Validity of the DSM-5 craving criterion for alcohol, tobacco, cannabis, cocaine, heroin, and non-prescription use of prescription painkillers (opioids)

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Abstract

Background: Although the DSM-5 was adopted in 2013, validity of the new substance use disorder (SUD) diagnosis and craving criterion has not been investigated systematically across substances.

Methods: Adults (N=588) who engaged in binge drinking or illicit drug use and endorsed at least one DSM-5 SUD criterion were included. DSM-5 SUD criteria were assessed for alcohol, tobacco, cannabis, cocaine, heroin, and opioids. Craving was considered positive if "wanted to use so badly that couldn't think of anything else" (severe craving) or "felt a very strong desire or urge to use" (moderate craving) was endorsed. Baseline information on substance-related variables and psychopathology was collected, and electronic daily assessment queried substance use for the following 90 days. For each substance, logistic regression estimated the association between craving and validators, i.e., variables expected to be related to craving/SUD, and whether association with the validators differed for DSM-5 SUD diagnosed with craving as a criterion versus without.

Results: Across substances, craving was associated with most baseline validators (p-values<0.05); neither moderate nor severe craving consistently showed greater associations. Baseline craving predicted subsequent use (odds ratios: 4.2 [alcohol] – 234.3 [heroin]; p's 0.0001), with stronger associations for moderate than severe craving (p's <0.05). Baseline DSM-5 SUD showed stronger associations with subsequent use when diagnosed with craving than without (p's <0.05).

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Conclusion: The DSM-5 craving criterion as operationalized in this study is valid. Including craving improves validity of DSM-5 SUD diagnoses, and clinical relevance, since craving may cause impaired control over use and development and maintenance of SUD.

Introduction

Substance use and substance use disorders (SUD) are leading preventable causes of morbidity and mortality (GBD Alcohol Drug Use Collaborators, 2018; Glei & Preston, 2020; Grant et al., 2020; Rehm & Shield, 2019; U. S. Burden of Disease Collaborators, 2018). SUD are associated with poorer physical, mental, social, and economic functioning (Chou et al., 2016; Grant et al., 2015; Grant et al., 2016; O'Brien et al., 2004), and are increasing in prevalence (Grant et al., 2017; Grant et al., 2020; Hasin et al., 2019; John & Wu, 2017; Kerridge et al., 2019; Martins et al., 2017; Saha et al., 2016). A better understanding of the elements of SUD is important to facilitate identification of risk factors, and to develop and implement effective prevention and intervention strategies.

Substance craving, i.e., a compulsion or strong desire to use a substance, is considered by many as key to substance use and SUD development and persistence (Auriacombe et al., 2018; Sayette, 2016; Tiffany & Wray, 2012). Craving is related to likelihood of use (Serre et al., 2015) and may lead to impaired control over use (Sayette, 2016; Tiffany & Wray, 2012) and recurrent SUD (American Psychiatric Association, 2013). Thus, the Diagnostic and Statistical Manual of Mental Disorders, DSM-5 (American Psychiatric Association, 2013) added a craving criterion to the SUD diagnostic criteria (Hasin et al., 2013). Indirect support for inclusion of the craving criterion came from neurobiological, pharmacological, genetic, and behavioral studies suggesting the centrality of craving to SUD (Hasin et al., 2013), while direct support came from item response theory (IRT) studies showing that across substances, craving fit well with the other DSM-5 SUD criteria (Casey et al., 2012; Castaldelli-Maia et al., 2015; Cherpitel et al., 2010; Chung et al., 2012; Gilder et al., 2014; Hasin et al., 2012; Hasin et al., 2013; Kervran et al., 2020; Keyes et al., 2011; Mewton et al., 2011; Saha et al., 2020; Serier et al., 2019; Shmulewitz et al., 2011; Yang et al., 2019). However, evidence on the reliability and validity of the DSM-5 craving criterion as an independent construct, and whether its addition improves the SUD diagnosis overall, is also important. The DSM-5 craving criterion is highly reliable across substances (Hasin et al., 2020), but information directly addressing the construct validity of the DSM-5 craving criterion across substances is lacking.

A standard approach to assessing validity is to determine if the DSM-5 craving criterion is associated with substance-related variables in predicted ways (Kendler, 1990), similar to previous validation studies of criteria for nicotine use disorder (Shmulewitz et al., 2013), alcohol use disorder (Chung & Martin, 2002; de Bruijn et al., 2005; Verges et al., 2021), and cannabis withdrawal (Budney et al., 2004). Additionally, as an indicator of SUD, craving should be related to correlates of SUD (Keyes et al., 2011). Across substances, other

assessments of craving (e.g., laboratory measures, multi-item scales) showed association with prospective and concurrent substance use and measures of problematic substance use and severity (Bohn et al., 1995; Chakravorty et al., 2010; Fatseas et al., 2018; Heishman et al., 2001; Murphy et al., 2014; Serre et al., 2015; Sussner et al., 2006), and with mental health indicators related to mood, personality, and stress disorders (Driessen et al., 2008; Fatseas et al., 2018; Franken, 2002; Joos et al., 2013; Sussner et al., 2006; Wolitzky-Taylor & Schiffman, 2019), which are also related to SUD (Chou et al., 2016; Grant et al., 2015; Grant et al., 2016). However, these studies did not operationalize craving as a binary criterion as in the DSM-5; thus, studies on association of the DSM-5 craving criterion with measures of substance use/disorder and mental health (validators) across substances are lacking. Evidence for such associations would support validity of the craving criterion.

Additionally, the DSM-5 text defines craving as "an intense desire or urge" for the substance, which could be assessed "by … such strong urges to take the drug that they could not think of anything else" (American Psychiatric Association, 2013). While this operationalization indicates severe craving (Keyes et al., 2011), more moderate craving, indicated by a strong desire or urge to use, may also be diagnostically important (Chung et al., 2012; Hasin et al., 2012). Alternatively, moderate craving may be an overly inclusive construct without a clear relationship to SUD. DSM-5 studies have assessed the craving criterion inconsistently (e.g., Casey et al., 2012; Cherpitel et al., 2010; Chung et al., 2012; Gilder et al., 2014; Hasin et al., 2012; Keyes et al., 2011; Mewton et al., 2011; Saha et al., 2020; Shmulewitz et al., 2011), indicating lack of consensus on the operationalization of craving. Validity information on the different constructs (severe, moderate) is lacking. Providing such information may impact future versions of the DSM-5 text and diagnostic studies.

Furthermore, no studies show that adding craving as a criterion improves the overall validity of the DSM-5 SUD diagnosis (Hasin et al., 2020), as advocated by the DSM-5 Scientific Review Committee to justify adding a new criterion (Kendler, 2013). Whether the validators show greater association with DSM-5 SUD diagnosed with the craving criterion than without it remains untested.

Given this lack of information, we used data from patients in substance use treatment and community participants with problematic substance use (Gorfinkel et al., 2021; Hasin et al., 2020; Livne et al., 2020) to investigate the validity of DSM-5 craving, and whether the validity of DSM-5 SUD diagnosis increased with the addition of craving across substances: alcohol, tobacco, non-medical cannabis, cocaine, heroin, and non-prescription use of prescription opioids. We addressed the following questions. Is each substance-specific craving criterion associated with a set of concurrent validators related to substance use and mental health? Is association with concurrent validators stronger for the severe craving construct than the moderate construct? Is each craving criterion/construct associated with prospective substance use, and does the association differ by construct? Finally, for each substance, does the association of the validators and SUD diagnosis with or without the craving criterion differ? The last evaluated whether adding craving improved the validity of the overall DSM-5 SUD diagnosis.

