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Shared and specific associations of substance use disorders on adverse outcomes: A national prospective study

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ABSTRACT

Background and aims: Substance use disorders (SUD) frequently co-occur and are associated with numerous adverse outcomes and lower quality of life. The goal of this study was to examine whether the associations of SUD with adverse outcomes occur through a shared liability or are disorder-specific even after taking into account their frequent co-occurrence.

Basic procedures: Data were drawn from the National Epidemiological Survey on Alcohol and Related Conditions. The association between nine SUDs assessed at Wave 1 (2001–2002) and a broad range of outcomes (divorce/separation, violence, unemployment, financial crisis, legal problems, problems with a neighbor, friend, or relative, and quality of life) at Wave 2 (2005 − 2005) were estimated separately and simultaneously using a latent variable model to account for their co-occurrence and identify potential disorder-specific effects.

Main findings: SUD at Wave 1 were associated with increased prevalence of all adverse outcomes at Wave 2 ($p < .05$). With the exception of nicotine dependence and tranquilizer use disorder, we found no specific associations of any SUD with any adverse outcome. Rather, associations occurred primarily through the latent variable representing the shared effects of the different SUDs.

Conclusions and relevance: Our findings underscore the importance of adopting dimensional approaches to model the co-occurrence of SUD. Because SUD increases the risk of adverse outcomes mainly through a general predisposition representing mechanisms shared across SUD rather than through drug-specific mechanisms, this dimension should be considered as a therapeutic target to substantially advance prevention of adverse outcomes caused by SUD.

1. Introduction

The shifting landscape of cannabis legalization (Pacula and Smart, 2017) and increases in the prevalence of use of alcohol (Grant et al., 2017), cannabis (Hasin et al., 2015), and other drug use disorders (SUD) (Grant et al., 2016) have brought to the fore the question of whether certain SUDs are more strongly associated with adverse outcomes and could therefore be considered more dangerous. The answer to this important question has been hampered by two important methodological limitations. First, most published studies examining the adverse outcomes related to SUDs have focused on a single substance (e.g., alcohol or nicotine dependence) rather than comparing SUDs with one another (Hall and Degenhardt, 2009; Sommers et al., 2006). Second, SUDs often co-occur in the same individual (Blanco et al., 2015, 2013a; Grant et al., 2016; Hoertel et al., 2018; Pascal et al., 2018), making it difficult to differentiate whether adverse outcomes are associated with a specific SUD or are shared across different disorders.

Multiple lines of evidence suggest the existence of drug-specific and shared mechanisms that may contribute to the development of SUDs and consequently their adverse outcomes. Shared mechanisms include shared genetic and epigenetic vulnerabilities (Cerda et al., 2010; Nestler, 2014; Tsuang et al., 1998), gene-environment interactions (Agrawal and Lynskey, 2008; Koob and Volkow, 2016), deficits in the brain reward systems (Fontenelle et al., 2011; Ross and Peselow, 2012)

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or HPA axis activity (Sinha, 2008), and environmental influences such as deficits in social support and early exposure to stress or trauma (Kelly and Daley, 2013). Drug-specific mechanisms also play a role in the development of individual SUD. For example, convergent results using genome-wide association support that a nicotinic receptor subunit gene cluster (CHRNA5/CHRNA3/CHRNB4) influences heavy smoking behavior (Berrettini et al., 2008). Genetic variation in nicotine metabolism and variations in the CYP2a6 region of chromosome 19 also play an important role in the development of nicotine use disorder (Audrain-McGovern et al., 2007). Polymorphisms in alcohol metabolizing enzymes strongly influence alcohol consumption and alcohol dependence (Bierut, 2011), with aldehyde dehydrogenase 2 deficiency exerting a protective role in the risk of alcohol use disorder (Harada et al., 1982). Variants in the alcohol metabolizing genes contribute to differences in alcohol use patterns but not to other drug use patterns. Similarly, variations of nicotine metabolizing genes increase smoking behavior but not other drug behavior (Bierut, 2011). Like their mechanisms, some adverse outcomes may be specific or more associated with certain SUDs, which would help stratify different SUDs risks; however, given their frequent co-occurrence, this can be an arduous task.

