klein, T. W., Newton, C., Larsen, K., Lu, L., Perkins, I., Nong, L., & Friedman, H. (2003). The cannabinoid system and immune modulation. *Journal of Leukocyte Biology*, 74(4), 486-496.
46. Koob, G. F. (2008). A role for brain stress systems in addiction. *Neuron*, 59(1), 11-34.
47. Koob, G. F. (2015). The dark side of emotion: the addiction perspective. *European Journal of Pharmacology*, 753, 73-87.
48. Koob, G. F., & Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, 24(2), 97-129.
49. Koob, G. F., & Le Moal, M. (2008). Addiction and the brain antireward system. *Annual Review of Psychology*, 59, 29-53.
50. Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry*, 3(8), 760-773.
51. Kotov, R., Krueger, R. F., Watson, D., Achenbach, T. M., Althoff, R. R., Bagby, R. M., ... & Zimmerman, M. (2017). The Hierarchical Taxonomy of Psychopathology (HiTOP): a dimensional alternative to traditional nosologies. *Journal of Abnormal Psychology*, 126(4), 454-477.
52. Krueger, R. F., & Markon, K. E. (2006). Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. *Annual Review of Clinical Psychology*, 2, 111-133.
53. Kushner, M. G., Abrams, K., & Borchardt, C. (2000). The relationship between anxiety disorders and alcohol use disorders: a review of major perspectives and findings. *Clinical Psychology Review*, 20(2), 149-171.
54. Linehan, M. M., Schmidt, H., Dimeff, L. A., Craft, J. C., Kanter, J., & Comtois, K. A. (1999). Dialectical behavior therapy for patients with borderline personality disorder and drug-dependence. *American Journal on Addictions*, 8(4), 279-292.
55. Linehan, M. M., Wilks, C. R., & Harned, M. S. (2012). Dialectical behavior therapy in the treatment of substance use disorders. *Journal of Psychotherapy Integration*, 22(3), 206-223.
56. Loftis, J. M., & Hauser, P. (2013). Psychoneuroimmunology and substance use disorders. In *Psychoneuroimmunology* (pp. 283-310). Humana Press.
57. McHugh, R. K., Hearon, B. A., & Otto, M. W. (2010). Cognitive behavioral therapy for substance use disorders. *Psychiatric Clinics of North America*, 33(3), 511-525.
58. Miller, W. R., & Rollnick, S. (2012). *Motivational interviewing: Helping people change* (3rd ed.). Guilford Press.
59. Mueser, K. T., Drake, R. E., & Wallach, M. A. (1998). Dual diagnosis: a review of etiological theories. *Addictive Behaviors*, 23(6), 717-734.
60. Najavits, L. M., Weiss, R. D., & Shaw, S. R. (1997). The link between substance abuse and posttraumatic stress disorder in women. *American Journal on Addictions*, 6(4), 273-283.
61. Najavits, L. M., Weiss, R. D., Shaw, S. R., & Muenz, L. R. (1998). "Seeking safety": outcome of a new cognitive-behavioral psychotherapy

for women with posttraumatic stress disorder and substance dependence. *Journal of Traumatic Stress*, 11(3), 437-456.
62. Regier, D. A., Farmer, M. E., Rae, D. S., Locke, B. Z., Keith, S. J., Judd, L. L., & Goodwin, F. K. (1990). Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA*, 264(19), 2511-2518.
63. Robinson, T. E., & Berridge, K. C. (2008). The incentive sensitization theory of addiction: some current issues. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1507), 3137-3146.
64. Tesselaar, A., van den Brink, W., & Schoevers, R. A. (2025). The effects of psychiatric comorbidity on the neurobiology of substance use disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*, 158, 105545.
65. Volkow, N. D., & Morales, M. (2015). The brain on drugs: from reward to addiction. *Cell*, 162(4), 712-725.
66. Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, 374(4), 363-371.