Methods

Participants and Procedures

As described elsewhere (Gorfinkel et al., 2021; Hasin et al., 2020; Livne et al., 2020), study participants constituted a convenience sample of adults (18 years old; N=588) recruited from two settings: a clinical research setting in an urban medical center (n=438) and a suburban inpatient addiction treatment program (n=150). Potential participants were informed about the study through advertisements (medical center) or hospital staff (inpatient addiction treatment). To be eligible for study participation, all participants were required to screen positive for potentially problematic substance use: binge drinking or illicit drug use (e.g., non-medical use of cannabis, cocaine, heroin, prescription opioids) in the prior 30 days or 30 days prior to inpatient admission, and endorsement of at least 1 DSM-5 SUD criterion. Exclusion criteria included: non-English speaking; currently homicidal, suicidal, or psychotic; plans to leave the area (since the study included 3-and 6-month follow-up interviews); and significant cognitive, hearing, or visual impairment precluding ability to participate. Participants gave written informed consent after study procedures were explained by study coordinators. Procedures were approved by the Institutional Review Boards of South Oaks Hospital and the New York State Psychiatric Institute. At baseline, trained interviewers administered the Psychiatric Research Interview for Substance and Mental Disorders, DSM-5 version (Hasin et al., 2020) (PRISM-5), participants completed a computerized self-administered questionnaire (SAQ), and were compensated $50 for their time. As described in detail elsewhere (Hasin et al., 2020), interviewers had graduate degrees and clinical experience, and underwent rigorous PRISM-5 training, including workshops, practice interviewing, role-playing, certification, and supervision. Supervisors maintained quality assurance by listening to recordings of 10% of the interviews to ensure that standardized interviewing practices were maintained and to identify any interviewing problems, meeting with interviewers to discuss issues that arose. For 90 days after the baseline interview, participants were asked to call or text into a daily electronic data assessment (EDA) of substance use and were compensated $1 for each day of EDA participation, with bonuses for full completion of up to $50 (Gorfinkel et al., 2021).

Measures

PRISM-5 interview—The PRISM-5 is a semi-structured, computer-assisted interview designed for clinician interviewers, which assesses sociodemographic background information and DSM-5 symptoms and criteria of substance use and other psychiatric disorders (Hasin et al., 2020). The PRISM-5 and previous versions show good reliability and validity in assessing psychiatric disorders among adults reporting substance use (Hasin et al., 2006; Hasin et al., 2020; Hasin et al., 1998; Hasin et al., 1996; Torrens et al., 2004) and general population studies (Hasin, Greenstein, et al., 2015; Hasin, Shmulewitz, et al., 2015).

<u>**DSM-5 substance related variables:**</u> Substances included in this study were alcohol, tobacco, cocaine, heroin, non-medical cannabis and non-medical opioid painkillers (opioids). These were selected due to their high prevalence of use in the US general population (Substance Abuse and Mental Health Services Administration, 2019). The substance disorder section starts with questions about non-medical use (without a

prescription or other than prescribed) of each substance. For any substance used non-medically at least 6 times within a 12-month period, SUD criteria were assessed, and the following measures were created: The craving criterion was considered positive for participants who "wanted to use so badly they couldn't think of anything else" (severe craving) or "felt a very strong desire or urge to use" (moderate craving) during the past 12 months, similar to measures used in previous studies (Hasin et al., 2012; Keyes et al., 2011; Muthen et al., 1993; Saha et al., 2020). The craving criterion and constructs (severe, moderate) were outcomes for concurrent (baseline) validation and predictors for prospective validation using EDA data. Current DSM-5 SUD was positive if participants endorsed 2 of 11 criteria in the past 12 months, while modified SUD (excluding craving) was positive with 2 of 10 criteria. Modified SUD severity was based on number of criteria endorsed: 0=no disorder (0–1 criteria); 1=mild (2–3 criteria); 2=moderate (4–5 criteria); and 3=severe (6–10 criteria). A modified dimensional variable indicated the number of criteria endorsed, not counting craving, and ranged from 0–10. These modified SUD variables were used as concurrent validators (predictors) of the craving criterion and constructs. Additionally, DSM-5 SUD and modified SUD were used in differential association analysis as outcomes for concurrent validators and predictors for prospective validation. In sensitivity analysis, past-year substance use for the 6 substances included and sedatives, stimulants, hallucinogens, and other illicit drugs were used as control variables.

DSM-5 mental health concurrent validators: In separate modules, four DSM-5 psychiatric disorders were assessed for their occurrence in the past 12 months, as described elsewhere (Mannes et al., 2020): major depressive disorder (MDD), post-traumatic stress disorder (PTSD), borderline personality disorder (BPD), and antisocial personality disorder (ASPD).

Self-administered questionnaire (SAQ)—Participants responded to the SAQ in computerized form, either on-site using a tablet or accessed online via a web link. The SAQ included widely-used, reliable, and valid self-report measures related to substance use, mental health, and functioning. Modules and measures relevant to this study are listed below.

Substance use severity (concurrent validators): The Addiction Severity Index (ASI) is a standardized instrument used to assess substance-related problems (Butler et al., 2001; McLellan, Kushner, et al., 1992; Rosen et al., 2000). For alcohol, cannabis, cocaine, heroin, and opioids, severity was indicated with two ASI variables: (1) a count variable indicating the number of days used substance in the past month, and a binary variable indicating whether participant had ever considered use a major problem. For tobacco, the National Cancer Institute Tobacco Use Supplement to the Current Population Survey was used to assess number of days used tobacco in the past month (Chahine et al., 2011; Soulakova et al., 2012; Trinidad et al., 2011).

Additional craving measures (concurrent validators): From the NIH PhenX Toolkit (Hamilton et al., 2011; PhenX, 2013), which includes measures recommended by expert panels, we used a high-quality, multi-item scale of craving for each substance. In these scales, craving was assessed using a series of statements about the participant's current

thoughts and feelings on using the substance, with responses forming a 7-item Likert scale ranging from "strongly disagree" to "strongly agree". Alcohol craving was assessed with the Alcohol Urge Questionnaire; scale scores were derived as the mean response to 8 statements and ranged from 1–7 (Bohn et al., 1995). The alcohol craving scale was assessed among those who either used alcohol in the past month or used alcohol regularly (3 or more times a week) for at least a year; thus, 31 individuals without such use were excluded from this analysis (N=557). Cigarette craving was assessed with the Brief Questionnaire of Smoking Urges; scale scores were derived as the sum of responses to 10 statements and ranged from 10–70 (Cox et al., 2001; Tiffany & Drobes, 1991). Cannabis craving was assessed with the Marijuana Craving Questionnaire - Short Form, which includes 12 statements that formed 4 sub-scales, each scored as the mean response from 3 statements. Total scale scores consisted of the sum of the 4 sub-scale scores and ranged from 4–28 (Heishman et al., 2009; Heishman et al., 2001). Cocaine craving was assessed with the Cocaine Craving Questionnaire-Brief; scale scores were derived as the mean response to 10 statements and ranged from 1–7 (Sussner et al., 2006; Tiffany et al., 1993). Heroin craving was assessed with the Heroin Craving Questionnaire - Short Form; scale scores were derived as the mean response to 14 statements and ranged from 1–7 (Heinz et al., 2006). For all substances, higher scores indicated greater craving. Those who never used the substance (alcohol, n=13; tobacco, n=135; cannabis, n=68; cocaine, n=133; heroin, n=357) were coded as the lowest value.

Alternate measures of problematic substance use (concurrent validators)

Alcohol.: The Alcohol Use Disorders Identification Test (AUDIT) (Allen et al., 1997; Daeppen et al., 2000; de Meneses-Gaya C et al., 2009; Higgins-Biddle & Babor, 2018; Saunders et al., 1993) is a 10-item screening tool that assesses drinking over the past year: the usual number of drinks, frequency of seven indications of harmful drinking (never; less than monthly; monthly; weekly; and daily/almost daily), alcohol-associated injuries, and familial/peer concern related to alcohol use (Babor TF et al., 2001). Items were summed to yield a total score of 0–40, with scores 8 or above indicating harmful alcohol use.

Tobacco.: The Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991) assessed past month cigarette dependence, based on number of cigarettes smoked and 5 items related to wanting to use (NIDA CTN Common Data Elements, 2014b). The items were summed to yield a total score of 0–10, with standard categorization (1=very low dependence [score: 0–2]; 2=low dependence [score: 3, 4]; 3=medium dependence [score: 5]; 4=high dependence [score: 6, 7]; 5=very high dependence [score: 8–10]).