In this report, we sought to address whether adverse outcomes are associated with specific SUDs or are shared across different disorders by using a latent variable approach in which each SUD is conceptualized as a manifestation of a general latent predisposition for SUDs. The approach of representing this predisposition or liability as a latent factor is uniquely equipped to disentangle which associations are shared by all SUDs and which (if any) are unique to specific SUDs without making a priori assumptions about the reasons for these associations. We drew on data from a large, prospective general population study, the National Epidemiological Survey on Alcohol and Related Conditions (NESARC), to maximize the generalizability of our results. Prior studies (Blanco et al., 2015, 2013a; Blanco et al., 2013b; Eaton et al., 2012, 2015; Hoertel et al., 2015b; Pascal et al., 2018) have found that a single factor represents an underlying predisposition to psychiatric disorders. Based on this prior literature, we sought to examine whether the associations of SUDs with adverse outcomes occurred through a shared liability or were disorder-specific even after taking comorbidity into account. We hypothesized that: 1) the latent structure of SUD would be well-described by a single liability factor for SUDs, and 2) this factor would explain the association of SUDs with adverse consequences.

Prior research has documented that SUDs are strongly associated with a variety of adverse outcomes that may co-occur, including financial (Robbins and Nugent, 1975), social (Robbins and Nugent, 1975), marital (Lander et al., 2013), employment (Platt, 1995), violence (Goldstein, 1985), and legal (Robbins and Nugent, 1975) problems. Furthermore, individuals with SUDs have an increased risk of general medical conditions (Lieber, 1998; Stein, 1999) and psychiatric disorders (Kessler et al., 1996; Regier et al., 1990), which can affect health-related quality of life (Schaar and Ojehagen, 2003). Because of the lack of prior prospective national studies comparing the adverse consequences of different SUDs, we did not make any assumption regarding the specific contribution of each disorder to each adverse consequence. One application of factor analysis is the potential to better understand SUDs mechanisms leading to adverse outcomes and to develop management strategies targeted at multiple SUDs (Kim et al., 2012).

2. Method

2.1. Sample

Data were drawn from the Wave 1 and Wave 2 of the NESARC, a nationally representative face-to-face survey of the US adult population conducted in 2001–2002 (Wave 1) and 2004–2005 (Wave 2) by the National Institute on Alcoholism and Alcohol Abuse (NIAAA) (Grant et al., 2009, 2016). The target population included the civilian non-institutionalized population, aged 18 years and older, residing in the United States. Face-to-face personal interviews were conducted with 43,093 respondents at Wave 1. The overall response rate at Wave 1 was 81%. The cumulative response rate at Wave 2 was 70.2%, resulting in 34,653 Wave 2 interviews. The Wave 1 and Wave 2 NESARC data were weighted to be representative of the US civilian population based on the 2000 census. The research protocol, including written informed consent procedures, received full ethical review and approval from the US Census bureau and the Office of Management and Budget (Grant et al., 2009). The prospective analysis includes the 34,653 participants who completed interviews at both wave 1 and wave 2.

2.2. Measures

2.2.1. Assessments of DSM-IV SUDs at wave 1

Participants were interviewed face-to-face with the Alcohol Use Disorder and Associated Disabilities Interview Schedule, DSM-IV version (AUDADIS-IV), a fully structured diagnostic instrument designed for experienced lay interviewers (Grant et al., 2009). DSM-IV SUD diagnoses included alcohol and nicotine dependence and abuse or dependence on cannabis, cocaine, opioids, tranquilizers, sedatives, stimulants, and other drugs (including hallucinogens, heroin, inhalants and solvents). For SUDs, the AUDADIS-IV shows good to excellent inter-rater and test reliability ($\kappa = 0.70 - 0.84$) and validity (Canino et al., 1999; Chatterji et al., 1997; Grant et al., 2003, 1995; Hasin et al., 1997).

2.2.2. Assessments of adverse outcomes

Adverse outcomes included divorce/separation, having problems with a neighbor, friend or relative, violence, unemployment, financial crisis, legal problems, and lower quality of life. In Wave 1, all outcomes were assessed using a past-year timeframe except violence, which was assessed using a lifetime timeframe. In Wave 2, all outcomes were also assessed using a past-year timeframe except violence, which included any occurrence since the Wave 1 interview. We studied the prospective association of SUDs assessed at Wave 1 with adverse outcomes assessed at Wave 2 while adjusting for prior adverse outcomes in Wave 1. Having problems with a neighbor was assessed by asking: “Have you had serious problems with a neighbor, friend or relative?” Marital status was assessed by self-report. Respondents were considered unemployed if they answered “yes” to either: “Were you fired or laid off from a job?” or “Were you unemployed and looking for a job for more than a month?” Having a financial crisis was assessed with the question: “Have you experienced a major financial crisis, declared bankruptcy or more than once been unable to pay your bills on time?”. Participants were considered to have legal problems if they answered positively to the question: “During the last 12 months did you have serious trouble with the police or the law?”. In accord with prior work (Elbogen and Johnson, 2009), violence was assessed using 9 questions (e.g., “Have you used a weapon like a stick, knife, or gun in a fight?”, “Have you hit someone so hard that you injured them or they had to see a doctor?”).

