Proposed Study Examining Associations between Psychiatric Comorbidities and Substance Abuse Patterns Through the Lens of Drugs' Pharmacological Effects

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Introduction

Understanding Substance Use Disorder (SUD) mandates the examination of comorbid psychiatric disorders - that is, the relationship between simultaneous SUD and non-SUD psychiatric disorders (NSPD) in the same individual. Approximately half of Americans diagnosed with SUD also have concurrent NSPD diagnoses, a statistic that has not deviated under or over 10% in the last decade (SAMSHA, 2019). As such, considering comorbid disorders when discussing SUD is imperative not just due to its high prevalence but also its poor treatment outcomes. Those who suffer from both SUD and NSPD have higher reported psychopathological severity (EMCDDA, 2016). Furthermore, the common co-occurrence of the two disorders suggests common pathology, etiology, and other possibly unexplored links between them (NIH, 2020).

This high rate of comorbidity has prompted decades of epidemiological research. National psychiatric epidemiological surveys have served as a vital method since the early 20th century in advancing the understanding of the link between SUD and NSPD. Notable examples include the National Comorbidity Survey (NCS), National Longitudinal Alcohol Epidemiologic Survey (NLAES), and National Household Survey on Drug Abuse (NHSDA), all of which preceded the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) used in this current study (Hasin & Grant et.al, 2015). Previous studies done across these surveys (including NESARC) have consistently shown that 1) broadly speaking, substance abuse and a co-occurring NSPD is the rule of thumb, not the exception (Demetrovics, 2009) 2) mood disorders have been found to have a stronger association with drug use disorders rather than anxiety disorders (Conway et.al,2006; Swendsen, 2011; Grant, 2004) 3) antisocial personality disorder (ASPD) diagnosis has the highest increase in risk of co-occurring SUD (Low, 2024; Kandel et.al, 2001) and 4) cannabis users have the lowest rates of a co-occurring NSPD (Hasin & Grant et.al, 2015; Demetrovics, 2009).

While these patterns are well-established, critical questions remain about the specific relationships between different substances and psychiatric disorders. For example, studies have reported mixed findings on whether the *type* of mood or anxiety disorder is relevant to comorbidities (i.e., generalized anxiety disorder vs panic disorder). Does ASPD have the highest risk of co-occurring SUD simply because there are far less clear treatment plans in comparison to other disorders, or is it specific to the psychopathology of ASPD? On the other hand, is there an

association between types or classes of drugs and co-occurring NSPD? How have cannabis comorbidity rates evolved since the drug's legalization?

Such questions remain unanswered in part due to methodological challenges. Historically, the diagnostic criteria for psychiatric illnesses and addictions have evolved, complicating the accumulation and analysis of data and producing variability in findings over time. Moreover, data on certain drugs of abuse and psychiatric disorders have been limited. For example, national data on cigarette *addiction* (not just usage) is sparse – most likely because there are no dedicated nicotine rehabilitation programs comparable to Alcoholics Anonymous or treatment facilities designed for other drug addictions (Kandel et.al, 2001). Less diagnosed disorders such as histrionic or obsessive compulsive personality disorder have also been limited due to smaller sample sizes and thus higher margins of error (Demetrovics, 2009).

Beyond these methodological limitations, existing research using epidemiological surveys have several practical limitations that need to be addressed. Most studies do not classify the substances of abuse, and those that do are now outdated; previous landmark studies conducted by Swendsen et.al and Kandel et.al (using NCS and NHSDA, respectively) classified substances as either cigarettes, alcohol, or illicit drugs. Not only were these studies conducted before cannabis legalization, but the classification also disregards the number of 'illicit' drugs that can still be abused via prescription and feeds into the misleading but widespread narrative that there is a clear distinction between alcohol and other 'hard drugs'.

Additionally, while previous studies have examined SUD comorbidities with either personality disorders or affective/anxiety disorders, few have simultaneously analyzed patterns across all three diagnostic categories. For example, the NCS reported associations between specific mood and anxiety disorders (excluding personality disorders) and the presence of any SUD. The NLAES examined the association between 7 drug use disorders (separately for abuse and dependence) and major depression only (Conway et.al, 2006). The tendency to study SUD comorbidities in isolation - examining either personality disorders *or* affective/anxiety disorders - has limited our ability to compare relative comorbidity patterns across the full spectrum of psychiatric diagnoses.

This study aims to address these gaps in two ways. First, comorbidity patterns are compared across all three major NSPD types (personality, affective, and anxiety). Second, drugs of abuse are categorized by their pharmacological effects on the central nervous system (stimulants, depressants, and analgesics. The rationale for using this lens stems from both clinical and policy considerations.

Grouping drugs by their central nervous system effects may provide critical insight into potential etiological and neurobiological links between NSPD and substance preferences. . Previous research suggests several potential patterns of association between specific psychiatric disorders and substance use preferences. At the neurobiological level, established links between certain

disorders and neurotransmitter systems may predict substance preferences based on pharmacological effects. For instance, the documented relationship between Cluster B personality disorders and dopamine dysregulation suggests these individuals may preferentially abuse stimulants over other substances- studies suggest that this dysfunction may predispose this population towards stimulants due to their direct mediation in dopamine signaling, rather than substances like opioids or alcohol that primarily act on non-dopaminergic receptors (Ersch et.al, 2013; Vonmoos et.al, 2019; Conway et.al, 2002). Similarly, the anxiolytic properties of depressants may result in higher rates of depressant abuse among individuals with anxiety disorders (Turner et.al 2018). Identifying such preferential patterns between psychiatric populations and specific CNS effects could elucidate both the underlying psychopathology that drives substance selection and the pharmacological properties that make certain substances particularly addictive and rewarding for specific psychiatric conditions.