Drugs.: The Drug Abuse Screening Test – version 10 (DAST-10) (Skinner, 1982; Yudko et al., 2007) assesses the degree of consequences related to any drug abuse during the past 12 months with 10 items, summed to yield a score of 0–10, with standard categorization (0=no problems [score: 0]; 1=low problems [score: 1, 2]; 2=moderate problems [score: 3–5]; 3=substantial problems [score: 6–8]; 4=severe problems [score: 9, 10]) (NIDA CTN Common Data Elements, 2014a). The DAST-10 was used as a validator for cannabis, cocaine, heroin, and opioid craving.

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Alternate measure of depression (concurrent validator): The Patient Health Questionnaire (PHQ-9) (Delgadillo et al., 2011; Kroenke et al., 2001; Lowe et al., 2004) assessed self-reported depressive symptoms over the prior two weeks using nine items, with responses ranging from 0 "not at all" to 3 "nearly every day". Items were summed to yield a total score of 0–27, with standard categorization (1=Minimal or no problems [score: 0–4]; 2=Mild problems [score: 5–9]; 3=Moderate problems [score: 10–14]; 4=Moderately Severe problems [score: 15–19]; 5=Severe problems [score: 20–27]) (Kroenke et al., 2001).

Electronic data assessment (EDA)—586 participants responded to a brief daily self-administered survey by telephone interactive voice response or text messaging, with binary questions assessing daily substance use, e.g., did you [drink alcohol/use a specific substance] yesterday. Daily assessments were used to avoid recall problems with retrospective follow-up assessments. Similar methods were validated and used in prior research (Aharonovich et al., 2017; Corkrey & Parkinson, 2002; Perrine et al., 1995). The repeated measures of substance use each day for the 90 days after the baseline interview were outcomes for prospective validity. For descriptive purposes, a variable measuring the percent of days used the substance over the 90-day period was constructed as 100*([number of days used]/[total number of days responded]).

Sociodemographic and clinical covariates

Sociodemographic control variables included age, sex (male; female), education (no college; at least some college), race/ethnicity (Hispanic; non-Hispanic White; Black; Other), participant type (inpatient; community sample), and baseline treatment for alcohol/drug use (yes; no) as queried in the SAQ using questions from the Treatment Services Review (McLellan, Alterman, et al., 1992).

Statistical analysis

Analyses were carried out using SAS 9.4 software (SAS Institute Inc, 2014). Descriptive statistics were calculated for covariates, craving constructs and criteria, and validators.

Concurrent validity—For each substance, logistic regression was used to estimate the association of each concurrent validator (predictor) with the craving criterion (outcome), adjusting for sociodemographic characteristics (age, sex, education, race/ethnicity) and participant type (patient/community). Association was reported as adjusted odds ratios (OR), as is appropriate in this non-representative sample that was enriched for the outcome (DSM-5 SUD) (Bovbjerg, 2020). For each substance and each validator, to determine if either of the craving constructs showed greater validity, i.e., stronger association with the validators, bivariate correlated-outcome logistic regressions modeled the two constructs (outcomes) simultaneously, adjusting for sociodemographics, using generalized estimating equations to account for within-participant correlation (Fitzmaurice et al., 1995). Modelling both constructs together allows direct comparison of the strength of their associations with the predictors. Similar models were used to determine if SUD diagnosed with or without craving showed greater validity, modelling the two alternate SUD diagnoses as the correlated outcomes.

Prospective validity—For each substance, logistic regression, using generalized linear mixed models with random slopes and intercepts to model within subject correlations and correlations over time, was used to estimate the association of the baseline craving criterion/ constructs (predictors) with the repeated measure of substance use on each of the 90 days after the baseline interview. Models were adjusted for sociodemographic characteristics, participant type, and baseline treatment. Results were reported as odds ratios from the fixed effect of baseline craving, and represent the odds of use on any given day among those with vs. without craving, holding the random effects constant. To determine if either of the craving constructs showed greater association with the outcome (i.e. greater validity), for each substance, 100 bootstrapped samples (DiCiccio & Efron, 1996; Efron & Tibshirani, 1986) were generated. Within each bootstrapped sample, the regression model was run separately for each predictor (e.g. severe then moderate) and the difference in the regression coefficients for the predictors was calculated. Across all samples, the mean difference and 95% empirical confidence intervals (CI) was calculated. Validity was considered significantly different if the 95% CI was above 0.0. To determine if SUD diagnosed with or without craving showed greater validity, similar analyses were conducted, modelling the two SUD diagnoses as the predictors.

Sensitivity analysis—First, for concurrent validators that were not substance-specific, to determine that the association with a specific substance craving criterion was not driven by use of a different substance, association models were re-run adjusting for other past-year substance use. Second, for prospective analyses, since participants were less likely to use substances while they were inpatients, analyses were re-run excluding all inpatient days.

Results

Sample descriptives

Participants' sociodemographic characteristics are reported in detail elsewhere (Livne et al., 2020) and summarized here: 69.7% male; 47.8% Black, 19.1% Hispanic, and 27.6% White; 54.8% less than college education; 75.5% community sample; 46.4% with any alcohol/drug use treatment; and mean age was 43.7 years. Prevalence of the craving criteria, constructs, and validators are shown in Table 1. Prevalence of craving for each substance: alcohol, 52.7%; tobacco, 54.8%; cannabis, 39.8%; cocaine, 38.3%; heroin, 23.0%; and prescription opioids, 11.4%. Greater prevalence was observed for moderate craving than severe. The prevalence of DSM-5 SUD ranged from 66.0% (alcohol) to 15.6% (opioids), with slightly lower prevalence for modified SUD (without craving; range: 63.9 [alcohol] to 15.3% [opioids]), and the prevalence of psychiatric disorders ranged from 20.1% (PTSD) to 39.3% (MDD). In the EDA data, the mean completion rate (number of days responded out of the total possible 90 days) was 71% (SD=31.6%), and the median completion rate was 86% (interquartile range=47.8%).

Concurrent validity of craving

For each substance, the craving criterion was significantly associated with all substance-related validators: (days used in last month [ORs 1.1–1.4]; considered use a major problem [ORs 6.1–142.7]; craving scale [ORs 1.1–8.1]; alternate measure of problematic use [ORs

2.2–16.5] and modified DSM-5 SUD measures), except that cannabis craving was not significantly associated with the DAST-10 (Table 2), which is not substance-specific. Most mental health variables were significantly associated with craving for alcohol, tobacco, cannabis, and cocaine, and PHQ-9 depression was significantly associated with craving for heroin and opioids (Table 2). In sensitivity analysis, after adjusting for past-year use of other substances, some associations with mental health variables lost significance, e.g., association of ASPD with craving for alcohol, cannabis, and cocaine (Supplemental Table 1), suggesting that these relationships were driven in part by poly-substance use.

For each substance, both craving constructs (severe, moderate) showed patterns of association similar to those observed for the craving criterion, with significant associations with all substance-related validators and some mental health validators (Table 3). Although neither construct consistently showed greater association across all substances for all validators, some differential association was observed for most substances: number of days used in past month showed greater association with moderate craving, while depression showed greater association with severe craving (Table 3).

Prospective validity of craving

Descriptively, on average, for each substance, those with the baseline craving criterion for that substance had a higher percent of days used over the 90-days than those without baseline craving (Supplemental Table 2). Additionally, the baseline craving criterion significantly predicted the odds of substance use on any given day over the next 90 days (Table 4; ORs 4.2–234.3). Similarly, substance use was significantly predicted by each construct (severe [ORs 3.2–162.9]; moderate [ORs 4.1–234.3]), with significantly stronger association with moderate craving (p's<0.05). In sensitivity analysis, excluding inpatient days, slight variations in numbers from the models did not affect overall results (Supplemental Table 3).

Differential validity of the overall SUD diagnosis with and without craving

For each substance, both versions of SUD were generally associated with the same concurrent validators, with few significant differences in association strength (Table 5). In prospective data, while both SUD versions significantly predicted substance use, associations were significantly stronger for SUD with than without craving for alcohol, tobacco, cannabis, and heroin (Table 6). Results were virtually the same when inpatient days were excluded (Supplemental Table 4).