Participants also completed version 2 of the Short Form 12 Health Survey (SF-12v2) (Ware et al., 2002), a 12-item measure that assesses life satisfaction and current functioning over the last four weeks. The SF-12v2 can be scored to generate a norm-based physical component summary score (PCS) and a norm-based mental component summary score (MCS). Higher scores indicate better functioning. The SF-12v2 scale scores have established reliability and convergent validity in community and clinical samples and demonstrated sensitivity to change in clinical status (Rubio et al., 2014, 2013). General health perception was assessed with the following question: “In general, would you say your health is excellent, very good, good, fair or poor?” which was coded as fair/poor, good, or very good/excellent.

2.2.3. Covariates

Because rates of SUD differ by age group, sex, and across racial/

ethnic groups, all analyses were adjusted for these variables (Grant et al., 2016). Age was used as a continuous variable and race/ethnicity as White vs. non-White. In addition, we adjusted for urbanicity (Penkalla and Kohler, 2014), family history of SUDs (alcohol use disorder and other drug use disorder) and other psychiatric disorders (major depressive disorder and antisocial personality disorder), and the presence of Wave 1 adverse consequences, as they can predispose for both SUDs and adverse outcomes (Lieb et al., 2002; Stinson et al., 2005).

2.2.4. Statistical analysis

Weighted percentages and their corresponding standard errors were calculated to provide descriptive information about the relationships of past-year SUDs assessed at Wave 1 with the occurrence of adverse outcomes assessed at Wave 2. Adjusted odds ratios and their 95% confidence intervals were calculated from logistic regressions with each dichotomous adverse consequence as the outcome predicted by each SUD (at Wave 1) while adjusting for age, race, sex, urbanicity, family history of SUD and other psychiatric disorders, and the presence of Wave 1 adverse consequences. By controlling for the Wave 1 outcomes, these odds ratios represent the association of the Wave 1 SUD on new and persistent adverse consequences at Wave 2. Adjusted betas and 95% confidence intervals were obtained from similar linear regression models for continuous MCS, PCS, and income measures.

Based on prior work (Blanco et al., 2013b; Hoertel et al., 2017, 2018; Hoertel et al., 2015b; Pascal et al., 2018), we hypothesized that one factor would provide a good fit to latent structure of SUDs. Goodness-of-fit was assessed by the comparative fit index (CFI), the Tucker–Lewis index (TLI), and the root mean squared error of approximation (RMSEA). CFI and TLI values greater than 0.95 and values of RMSEA less than 0.06 are commonly used to indicate good model fit and were used as cutoffs (Hu and Bentler, 1999).

We used structural equation modeling (Hox and Bechger, 1998; Liu et al., 2005; McMahon et al., 2018; Wall and Amemiya, 2000) to assess the shared and specific associations of the different SUDs measured at Wave 1 on the risk of adverse outcomes measured at Wave 2 while adjusting for sex, age, race/ethnicity, urbanicity, family history of SUD and other psychiatric disorders, and Wave 1 adverse outcomes. In this model, we hypothesized that a latent variable measured by SUDs at Wave 1 would significantly affect all adverse outcomes assessed at Wave 2. Specifically, we examined (i) the association of the SUD latent factor (representing the associations shared across all SUDs) with each adverse outcome and (ii) the association of each SUD with each adverse outcome above and beyond the shared association through the SUD latent factor.

The relationship between the SUD latent factor and the likelihood of each adverse outcome is interpreted as the association of the overall shared SUD liability with the likelihood of each adverse outcome. Standardized estimates of the relationship between each latent factor and each outcome indicate how many standard deviations higher (or lower) the mean of the latent variable underlying the binary outcome are expected to be for each increase in an additional unit of that latent factor, while adjusting for covariates. We used standardized data because they are less affected by the scales of measurement.

Relationships between the specific individual SUD and each outcome are interpreted as direct associations because they indicate associations above and beyond those explained by the SUD latent factor. Thus, those associations indicate the specific or differential association of the individual SUDs with each outcome. An absence of direct effects in the model would indicate a lack of differences in the strength of association between the SUDs and the outcomes examined. To determine whether a particular SUD is associated with specific adverse outcome above and beyond the association attributable to the latent variable, modification indices (i.e., chi-square tests with 1 ° of freedom) were examined to test whether any residuals associated with individual SUDs were correlated with the specific adverse outcome. To avoid including direct associations that could be significant because of multiple testing (Muthen and Muthen, 2012), we considered significant direct effects with modification index greater or equal to 12 corresponding to a $p < .00055$ (.05/90 tests from 9 SUDs x 10 outcomes being tested).