A large body of existing literature was published under the diagnostic framework of either the 3rd or 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV), in which drug abuse was distinguished from drug dependence. This distinguishment, primarily marked by the presence of withdrawal/tolerance symptoms, has since been recognized as clinically invalid and arbitrary. Not only did abuse often lead to dependence, but substance-related issues exist on a spectrum of severity rather than two rigid categories. Moreover, these versions of the DSM did *not* align with the World Health Organization's International Classification of Diseases and thus perpetuated conflicting results with studies from other countries. The fifth and latest version, DSM V, was published in 2013 and eliminated the distinction in favor of the unified diagnosis 'substance use disorder'. (Substance Abuse and Mental Health Services Administration, 2016). The current study reanalyzes NESARC data using contemporary DSM V criteria, offering a fresh and updated perspective in a body of literature that has primarily used older diagnostic manuals

Traditional research on substance use and mental health often relies on simple legal versus illegal drug classifications. However, this study takes a more nuanced approach by categorizing substances according to their pharmacological properties - specifically as stimulants, depressants, and analgesics. Through this refined classificatory lens, we investigate the relationships between specific drug categories and various psychiatric conditions, including affective, anxiety, and personality disorders. This approach aims to provide a more comprehensive understanding of how different substance types may relate to specific psychiatric diagnoses. These findings could have important implications for further understanding the complex relationship between comorbid substance use and psychiatric disorders.

Methods

Wave 1 of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) was conducted in 2001-2002 and included 43,093 adult participants aged 18 and older from civilian, non-institutionalized sectors of the United States. The survey Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS) was conducted in-person and computer-

assisted. The resulting data includes information related to diagnoses and symptoms of psychiatric and substance use disorders as defined by the DSM-IV, family history of such disorders, usage of treatment services, socioeconomic details, and stressful life events from the past year. AUDADIS has been externally validated in cross-national studies involving multiple diagnostic instruments, including the Composite International Diagnostic Interview (CIDI) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) and multiple test-retest studies.

Measures

The NESARC assessed substance abuse diagnoses through a hierarchical screening process. Respondents first answered broad questions about addiction-related behaviors and perceptions in the previous 12 months (e.g., 'arguments with family or friends due to drug use') without reference to specific substances. Affirmative respondents were then asked whether these behaviors occurred with specific substances in the previous 12 months. These substance-specific responses were represented by ordinal categorical variables, scaled from 0 to 3, abuse/dependence severity for each substance; 0 indicating no diagnosis, and higher values indicating increasing severity (1: abuse only, 2: dependence only, 3: both abuse and dependence combined).

It is important to note that during the data collection period, the DSM-IV criteria were used, which considers presence of withdrawal and tolerance symptoms as the main markers separating dependence from abuse diagnoses (Treatment for Substance Abuse, 1970). With the advent of DSM-V, which no longer employs this distinction, new binary variables were constructed: responses ranging from 1 to 3 were recoded as 1 (indicating the presence of a SUD), while a response of 0 remained indicative of no such disorder.

To categorize the substances of abuse, three new binary variables were constructed: stimulants, depressants, and analgesics (eg, ‘stimulants = 1’ would indicate the presence of nicotine, amphetamine, and/or cocaine abuse). These classifications were determined based on FDA documentation (Center for Drug Evaluation and Research, n.d.). Table 1 clarifies the breakdown of the variables constructed to classify the substances of abuse.

Table 1

Classification	**Drugs**
Stimulants	Nicotine, amphetamines, cocaine
Depressants	Alcohol, sedatives, tranquilizers
Analgesic	Heroin, opioids, cannabis

For each NSPD included in the study, diagnostic questions aligned with DSM-IV were administered. These questions aimed to assess symptoms and behaviors indicative of specific

disorders. Based on participant responses to these diagnostic questions, binary variables were then constructed to indicate the presence or absence of each disorder. Each binary variable was coded such that a value of 1 represented the presence of the disorder, and a value of 0 indicated its absence. These diagnostic variables were then systemically categorized by the type of disorder based on the DSM V (Reigier, 2013). These classifications are shown in Table 2. Each disorder type was encoded into 3 constructed binary variables that indicated the presence (1) or absence (0) of the disorder.

Table 2

NSPD	
Affective	Major depression, manic (bipolar I), hypomanic (bipolar II)
Anxiety	Generalized anxiety disorder, panic without agoraphobia, panic with agoraphobia
Personality	Antisocial, obsessive compulsive personality disorder, paranoid, schizoid, dependent, avoidant

The primary analysis consisted of three separate logistic regression models, each using one of the constructed CNS drug categories (stimulant, depressant, or analgesic) as the response variable. Given that nicotine use accounted for over 50% of stimulant cases, additional logistic regression analyses were conducted separately for each specific stimulant substance (nicotine, amphetamine, and cocaine). This supplementary analysis helped determine whether the associations found in the aggregate stimulant model were primarily driven by nicotine use or reflected patterns consistent across all stimulant substances.

While the initial logistic regression models provided insights into the relationships between psychiatric disorders and each substance category independently, they could not account for individuals who used multiple substances or distinguish between single-substance versus polysubstance use patterns. Therefore, a multinomial logistic regression model was employed to simultaneously examine five distinct usage patterns: no drug use (reference category), exclusive use of stimulants, exclusive use of depressants, exclusive use of analgesics, and polysubstance use. This approach allowed for a more nuanced understanding of how psychiatric disorders might differentially associate with single-substance versus polysubstance use patterns, providing insights that would not be captured by the individual logistic regression models alone.

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