Discussion

In 588 adults with problematic substance use evaluated at baseline and followed with daily substance use assessments for 90 days, validity of the DSM-5 craving criterion and DSM-5 SUD diagnoses with and without the craving criterion was examined. Craving for alcohol, tobacco, cannabis, cocaine, heroin, and opioids showed concurrent and prospective validity across an array of substance-related and mental health validators through significant associations with the validators. Both the severe and moderate craving constructs showed validity, with no consistent pattern favoring either one across the baseline concurrent

validators. However, prospective validity was stronger for moderate than severe craving. While SUD diagnoses with or without craving in the criterion set were associated with the validators, prospective validity was generally stronger for SUD diagnoses when the SUD diagnosis included the craving criterion. Thus, evidence supports inclusion of the craving criterion in the DSM-5 SUD diagnostic set.

The substance-related validators (number of days used, alternate craving measure, problematic use, modified SUD measures) were associated with the craving criterion, confirming many prior studies showing relationships between substance use/problematic use and other measures of craving (Auriacombe et al., 2018; Bohn et al., 1995; Chakravorty et al., 2010; Fatseas et al., 2018; Hasin et al., 2013; Heishman et al., 2001; Keyes et al., 2011; Murphy et al., 2014; Serre et al., 2015; Sussner et al., 2006). However, concurrent validators do not indicate directionality. Although the concurrent validators were modeled as predictors, the relationship is likely bi-directional, i.e., substance use/disorder leads to craving and craving leads to substance use/disorder. In contrast, prospective data showing that each baseline substance-specific craving criterion predicted subsequent use of that substance made the direction clearer. Additional longitudinal studies should investigate the complex interplay of craving and substance use/disorder, particularly since craving is considered a target for SUD treatment (Auriacombe et al., 2018; Sayette, 2016; Tiffany & Wray, 2012).

The craving criteria were associated with some of the mental health validators, with similarities observed across substances. For all substances, the craving criterion showed greater odds of endorsement among those with MDD or higher levels of the depression scale. These results are similar to others showing association between craving and depression/negative affect (Fatseas et al., 2018; Sussner et al., 2006; Wolitzky-Taylor & Schiffman, 2019; Yoon et al., 2021), which might partially explain the high comorbidity of MDD and SUD, based on negative affect leading to craving leading to substance use/disorder. Clinical studies showed that treating (and reducing) craving in response to depression/negative affect reduced the risk of heavy drinking after treatment for alcohol dependence, supporting this hypothesized pathway (Witkiewitz & Bowen, 2010; Witkiewitz et al., 2011). Studies should assess similar effects for other substances. Furthermore, craving may lead to depressed mood (Wolitzky-Taylor & Schiffman, 2019), so patients being treated for depression should be screened and treated for craving; reducing craving might both improve their mood and reduce risk of substance use (Yoon et al., 2021).

Craving was not associated with all tested psychiatric disorders across all substances. Although SUD are associated with many other psychiatric disorders (Chou et al., 2016; Grant et al., 2015; Grant et al., 2016), craving indicates one aspect of SUD, which may show a weaker relationship with some disorders than others. Few studies have examined associations of craving with a range of psychiatric disorders. One study showed association of alcohol craving with MDD, BPD, and ASPD, but not PTSD (Yoon et al., 2021), similar to our results. Furthermore, craving may be associated with specific traits, e.g., impulsivity and stress reactivity, rather than particular disorders (e.g., personality disorders and PTSD), and the associated symptoms may differ across substances (Joos et al., 2013; Simpson et al., 2012; Somohano et al., 2019; Yoon et al., 2021). Additional studies should explore the

relationship of craving to psychiatric disorders and symptoms and the directionality of these relationships.

Both craving constructs (moderate, severe) showed validity, and neither showed consistently greater concurrent associations across all substances and validators. However, some patterns of differential association were observed. First, moderate craving showed stronger associations with concurrent and prospective substance use. This suggests that even moderate craving may be enough to trigger substance use, with potential impaired control over use, and thus may be a clinically important indicator of SUD. Second, depression showed stronger association with severe craving. Patients with depressed mood might generally perceive their life experiences more negatively, and thus may report severe craving. While almost all of those who endorsed "couldn't think of anything else" (severe) also endorsed "very strong desire or urge" (moderate), using both to assess craving is valid, consistent with the text of the DSM-5 (American Psychiatric Association, 2013), and provides information on both the physiological and cognitive aspects of craving (Yoon et al., 2021). Third, in contrast to other substances, tobacco craving constructs showed differential association with many validators; additional studies should investigate why tobacco craving may behave somewhat differently.

Including craving in the set of diagnostic criteria increased SUD validity for prospective substance use but not for concurrent validators, perhaps due to redundancy between craving and other criteria, one reason that adding craving to the diagnostic set did not increase overall diagnostic information in IRT studies (Hasin et al., 2012; Hasin et al., 2013; Kervran et al., 2020; Shmulewitz et al., 2011). If refinements of the criteria set are of interest, retaining craving and dropping other redundant criteria could be considered for several reasons. First, across substances, in IRT studies, the craving criterion showed high discrimination, i.e., information about SUD status (Chung et al., 2012; Gilder et al., 2014; Hasin et al., 2012; Kervran et al., 2020; Serier et al., 2019; Shmulewitz et al., 2011). Second, some consider craving to be central to SUD, given its relationship to use and potential relapse. Third, craving is an important treatment endpoint, since reducing craving may improve treatment outcomes (Sayette, 2016; Tiffany & Wray, 2012). Additionally, in a set optimization study of SUD diagnostics for alcohol, cannabis, and opioids, the subscales with greatest validity (correlation with validators) were those that included craving (Raffo, 2018; Raffo et al., 2019). Further studies in different datasets should investigate how the criteria set could be shortened to reduce redundancy and increase efficiency without loss of information.

Limitations

Study limitations are noted. Participants may have under-reported substance use and disorder symptoms, but the SAQ and EDA were self-administered, reducing potential bias. Further, potential recall problems were minimized through the use of EDA data, which was collected daily. Forms of tobacco other than cigarettes (e.g., cigars) were not assessed. Prospective validation was not conducted for opioids because respondents were asked about non-prescription use of any prescription drugs, not specifically about opioids. While one strength of this study was using a convenience sample of adults with substance problems

at baseline, which provided a sample enriched for SUD and an efficient way to study craving across a broad range of substances, generalizability of results to other samples (e.g., with lower prevalence of problematic substance use or SUD) should be investigated, e.g., the general population, patients in other types of settings (psychiatric care, primary care), and adolescents. Also, studies for lower-prevalence drugs (e.g., stimulants, sedatives, hallucinogens, inhalants) should be conducted in appropriate datasets. While it is beyond the scope of this study, this approach can be used to explore the validity of all DSM-5 criteria across substances.

Conclusion

This study shows that in a sample of adults with problematic substance use, the DSM-5 SUD craving criterion, as operationalized in the PRISM-5, is valid across substances, as is DSM-5 SUD diagnosed with craving in the diagnostic set, supporting inclusion of craving among the 11 DSM-5 SUD criteria. Moderate craving, as indicated by a strong urge to use, might capture the mild end of the severity spectrum and thus be a good early indicator of SUD (Chung et al., 2012; Hasin et al., 2012; Kervran et al., 2020) or relapse. Additionally, many consider craving to be an important clinical indicator of SUD, since craving can lead to uncontrollable substance use and other subsequent symptoms of problematic use. Furthermore, craving is a target for SUD treatment, since reducing craving may improve the ability to refrain from use, reducing relapse risk. Thus, including craving in the DSM-5 provides more valid and clinically relevant SUD diagnoses, which may help with the identification of risk factors for SUD and the development of better treatment strategies, with the ultimate goal of decreasing the personal and societal toll of SUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Statement:

Conflicts of Interest:

Dr. Shmulewitz, Ms. Stohl, Ms. Greenstein, Ms. Roncone, Ms. Walsh, Dr. Aharonovich, and Dr. Wall report no conflicts of interest. Dr. Hasin reports funding for a separate project from Syneos Health.

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Table 1.