We decided a priori to evaluate statistical significance using a two-sided design with alpha set at 0.05. All analyses were conducted in Mplus Version 7.4 to account for NESARC's complex sampling design (Muthen and Muthen, 2012). The default estimator for the analysis was the variance-adjusted weighted least squares (WLSMV), a robust estimator appropriate for ordered categorical and dichotomous observed variables such as the ones used in this study (Muthen and Muthen, 1998–2012).

3. Results

3.1. Associations between SUD at wave 1 and adverse outcomes at wave 2

In Wave 1, 12.66% of individuals had 1 SUD, 1.76%, had 2 SUDs, and 0.67% had 3 or more SUDs. In Wave 2, the most common adverse outcome was financial crisis, ranging from 22.8% (for alcohol dependence) to 42.6% (for amphetamine use disorder), whereas the least common was legal problems, ranging from 3.0% (for nicotine dependence) to 24.4% (for cocaine use disorder). After adjusting for sex, age, race/ethnicity, urbanicity, family history of SUDs and other psychiatric disorders, and Wave 1 adverse consequences, almost all SUDs were significantly associated with an increased likelihood for all Wave 2 adverse outcomes at Wave 2 (Table 1).

3.2. Associations of SUD with adverse outcomes

A one-factor model of Wave 1 SUDs provided an excellent fit of the data (CFI = 0.982, TLI = 0.977, and RMSEA = 0.009). All loadings were significant and elevated (> 0.63). After adjusting for sex, age, race/ethnicity, urbanicity, family history of SUD and other psychiatric disorders, the SUD factor in Wave 1 was associated with all adverse outcomes at Wave 2. Therefore, our results support that all SUDs significantly increase all adverse consequences through this latent variable representing the shared mechanisms across all SUDs, and risks of adverse consequences increase with the number of co-occurring disorders. The magnitude of the effect of the SUD factor was substantial for all adverse outcomes, ranging from 0.14 (decreased income) to 0.35 (violence). Nicotine dependence at Wave 1 had a direct association with the 3-year odds of having a financial crisis, poor general health, and lower scores on the physical component summary of the SF-12. Tranquilizer use disorder at Wave 1 had a direct association with the 3-year odds of having higher scores on the physical component summary of the SF-12 compared to the other SUD. There were no other direct associations of any specific SUD on Wave 2 outcomes (Fig. 1).

4. Discussion

The use of a latent variable model allowed us to examine the underlying structure of SUDs and to address for the first time in a large, nationally representative sample the question of whether certain SUDs are more often associated with adverse outcomes. We had three main findings. First, we found that a one-factor model provided a good fit to the latent structure of SUD. Second, with the exception of nicotine dependence and tranquilizer use disorder, we found no specific associations of any SUD with any adverse outcome, indicating that all SUDs are similarly associated with all the adverse outcomes examined. Third, the common factor was associated with all adverse outcomes examined at the 3-year follow-up. The severity on the factor, reflecting the co-occurrence of SUDs, is the main predictor of the association of SUDs with adverse outcomes.

The latent structure of SUDs was well-described by a single liability

Table 1
Frequency distributions and associations of substance use disorders (assessed in Wave 1 of the NESARC) with social adverse outcomes and quality of life (assessed in Wave 2 of the NESARC) (n = 34,653).