Prevalence and means of DSM-5 SUD, substance-related and mental health validators, and craving (N=588)

Substance-related variables	Alcohol	Tobacco	Cannabis	Cocaine	Heroin	Opioids
DSM-5 craving criterion - % (n)	52.7 (310)	54.8 (322)	39.8 (234)	38.3 (225)	23.0 (135)	11.4 (67)
Severe craving[a] - % (n)	27.6 (162)	33.5 (197)	22.6 (133)	28.7 (169)	19.6 (115)	9.7 (57)
Moderate craving[b] - % (n)	51.0 (300)	53.7 (316)	38.6 (227)	37.4 (220)	23.0 (135)	11.4 (67)
DSM-5 SUD - % (n)	66.0 (388)	62.1 (365)	44.6 (262)	44.7 (263)	24.1 (142)	15.6 (92)
Modified SUD (excluding craving)						
Binary SUD[c] - % (n)	63.9 (376)	59.0 (347)	40.6 (239)	43.7 (257)	24.0 (141)	15.3 (90)
SUD severity[d] - % (n)						
Mild	13.8 (81)	18.9 (111)	14.6 (86)	5.8 (34)	1.2 (7)	3.1 (18)
Moderate	14.0 (82)	23.0 (135)	12.1 (71)	7.0 (41)	2.0 (12)	2.6 (15)
Severe	36.2 (213)	17.2 (101)	14.0 (82)	31.0 (182)	20.8 (122)	9.7 (57)
Dimensional measure[e] - M (SD)	3.9 (3.46)	2.8 (2.69)	2.0 (2.66)	3.0 (3.78)	2.0 (3.63)	1.0 (2.58)
Craving scale[f] - M (SD)	2.7 (1.46)	31.0 (19.63)	11.6 (7.03)	2.1 (1.30)	1.8 (1.27)	Not available
Substance use severity						
Days used in past month - M (SD)	11.3 (9.90)	16.2 (14.19)	10.4 (12.29)	6.0 (8.93)	3.9 (8.80)	2.0 (5.67)
Considered use a major problem - % (n)	48.0 (282)	Not available	26.9 (158)	42.3 (249)	26.4 (155)	10.7 (63)
Measure of problematic use						
Harmful use of alcohol[g] - % (n)	61.4 (361)					
Nicotine dependence level[h] - M (SD)		2.0 (1.28)				
Drug use problems[i] - M (SD)					2.3 (1.15)	
Data from 90-days post interview (EDA) for prospective validation						
Number of observation days	37,674	37,657	37,638	37,621	37,615	Not available
Prevalence of substance use days - % (n)	29.5 (11,120)	40.9 (15,407)	27.5 (10,332)	10.4 (3,931)	6.8 (2,567)	Not available
Mental health measures						
DSM-5 Antisocial personality disorder - % (n)			26.0 (153)			
DSM-5 Borderline personality disorder - % (n)			37.9 (223)			
DSM-5 Major depressive disorder - % (n)			39.3 (231)			

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Substance-related variables	Alcohol	Tobacco	Cannabis	Cocaine	Heroin	Opioids
DSM-5 Post-traumatic stress disorder - % (n)			20.1 (118)			
PHQ-9 depression scale[j] - M (SD)			2.2 (1.20)			

M = mean; SD = standard deviation; EDA = electronic data assessment; PHQ-9 = patient health questionnaire version 9

[a] Based on "Have you ever wanted [a drink/to use substance] so badly that you couldn't think of anything else?"

[b] Based on "Have you ever felt a very strong desire or urge to [drink/use]?"

[c] 2+ (of 10) criteria endorsed

[d] mild = 2 or 3 criteria; moderate = 4 or 5 criteria; severe = 6–10 criteria

[e] count variable indicating total number of criteria endorsed (range 0–10)

[f] count variable with higher values indicating greater current craving. Only lifetime users screened into the craving section; non-users were assigned the lowest values for the craving scale. For alcohol, respondents also needed past month use or regular use over the past year to screen in; those without such use (n=31) were excluded from the analysis

[g] based on score of 8 or more on the Alcohol Use Disorders Identification Test

[h] based on the Fagerstrom Test of Nicotine Dependence; count variable, 1=very low dependence to 5=very high dependence

[i] based on the Drug Abuse Screening Test; count variable, 0=no problems to 4=severe problems

[j] count variable, 1=no problems to 5=severe problems

Table 2:

Association of concurrent (baseline) validators with DSM-5 craving criterion[a] (N=588)

	OR (95% CI)[b]					
	Alcohol	Tobacco	Cannabis	Cocaine	Heroin	Opioids
Substance related variables						
Days used in past month	**1.12 (1.10, 1.15)**	**1.12 (1.10, 1.14)**	**1.15 (1.13, 1.18)**	**1.24 (1.19, 1.29)**	**1.36 (1.26, 1.45)**	**1.25 (1.18, 1.32)**
Considered use a major problem[c]	**6.09 (4.20, 8.84)**	Not available	**10.27 (6.39, 16.52)**	**12.51 (8.13, 19.25)**	**142.69 (63.44, 320.94)**	**21.88 (11.09, 43.20)**
Craving scale[d]	**1.99 (1.69, 2.34)**	**1.10 (1.09, 1.12)**	**1.29 (1.24, 1.35)**	**3.21 (2.60, 3.97)**	**8.06 (5.47, 11.86)**	Not available
Measure of problematic use[e]	**16.50 (10.65, 25.57)**	**3.39 (2.67, 4.29)**	1.10 (0.93, 1.29)	**2.48 (2.02, 3.03)**	**2.94 (2.26, 3.82)**	**2.15 (1.60, 2.91)**
DSM-5 SUD measures (excluding craving)						
Disorder[c]	**43.40 (24.54, 76.78)**	**83.62 (45.60, 153.35)**	**32.52 (19.84, 53.29)**	**182.76 (86.03, 388.27)**	**2202.12 (493.36, 9829.27)**	**604.46 (156.26, 2338.32)**
Severity[f]	**4.91 (3.94, 6.11)**	**10.61 (7.38, 15.27)**	**6.68 (4.85, 9.18)**	**8.54 (6.30, 11.59)**	**28.07 (12.66, 62.22)**	**14.10 (8.24, 24.15)**
Dimensional measure[g]	**2.03 (1.83, 2.25)**	**3.28 (2.73, 3.94)**	**2.60 (2.22, 3.05)**	**2.51 (2.17, 2.89)**	**4.26 (2.84, 6.38)**	**3.18 (2.43, 4.16)**
Mental health						
DSM-5 Antisocial personality disorder[c]	**1.55 (1.05, 2.29)**	**1.72 (1.16, 2.57)**	**1.72 (1.13, 2.60)**	**1.59 (1.07, 2.37)**	1.51 (0.94, 2.43)	1.24 (0.70, 2.20)
DSM-5 Borderline personality disorder[c]	**1.61 (1.13, 2.29)**	1.41 (0.99, 2.02)	**1.84 (1.25, 2.71)**	1.36 (0.95, 1.96)	1.15 (0.73, 1.79)	1.49 (0.87, 2.54)
DSM-5 Major depressive disorder[c]	**2.14 (1.50, 3.05)**	**1.66 (1.17, 2.37)**	**1.64 (1.12, 2.39)**	**2.03 (1.41, 2.91)**	1.06 (0.68, 1.65)	1.59 (0.93, 2.71)
DSM-5 Post-traumatic stress disorder[c]	1.52 (1.00, 2.31)	**2.79 (1.75, 4.44)**	1.33 (0.85, 2.07)	1.34 (0.87, 2.06)	1.08 (0.64, 1.82)	0.92 (0.48, 1.75)
Patient Health Questionnaire-9 depression scale[h]	**1.31 (1.14, 1.52)**	**1.23 (1.06, 1.42)**	1.00 (0.86, 1.16)	**1.19 (1.03, 1.37)**	**1.41 (1.18, 1.68)**	**1.44 (1.17, 1.77)**

Bold indicates significance at the p<0.05 level.

[a] based in endorsing "Have you ever wanted [a drink/to use substance] so badly that you couldn't think of anything else?" or "Have you ever felt a very strong desire or urge to [drink/use substance]?"

[b] Estimated from logistic regression analysis of validator predicting craving criterion, adjusted for gender, age, race/ethnicity, education level, and participant type.