	%/Median									
	Alcohol dependence	Nicotine dependence	Sedative use disorder	Tranquilizer use disorder	Opioid use disorder	Amphetamine use disorder	Cannabis use disorder	Cocaine use disorder	Other Drug use disorder[a]	No Drug use disorder
N	1172	4017	51	37	104	50	444	69	50	29733
% (S.E.)	3.65 (0.15)	12.41 (0.39)	0.15 (0.02)	0.11 (0.02)	0.33 (0.05)	0.14 (0.02)	1.44 (0.08)	0.24 (0.04)	0.18 (0.03)	84.91 (0.39)
Gender (Male)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR) 50.75 (8.0)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR)	% (S.E) / Median (IQR)
	68.02 (1.6)	52.88 (0.9)	52.92 (8.2)	67.54 (7.6)	63.48 (5.7)		71.86 (2.4)	74.54 (5.8)	70.47 (7.3)	46.54 (0.4)
(Female)	31.98 (1.6)	47.12 (0.9)	47.08 (8.2)	32.46 (7.6)	36.52 (5.7)	49.25 (8.0)	28.14 (2.4)	25.46 (5.8)	29.53 (7.3)	53.46 (0.4)
Race (White)	69.92 (2.4)	79.58 (1.0)	68.23 (7.5)	85.74 (5.2)	72.54 (5.7)	77.67 (7.3)	69.27 (2.9)	63.67 (7.4)	75.93 (6.8)	69.85 (1.6)
(Black)	10.84 (1.2)	8.27 (0.7)	12.77 (4.8)	5.18 (3.3)	7.02 (2.6)	3.25 (2.1)	11.60 (1.8)	11.28 (3.5)	1.40 (1.1)	11.37 (0.7)
(Native American)	3.26 (0.8)	4.06 (0.5)	5.86 (4.0)	2.77 (2.8)	7.37 (2.8)	6.12 (3.5)	4.57 (1.3)	8.76 (4.8)	2.17 (2.2)	1.91(0.2)
(Asian)	2.33 (0.6)	2.02 (0.4)	3.04 (2.2)	0.00 (0.0)	4.24 (2.6)	0.00 (0.0)	3.35 (1.5)	1.10 (1.1)	1.04 (1.1)	4.65 (0.6)
(Hispanic)	13.64 (2.0)	6.07 (0.6)	10.10 (4.6)	6.31 (2.9)	8.83 (3.1)	12.96 (6.6)	11.21 (1.9)	15.19 (5.2)	19.45 (6.4)	12.22 (1.3)
Divorced or Separated	15.08 (1.2)	18.74 (0.7)	19.00 (5.3)	22.40 (6.9)	15.35 (3.5)	23.35 (6.7)	13.75 (2.2)	22.50 (6.0)	8.79 (3.4)	10.54 (0.2)
Problems with neighbor	10.46 (1.1)	8.95 (0.6)	24.79 (6.9)	9.41 (4.1)	9.88 (4.5)	17.40 (6.9)	12.91 (2.3)	17.21 (5.9)	14.19 (5.3)	4.90(0.2)
Violence	16.96 (1.4)	8.02 (0.5)	12.60 (5.1)	21.62 (7.1)	15.83 (4.0)	23.16 (6.8)	21.20 (2.4)	33.69 (6.5)	40.04 (7.9)	1.77 (0.1)
Unemployment	22.80 (1.4)	18.23 (0.9)	17.65 (6.3)	35.33 (9.4)	25.75 (5.2)	36.10 (8.8)	27.13 (2.5)	35.37 (7.3)	38.66 (7.1)	9.39 (0.2)
Financial crisis	22.82 (1.6)	23.97 (0.8)	36.96 (7.8)	34.99 (8.6)	33.56 (5.4)	42.61 (8.2)	29.28 (2.6)	35.99 (7.4)	28.49 (6.7)	9.98 (0.3)
Legal problems	6.33 (0.8)	3.04 (0.3)	12.73 (5.6)	8.99 (5.3)	4.87 (2.3)	4.36 (3.0)	8.28 (1.6)	24.35 (6.3)	19.64 (6.8)	0.84 (0.1)
General Health										
Fair/Poor	14.08 (1.4)	22.02 (0.8)	22.44 (6.5)	14.08 (5.3)	30.53 (5.3)	15.71 (4.8)	11.88 (2.1)	23.76 (6.8)	8.66 (3.7)	14.89 (0.3)
Good	27.32 (1.5)	30.45 (0.9)	26.72 (6.9)	22.15 (7.4)	24.00 (5.8)	34.35 (7.8)	28.94 (2.6)	29.75 (6.5)	26.45 (6.9)	25.08 (0.4)
Excellent/ Very Good	58.60 (1.8)	47.53 (1.0)	50.84 (8.2)	63.77 (8.1)	45.46 (6.3)	49.94 (8.7)	59.19 (2.9)	46.49 (6.9)	64.89 (7.4)	60.03 (0.6)
Age	27.54 (18.0)	38.45 (21.2)	30.89 (21.4)	23.62 (16.5)	33.63 (20.9)	25.96 (12.9)	23.28 (14.4)	28.52 (18.5)	18.80 (N/A)	43.99 (26.4)
Mental Component Summary Score	51.02 (13.6)	51.47 (15.0)	46.92 (14.0)	45.20 (18.1)	49.05 (20.9)	49.34 (13.5)	50.13 (11.8)	45.12 (18.9)	51.03 (8.8)	54.13 (10.1)
Physical Component Summary Score	55.10 (8.1)	53.02 (13.3)	53.85 (15.2)	56.47 (7.7)	51.66 (18.6)	55.73 (10.5)	55.27 (7.3)	55.80 (13.7)	57.27 (7.6)	54.41 (10.5)
Income (in thousands)	20.72 (26.1)	19.72 (26.8)	12.44 (24.3)	10.76 (23.9)	16.84 (26.1)	12.05 (15.1)	17.88 (22.0)	15.43 (20.2)	11.91 (17.6)	22.01 (31.8)
	AOR / Adjusted Beta[b]									
Divorced or Separated	0.97	1.34	1.51	1.23	1.95	2.10	1.34	2.92	1.28	0.73
Problems with neighbor	1.36	1.25	2.78	0.79	0.99	1.11	1.41	1.69	1.33	0.77
Violence	2.54	2.02	1.37	1.70	1.76	1.83	2.19	3.24	4.10	0.42
Unemployment	1.25	1.55	0.79	1.57	1.48	1.74	1.11	1.37	1.49	0.69
Financial crisis	1.24	1.79	1.58	1.56	1.71	1.60	1.37	1.28	1.14	0.59
Legal problems	2.64	2.19	5.89	2.68	1.25	0.80	2.39	7.87	4.88	0.41
General Health										
Fair/Poor	1.24	1.73	1.53	0.64	2.45	1.31	0.95	1.54	0.92	0.62
Good	1.19	1.47	1.19	0.75	1.19	1.50	1.33	1.38	1.46	0.71
Excellent/ Very Good	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Mental Component Summary Score	−1.14	−1.67	−2.58	−3.22	−3.95	−1.85	−1.35	−4.08	0.23	1.62
Physical Component Summary Score	−0.90	−1.41	−1.76	1.57	−2.17	0.29	−0.62	−1.43	−0.17	1.26
Income (in thousands)	−4.05	−3.89	−8.09	−11.00	−6.03	−8.81	−7.19	−9.22	−11.00	3.76