[c] Reference group is No

[d] Count scale with higher values indicating greater current craving. Only lifetime users screened into the craving section; non-users were assigned the lowest values for the craving scale. For alcohol, respondents also needed past month use or regular use over the past year to screen in; those without such use (n=31) were excluded from the analysis.

[e] Alcohol Use Disorders Identification Test (binary) for alcohol; Fagerstrom Test of Nicotine Dependence (count variable, 1=very low dependence to 5=very high dependence) for tobacco; and Drug Abuse Screening Test-10 (count variable, 0=no problems to 4=severe problems) for cannabis, cocaine, heroin, and opioids

[f] count variable: 0=no disorder (0, 1 criteria); 1=mild (2, 3 criteria); 2=moderate (4, 5 criteria); 3=severe (6–10 criteria)

[g] count variable indicating total number of DSM-5 criteria endorsed (range 0–10)

[h] count variable, 1=no problems to 5=severe problems

Table 3:

Differential association of concurrent validators with DSM-5 craving constructs (N=588)

Table 3a.	Alcohol			Tobacco			Cannabis		
	Association with severe craving[a]	Association with moderate craving[b]	Difference in association[c]	Association with severe craving[a]	Association with moderate craving[b]	Difference in association[c]	Association with severe craving[a]	Association with moderate craving[b]	Difference in association[c]
	OR (95% CI)	OR (95% CI)	ratio (95% CI)	OR (95% CI)	OR (95% CI)	ratio (95% CI)	OR (95% CI)	OR (95% CI)	ratio (95% CI)
Substance related variables									
Days used in past month	1.09 (1.06, 1.11)	1.12 (1.09, 1.14)	1.03 (1.01, 1.05)	1.07 (1.06, 1.09)	1.11 (1.10, 1.13)	1.04 (1.02, 1.05)	1.11 (1.09, 1.13)	1.15 (1.12, 1.17)	1.03 (1.01, 1.05)
Considered use a major problem[d]	4.73 (3.12, 7.16)	5.78 (4.01, 8.33)	1.22 (0.82, 1.83)	Not available	Not available	Not available	7.53 (4.72, 12.01)	8.98 (5.68, 14.20)	1.19 (0.74, 1.92)
Craving scale[e]	1.91 (1.66, 2.21)	2.01 (1.72, 2.35)	1.05 (0.90, 1.23)	1.06 (1.05, 1.08)	1.09 (1.08, 1.11)	1.03 (1.01, 1.04)	1.26 (1.20, 1.31)	1.29 (1.23, 1.34)	1.02 (0.98, 1.07)
Measure of problematic use[f]	20.96 (9.90, 44.40)	16.66 (10.55, 26.31)	0.79 (0.38, 1.68)	1.98 (1.69, 2.32)	3.15 (2.43, 4.09)	1.59 (1.25, 2.02)	1.42 (1.16, 1.73)	1.13 (0.95, 1.34)	0.79 (0.68, 0.93)
DSM-5 SUD measures (excluding craving)									
Disorder[d]	31.85 (12.56, 80.75)	50.08 (26.56, 94.44)	1.57 (0.59, 4.16)	73.59 (26.57, 203.79)	60.37 (35.21, 103.51)	0.82 (0.32, 2.09)	46.09 (20.44, 103.93)	27.87 (17.05, 45.56)	0.60 (0.28, 1.30)
Severity[g]	4.55 (3.40, 6.10)	4.81 (3.93, 5.89)	1.06 (0.76, 1.47)	5.08 (4.04, 6.40)	7.83 (5.51, 11.12)	1.54 (1.07, 2.22)	4.74 (3.68, 6.11)	5.40 (3.88, 7.51)	1.14 (0.80, 1.62)
Dimensional measure[h]	1.86 (1.69, 2.06)	1.97 (1.80, 2.16)	1.06 (0.92, 1.21)	2.15 (1.92, 2.41)	2.79 (2.34, 3.32)	1.30 (1.08, 1.56)	2.06 (1.83, 2.33)	2.31 (1.93, 2.76)	1.12 (0.93, 1.34)
Mental health									
DSM-5 ASPD[d]	1.43 (0.95, 2.16)	1.43 (0.97, 2.10)	1.00 (0.67, 1.49)	1.85 (1.25, 2.73)	1.74 (1.18, 2.55)	0.94 (0.66, 1.33)	1.82 (1.17, 2.82)	1.82 (1.20, 2.74)	1.00 (0.67, 1.49)
DSM-5 BPD[d]	2.14 (1.46, 3.14)	1.53 (1.07, 2.18)	0.72 (0.50, 1.01)	1.79 (1.24, 2.58)	1.46 (1.03, 2.08)	0.82 (0.60, 1.12)	2.15 (1.40, 3.31)	1.88 (1.28, 2.76)	0.87 (0.60, 1.27)
DSM-5 MDD[d]	2.88 (1.95, 4.26)	1.96 (1.37, 2.80)	0.68 (0.48, 0.97)	2.34 (1.62, 3.37)	1.67 (1.18, 2.37)	0.71 (0.52, 0.98)	2.06 (1.35, 3.15)	1.60 (1.09, 2.34)	0.77 (0.54, 1.12)
DSM-5 PTSD[d]	1.31 (0.84, 2.04)	1.51 (0.99, 2.31)	1.16 (0.75, 1.78)	3.45 (2.25, 5.29)	2.27 (1.47, 3.50)	0.66 (0.44, 0.99)	1.77 (1.09, 2.87)	1.30 (0.82, 2.07)	0.73 (0.49, 1.11)
PHQ-9 depression scale[i]	1.45 (1.25, 1.68)	1.27 (1.10, 1.47)	0.88 (0.76, 1.02)	1.44 (1.24, 1.67)	1.22 (1.05, 1.41)	0.85 (0.75, 0.96)	1.32 (1.13, 1.56)	0.99 (0.85, 1.15)	0.75 (0.65, 0.85)

Table 3b.