Weighted percentages and their standard errors are indicated for categorical variables, while medians and the interquatile ranges are indicated for continuous variables.
Abbreviations: S.E: Standard error. IQR: Interquartile Range.
[c]Underlined adjusted odds ratios and betas are significant at $p < 0.05$.
[a] Includes hallucinogen use disorder, inhalant/solvent use disorder, heroin use disorder and other drugs use disorders.
[b] Adjusted for wave 1 age, gender, race, urbanicity, family history of substance use disorders, family history of other psychiatric disorders and each corresponding social adverse consequence at baseline.

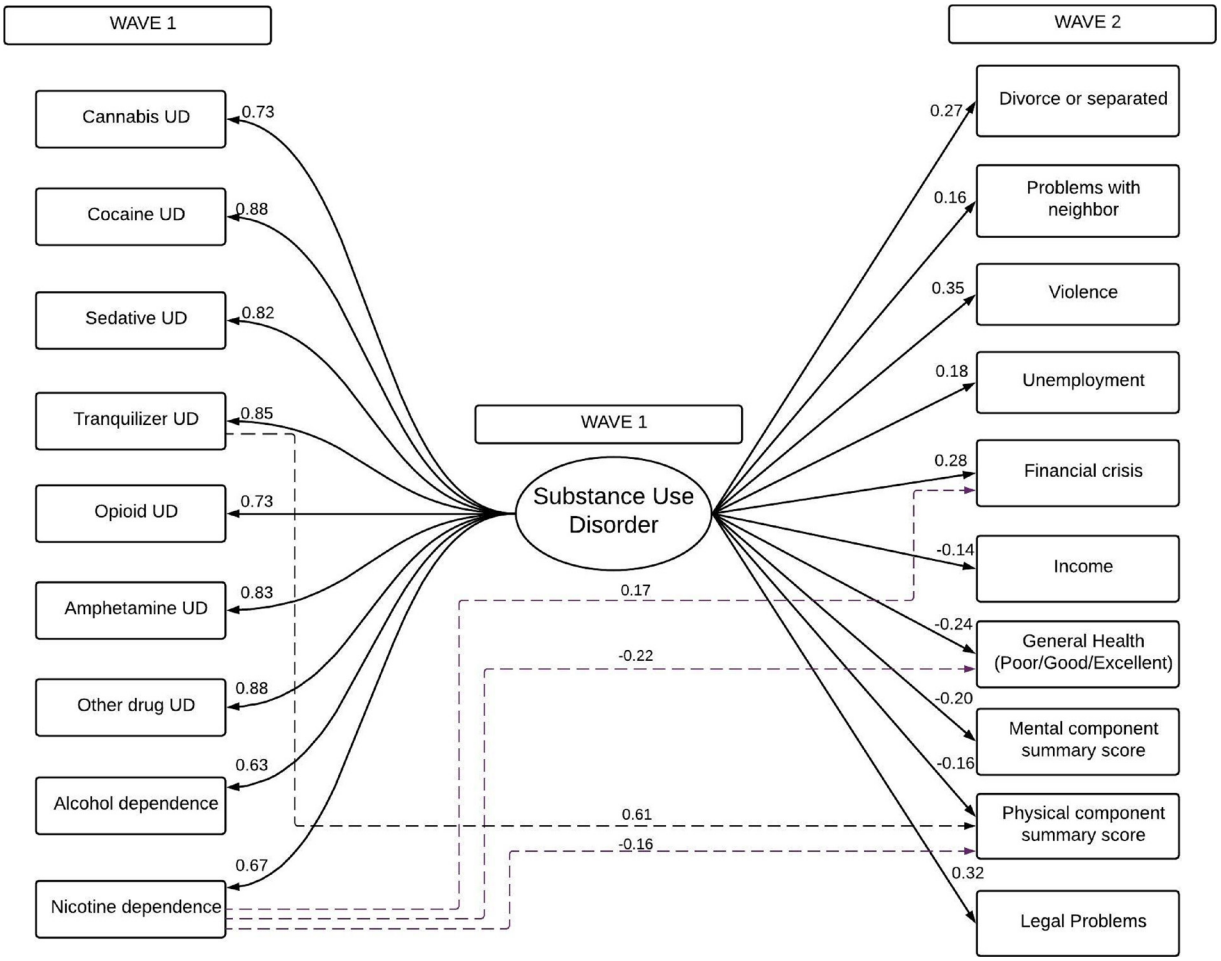

Fig. 1. Shared and specific effects of substance use disorders on the 3-year odds of social adverse outcomes and on measures of quality of life at Wave 2 in a general population sample (N = 34,653).

The Multiple Indicators Multiple Outcomes (MIMIC) model examines the effects of substance use disorders (assessed at Wave 1) on adverse consequences and quality of life (assessed in Wave 2) using the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). The model adjusted for age, sex and race-ethnicity, urbanicity, family history of substance use disorders and other psychiatric disorders, and Wave 1 adverse outcomes. Ellipse is used to denote the latent construct representing the shared effect across all substance use disorders. Rectangles are used to denote the observed variables measuring this construct (i.e., substance use disorders) and the observed outcomes (i.e., social consequences and quality of life measures). Regression coefficients shown are standardized. Only significant effects (two-sided $p < 0.05$) are represented in the model. Dotted arrows indicate significant direct effects (i.e., with modification index greater or equal to 12) beyond the effect of the substance use disorder factor. Abbreviation: UD = use disorders.

factor. This result is consistent with current dimensional conceptualizations of psychopathology (Blanco et al., 2013a; Hoertel et al., 2017, 2018; Hoertel et al., 2015a, b; Insel et al., 2010; Krueger, 1999) and supports the view that SUDs can be understood as manifestations of a limited number of correlated latent liability (i.e., predisposing) factors. This liability model implies that the same characteristics that place individuals at risk for disorders of one drug class also put them at risk for disorders of other drug classes (Tsuang et al., 1998). The use of one substance may also increase the risk of transition from use to dependence or the risk of subsequent use of other substances, decrease the probability of remission, and increase the probability of relapse, leading to increased likelihood of co-occurrence (Blanco et al., 2016, 2013a).

Several overlapping genetic, psychological, and environmental factors may contribute to this shared predisposition (Kendler, 2012; Tsuang et al., 1998). There is extensive evidence of overlap in brain circuitry and neurochemical abnormalities related to different types of SUDs. Converging evidence also supports the genetic influences and gene-environment interactions on risk for addiction (Agrawal and Lynskey, 2008; Koob and Volkow, 2016). The use of one drug can also lead to epigenetic changes that increase cross-addiction vulnerability. For example, epigenetic modifiers in methamphetamine–associated memory increase relapse vulnerability to SUD by triggering craving. In addition, environmental risk factors such as childhood trauma, family disruption, and long-term low social support may impact emotion regulation, which may in turn increase the risk of substance use and SUD (Blanco et al., 2014b).

A second important finding was that the association of SUDs with a wide range of adverse outcomes observed in the bivariate analysis occurred primarily through the SUD factor. This is indicated by the paucity of direct effects observed beyond the effect of the overall SUD factor. These results reveal that the association of SUD with adverse outcomes is mostly shared across SUDs and highly dependent on the co-occurrence of disorders rather than being disorder-specific. Few SUDs had additional associations with the likelihood of having specific social adverse outcomes. Nicotine dependence had an additional direct effect on the likelihood of having poor general health and low overall physical health. These findings are in accordance with prior research that has consistently ranked tobacco among the substances that pose the greatest hazard to individual's health (Lachenmeiera and Rehm, 2015; Nutt et al., 2010). Tobacco smoking can lead to several diseases including cardiovascular diseases, cancers, chronic bronchitis, and emphysema among others. Additionally, secondhand smoke exposure can

lead to severe health problems in both adults and children. Given the high prevalence of tobacco dependence, it continues to be a leading public health priority. The associations of nicotine dependence with financial crises and the lesser negative effect of tranquilizer use disorder on physical health compared to other drugs are more surprising and require replication to exclude idiosyncratic sample-specific explanations. These few direct effects may also be due to multiple testing despite our use of a Bonferroni correction that only reduces the chances of obtaining false-positive results, and therefore caution is needed in their interpretation.