	Cocaine			Heroin			Opioids		
	Association with severe craving[a]	Association with moderate craving[b]	Difference in association[c]	Association with severe craving[a]	Association with moderate craving[b]	Difference in association[c]	Association with severe craving[a]	Association with moderate craving[b]	Difference in association[c]
	OR (95% CI)	OR (95% CI)	ratio (95% CI)	OR (95% CI)	OR (95% CI)	ratio (95% CI)	OR (95% CI)	OR (95% CI)	ratio (95% CI)
Substance related variables									
Days used in past month	**1.16 (1.12, 1.19)**	**1.24 (1.17, 1.31)**	**1.07 (1.03, 1.12)**	**1.22 (1.16, 1.27)**	**1.37 (1.18, 1.58)**	1.12 (1.00, 1.27)	**1.21 (1.13, 1.29)**	**1.24 (1.15, 1.34)**	1.03 (0.99, 1.07)
Considered use a major problem[d]	**12.12 (7.52, 19.55)**	**11.43 (7.48, 17.48)**	0.94 (0.68, 1.31)	**81.82 (35.27, 189.78)**	**126.56 (57.43, 278.90)**	**1.55 (1.03, 2.33)**	**20.18 (9.74, 41.80)**	**22.98 (11.26, 46.91)**	1.14 (0.83, 1.57)
Craving scale[e]	**2.48 (2.04, 3.00)**	**3.18 (2.53, 3.99)**	**1.28 (1.08, 1.53)**	**5.27 (3.86, 7.20)**	**8.30 (5.79, 11.91)**	**1.58 (1.22, 2.03)**	Not available	Not available	Not available
Measure of problematic use[f]	**2.54 (2.05, 3.15)**	**2.50 (2.05, 3.05)**	0.98 (0.87, 1.12)	**2.83 (2.10, 3.81)**	**2.88 (2.21, 3.77)**	1.02 (0.91, 1.14)	**2.07 (1.49, 2.87)**	**2.18 (1.59, 2.98)**	1.05 (0.95, 1.17)
DSM-5 SUD measures (without craving)									
Disorder[d]	**303.69 (73.33, 1257.78)**	**194.12 (85.95, 438.41)**	0.64 (0.15, 2.67)	**2318.06 (323.78, 16596.02)**	**2168.57 (582.71, 8070.46)**	0.94 (0.15, 5.88)	**482.49 (118.72, 1960.97)**	**524.55 (168.17, 1636.10)**	1.09 (0.46, 2.57)
Severity[g]	**7.11 (5.31, 9.52)**	**7.55 (5.77, 9.87)**	1.06 (0.76, 1.49)	**17.33 (9.40, 31.96)**	**28.11 (13.34, 59.24)**	1.62 (0.80, 3.27)	**12.04 (6.72, 21.56)**	**14.00 (8.02, 24.45)**	1.16 (0.81, 1.67)
Dimensional measure[h]	**2.16 (1.95, 2.40)**	**2.35 (2.07, 2.66)**	1.08 (0.94, 1.25)	**2.72 (2.20, 3.36)**	**3.99 (2.85, 5.59)**	**1.47 (1.06, 2.03)**	**2.67 (2.14, 3.33)**	**3.15 (2.38, 4.16)**	1.18 (0.97, 1.43)
Mental health									
DSM-5 ASPD[d]	**1.54 (1.01, 2.33)**	1.46 (0.98, 2.18)	0.95 (0.72, 1.26)	**1.73 (1.06, 2.80)**	1.50 (0.94, 2.40)	0.87 (0.70, 1.07)	1.29 (0.71, 2.36)	1.27 (0.71, 2.25)	0.98 (0.77, 1.25)
DSM-5 BPD[d]	**1.68 (1.14, 2.47)**	1.34 (0.92, 1.94)	0.80 (0.63, 1.01)	1.43 (0.89, 2.31)	1.11 (0.70, 1.76)	0.77 (0.63, 0.95)	1.50 (0.84, 2.70)	1.51 (0.88, 2.61)	1.01 (0.80, 1.27)
DSM-5 MDD[d]	**2.70 (1.83, 3.99)**	**1.94 (1.34, 2.81)**	**0.72 (0.56, 0.92)**	1.14 (0.71, 1.83)	1.03 (0.65, 1.63)	0.90 (0.73, 1.12)	1.29 (0.72, 2.29)	1.61 (0.94, 2.75)	1.25 (1.00, 1.57)
DSM-5 PTSD[d]	1.54 (0.98, 2.43)	1.34 (0.87, 2.09)	0.87 (0.66, 1.15)	1.36 (0.78, 2.39)	1.05 (0.61, 1.83)	0.77 (0.65, 0.92)	1.05 (0.53, 2.06)	0.92 (0.48, 1.77)	0.88 (0.71, 1.09)
PHQ-9 depression scale[i]	**1.29 (1.11, 1.50)**	**1.20 (1.04, 1.39)**	0.94 (0.86, 1.02)	**1.45 (1.20, 1.74)**	**1.42 (1.19, 1.69)**	0.98 (0.91, 1.05)	**1.43 (1.18, 1.73)**	**1.44 (1.19, 1.74)**	1.01 (0.92, 1.10)

All logistic regression models are adjusted for gender, age, race/ethnicity, education level, and participant type. Bold indicates significance at the p<0.05 level. OR=odds ratio; CI=confidence interval; ASPD = Antisocial personality disorder; BPD = Borderline personality disorder; MDD = Major depressive disorder; PTSD = Post-traumatic stress disorder; PHQ-9 = Patient Health Questionnaire version 9

[a] Based on "Have you ever wanted [a drink/to use substance] so badly that you couldn't think of anything else?"

[b] Based on "Have you ever felt a very strong desire or urge to [drink/use substance]?"

[c] Difference in association is indicated by the ratio of odds ratios (exponentiated coefficient for the interaction term): OR for strong desire /OR for compulsion

[d] Reference group is No

[e] Count scale with higher values indicating greater current craving. Only lifetime users screened into the craving section; non-users were assigned the lowest values for the craving scale. For alcohol, respondents also needed past month use or regular use over the past year to screen in; those without such use (n=31) were excluded from the analysis.

[f] Alcohol Use Disorders Identification Test (binary) for alcohol; Fagerstrom Test of Nicotine Dependence (count variable, 1=very low dependence to 5=very high dependence) for tobacco; and Drug Abuse Screening Test-10 (count variable, 0=no problems to 4=severe problems) for cannabis, cocaine, heroin, and opioids

[g] count variable: 0=no disorder (0, 1 criteria); 1=mild (2, 3 criteria); 2=moderate (4, 5 criteria); 3=severe (6–10 criteria)

[h] count variable indicating total number of DSM-5 criteria endorsed (range 0–10)

[i] count variable, 1=no problems to 5=severe problems

Table 4.

Baseline DSM-5 craving predicting use on any given day of the 90 day post-interview period (N=586)

	Association with craving criterion[a]	Association with constructs[a]				Difference in association between constructs[d]
		Severe craving[b]		Moderate craving[c]		
Substance	Odds Ratio (95% CI)	Beta coefficient	Odds Ratio (95% CI)	Beta coefficient	Odds Ratio (95% CI)	Mean difference (95% CI)
Alcohol	4.24 (3.03, 5.92)	1.17	3.21 (2.18, 4.75)	1.41	4.11 (2.94, 5.75)	0.25 (0.15, 0.36)
Tobacco	52.22 (32.55, 83.78)	2.93	18.79 (11.01, 32.04)	3.94	51.31 (32.00, 82.27)	1.03 (0.92, 1.16)
Cannabis	29.35 (19.15, 44.99)	2.91	18.37 (11.00, 30.68)	3.29	26.87 (17.46, 41.34)	0.41 (0.32, 0.51)
Cocaine	23.33 (14.77, 36.83)	2.56	12.95 (7.82, 21.44)	3.12	22.69 (14.36, 35.84)	0.59 (0.49, 0.71)
Heroin	234.30 (119.73, 458.50)	5.09	162.85 (74.84, 354.36)	5.46	234.30 (119.73, 458.50)	0.40 (0.27, 0.52)

All generalized linear mixed model (GLMM) models include random slope and intercept. Bold indicates significance at the p<0.05 level. CI = confidence interval.

[a] Model adjusted for gender, age, race/ethnicity, education level, site, and treatment at baseline

[b] Based on "Have you ever wanted [a drink/to use substance] so badly that you couldn't think of anything else?"

[c] Based on "Have you ever felt a very strong desire or urge to [drink/use substance]?"

[d] Difference is calculated by estimating the regression coefficient (Beta) for association with each construct in each of 100 bootstrapped samples, subtracting beta for compulsion to use from strong desire, and generating empirical 95% confidence intervals for the difference. Differences with 95% CI that are above 0 are considered significant at the p<0.05 level.

Table 5:

Differential association of validators with DSM-5 SUD, with and without craving

Panel 1: Alcohol, Tobacco, Cannabis

	Alcohol			Tobacco			Cannabis		
	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)
Substance related variables									
Days used in past month	1.16 (1.12, 1.21)	1.15 (1.11, 1.19)	0.99 (0.97, 1.00)	1.15 (1.12, 1.17)	1.13 (1.11, 1.15)	0.98 (0.97, 0.99)	1.16 (1.13, 1.20)	1.13 (1.10, 1.15)	0.97 (0.95, 0.99)
Considered use a major problem[b]	8.55 (5.45, 13.42)	8.04 (5.21, 12.41)	0.94 (0.81, 1.10)	Not available	Not available	Not available	13.86 (8.07, 23.82)	15.32 (9.02, 26.02)	1.11 (0.89, 1.37)
Craving scale[c]	2.11 (1.74, 2.54)	2.10 (1.75, 2.52)	1.00 (0.94, 1.05)	1.12 (1.09, 1.14)	1.10 (1.08, 1.12)	0.98 (0.97, 1.00)	1.33 (1.27, 1.40)	1.27 (1.22, 1.33)	0.96 (0.93, 0.98)
Measure of problematic use[d]	23.84 (15.06, 37.76)	24.21 (15.39, 38.09)	1.02 (0.85, 1.21)	4.63 (3.02, 7.10)	3.98 (2.88, 5.51)	0.86 (0.72, 1.03)	1.31 (1.11, 1.55)	1.44 (1.22, 1.71)	1.10 (1.02, 1.18)
Mental health									
DSM-5 ASPD[b]	1.37 (0.91, 2.06)	1.43 (0.95, 2.14)	1.04 (0.94, 1.16)	1.44 (0.96, 2.16)	1.35 (0.91, 2.00)	0.93 (0.80, 1.10)	1.53 (1.02, 2.29)	1.48 (0.98, 2.23)	0.97 (0.81, 1.15)
DSM-5 BPD[b]	1.48 (1.01, 2.16)	1.45 (0.99, 2.10)	0.98 (0.88, 1.09)	1.57 (1.08, 2.28)	1.69 (1.16, 2.44)	1.08 (0.96, 1.21)	1.92 (1.31, 2.81)	1.84 (1.25, 2.72)	0.96 (0.82, 1.13)
DSM-5 MDD[b]	1.68 (1.16, 2.44)	1.65 (1.14, 2.38)	0.98 (0.88, 1.10)	1.72 (1.19, 2.48)	1.80 (1.25, 2.58)	1.05 (0.93, 1.19)	1.28 (0.88, 1.84)	1.37 (0.94, 1.99)	1.07 (0.93, 1.24)
DSM-5 PTSD[b]	1.64 (1.04, 2.58)	1.65 (1.05, 2.59)	1.01 (0.88, 1.15)	2.89 (1.76, 4.73)	3.20 (1.97, 5.19)	1.11 (0.98, 1.26)	1.00 (0.63, 1.59)	1.14 (0.72, 1.81)	1.14 (0.99, 1.31)
PHQ-9 depression scale[e]	1.20 (1.03, 1.39)	1.22 (1.05, 1.42)	1.02 (0.98, 1.06)	1.22 (1.04, 1.43)	1.25 (1.07, 1.46)	1.02 (0.97, 1.08)	1.03 (0.88, 1.19)	1.07 (0.92, 1.24)	1.04 (0.98, 1.11)

Panel 2: Cocaine, Heroin, Opioids

	Cocaine			Heroin			Opioids		
	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)
Substance related variables									
Days used in past month	1.42 (1.25, 1.60)	1.39 (1.24, 1.56)	0.98 (0.95, 1.02)	1.52 (1.18, 1.96)	1.53 (1.18, 1.98)	1.00 (1.00, 1.01)	1.25 (1.14, 1.38)	1.26 (1.15, 1.38)	1.00 (1.00, 1.01)

	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)	Association: SUD with craving OR (95% CI)	Association: SUD without craving OR (95% CI)	Difference in association[a] ratio (95% CI)
Considered use a major problem[b]	**13.04 (8.53, 19.94)**	**13.99 (9.11, 21.49)**	1.07 (0.98, 1.18)	**117.38 (52.99, 259.99)**	**112.47 (50.90, 248.54)**	0.96 (0.88, 1.04)	**15.80 (8.26, 30.21)**	**13.77 (7.28, 26.04)**	0.87 (0.72, 1.05)
Craving scale[c]	**3.17 (2.50, 4.00)**	**3.14 (2.49, 3.96)**	0.99 (0.93, 1.05)	**6.73 (4.97, 9.11)**	**6.57 (4.86, 8.88)**	0.98 (0.93, 1.02)	Not available	Not available	Not available
Measure of problematic use[d]	**2.28 (1.89, 2.75)**	**2.31 (1.91, 2.79)**	1.01 (0.99, 1.03)	**3.28 (2.46, 4.39)**	**3.22 (2.41, 4.29)**	0.98 (0.94, 1.02)	**1.93 (1.48, 2.50)**	**1.97 (1.51, 2.58)**	1.02 (0.99, 1.06)
Mental health									
DSM-5 ASPD[b]	**1.53 (1.03, 2.27)**	**1.50 (1.01, 2.22)**	0.98 (0.90, 1.07)	**1.75 (1.12, 2.73)**	**1.69 (1.07, 2.65)**	0.97 (0.90, 1.03)	1.29 (0.79, 2.12)	1.34 (0.81, 2.21)	1.04 (0.99, 1.10)
DSM-5 BPD[b]	1.29 (0.90, 1.85)	1.26 (0.88, 1.81)	0.98 (0.91, 1.06)	1.19 (0.77, 1.84)	1.16 (0.75, 1.80)	0.97 (0.93, 1.03)	1.27 (0.80, 2.01)	1.33 (0.83, 2.12)	1.05 (0.98, 1.12)
DSM-5 MDD[b]	1.42 (1.00, 2.03)	**1.44 (1.01, 2.05)**	1.01 (0.94, 1.08)	0.99 (0.64, 1.53)	0.97 (0.63, 1.50)	0.97 (0.93, 1.03)	1.46 (0.92, 2.31)	1.46 (0.92, 2.32)	1.00 (0.93, 1.08)
DSM-5 PTSD[b]	1.16 (0.76, 1.77)	1.11 (0.73, 1.71)	0.96 (0.87, 1.07)	1.13 (0.68, 1.88)	1.15 (0.69, 1.91)	1.01 (0.99, 1.04)	0.84 (0.47, 1.50)	0.87 (0.49, 1.55)	1.03 (0.99, 1.08)
PHQ-9 depression scale[e]	1.12 (0.97, 1.29)	1.12 (0.98, 1.29)	1.01 (0.98, 1.03)	**1.37 (1.15, 1.62)**	**1.37 (1.16, 1.62)**	1.00 (1.00, 1.01)	**1.40 (1.17, 1.67)**	**1.40 (1.17, 1.67)**	1.00 (0.97, 1.04)

All logistic regression models are adjusted for gender, age, race/ethnicity, education level, and participant type. Bold indicates significance at the p<0.05 level. OR=odds ratio; CI=confidence interval; ASPD = Antisocial personality disorder; BPD = Borderline personality disorder; MDD = Major depressive disorder; PTSD = Post-traumatic stress disorder; PHQ-9 = Patient Health Questionnaire version 9

a Difference in association is indicated by the ratio of odds ratios (exponentiated coefficient for the interaction term): OR for SUD with craving /OR for SUD without craving

b Reference group is No

c Count scale with higher values indicating greater current craving. Only lifetime users screened into the craving section; non-users were assigned the lowest values for the craving scale. For alcohol, respondents also needed past month use or regular use over the past year to screen in; those without such use (n=31) were excluded from the analysis.

d Alcohol Use Disorders Identification Test (binary) for alcohol; Fagerstrom Test of Nicotine Dependence (count variable, 1=very low dependence to 5=very high dependence) for tobacco; and Drug Abuse Screening Test-10 (count variable, 0=no problems to 4=severe problems) for cannabis, cocaine, heroin, and opioids

e count variable, 1=no problems to 5=severe problems

Table 6.

Baseline DSM-5 SUD predicting use on any given day of the 90 day post-interview period (N=586)

| | Association with SUD[a] | | | | Difference in association between SUD versions[b] |
| | SUD with craving | | SUD without craving | | |
Substance	Beta coefficient	Odds Ratio (95% CI)	Beta coefficient	Odds Ratio (95% CI)	Mean difference (95% CI)
Alcohol	1.72	**5.56 (3.89, 7.96)**	1.68	**5.35 (3.77, 7.52)**	**0.04 (0.02, 0.08)**
Tobacco	4.34	**76.47 (47.67, 122.67)**	3.99	**53.95 (33.48, 86.93)**	**0.37 (0.30, 0.43)**
Cannabis	3.36	**28.77 (18.74, 44.16)**	2.87	**17.68 (11.29, 27.69)**	**0.51 (0.47, 0.57)**
Cocaine	3.62	**37.16 (23.81, 57.98)**	3.58	**35.96 (23.11, 55.96)**	0.04 (−0.01, 0.08)
Heroin	5.47	**236.70 (125.56, 446.22)**	5.29	**198.34 (105.50, 372.90)**	**0.19 (0.15, 0.23)**

All generalized linear mixed model (GLMM) models include random slope and intercept. Bold indicates significance at the p<0.05 level. CI = confidence interval.

[a]Model adjusted for gender, age, race/ethnicity, education level, site, and treatment at baseline

[b]Difference is calculated by estimating the regression coefficient (Beta) for association with each version of SUD in each of 100 bootstrapped samples, subtracting beta for SUD without craving from SUD with craving, and generating empirical 95% confidence intervals for the difference. Differences with 95% CI that are above 0 are considered significant at the p<0.05 level.