Our results help explain findings that all SUDs, their number (Yamaguchi and Kandel, 1984), and their severity (Rehm and Gmel, 1999) increase the risk of all adverse outcomes. They also suggest that although interventions to treat individual SUDs are likely to decrease these risks, interventions directed at global psychopathological processes shared by all SUDs, such as interventions targeted at decreasing impulsivity or increasing motivation for non-drug related activities (e.g., through contingency management), are likely to have robust beneficial effects. Because higher scores (i.e., greater severity) on the general SUD latent variable are associated with a greater risk for adverse outcomes, remission of one or several SUDs, leading to lower severity on the SUD factor, may be associated with improvement across several outcomes. This finding is in-line with prior work demonstrating that remission of one SUD decreases the risk of developing new SUDs (Blanco et al., 2014a).

Our results suggest that SUDs may lead to deleterious outcomes through mechanisms shared across drugs rather than through drug-specific mechanisms. From a biological perspective, abnormalities in brain reward systems due to the chronic use of any substance may contribute to the negative motivational state often associated with SUDs, a decreased sensitivity to natural rewards (such as sex or food) and neglect of daily activities which favors development of negative social outcomes and poorer quality of life (Koob and Volkow, 2016). From a psychological perspective, impairments in self-control, decision-making, planning and memory, and certain personality traits such as hostility (Airagnes et al., 2017) may increase the risk of adverse social outcomes (Bechara, 2005) and SUDs. Poor control over regulating behaviors is likely shared across SUDs (Bechara, 2005). From a social perspective, prior work has demonstrated the association between social determinants and health-damaging behaviors such as drug use and adverse outcomes. The relationship between deprivation, whether personal (i.e., low social support, ineffective parenting), material (i.e., economic and work-related stressors, homelessness), or cultural (i.e., limited access to education) and damaging health behaviors has been consistently demonstrated (Airagnes et al., 2017; Blanco et al., 2014b; Hawkins et al., 1992). Future work should examine the mechanisms underlying this latent factor (i.e., general liability for SUD) and how the mechanisms relate to each adverse outcome.

Our findings have several implications. From an etiological perspective, our findings underscore the importance of modeling SUD comorbidity to advance our understanding of mechanisms underpinning relationships of SUDs with adverse outcomes. From a clinical perspective, our findings are a powerful reminder of the frequency and importance of the co-occurrence of SUDs and their importance to clinical assessment and treatment. The results further suggest that all SUDs increase the risk of adverse outcomes and that remission of one specific SUD may be insufficient to eliminate the risk of adverse outcomes unless other SUDs remit as well. From a prevention perspective, our results support interventions targeting broader liabilities or multiple drug disorders concurrently rather than targeting individual SUDs (Hawkins et al., 1992).

Our findings should be interpreted in light of some limitations. First, information on SUDs was based on self-report and not confirmed by objective methods. Second, despite its prospective design, because of the possibility of uncontrolled confounds, our study cannot establish a causal relationship between SUDs and the occurrence of adverse outcomes. Third, our study did not allow us to conclude on the temporal relationship between SUDs and adverse outcomes, as the design of the NESARC does not permit determining whether the adverse consequences examined in Wave 2 preceded or followed potential changes in SUDs between the two waves. Finally, our study examined the association between SUDs and adverse outcomes over a 3-year period. Longer follow-up periods might have uncovered different patterns of associations.

Despite these limitations, our findings underscore strong associations of all SUDs examined with a broad range of adverse outcomes, which is particularly important in light of recent increases in the prevalence of alcohol (Grant et al., 2017), cannabis (Hasin et al., 2015), and other drug use disorders (Grant et al., 2016). Our results suggest that SUDs increase these risks mainly through a general predisposition representing mechanisms shared across SUDs rather than through drug-specific mechanisms. Our findings highlight the importance of adopting dimensional approaches to model the co-occurrence of SUDs, which may help disentangle biological and psychological mechanisms underlying predispositions to substance disorders and promote progress in the prevention of SUD and their deleterious effects.

Conflict of interest

Dr. Blanco owns stock in Eli Lilly, Sanofi and General Electric.

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Contributors

Dr. Franco conceptualized the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Olfson, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. Dr. Wall helped design the study, reviewed the manuscript and approved the final manuscript as submitted. Dr. Wang carried out the initial analyses and approved the final manuscript as submitted. Dr. Hoertel designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. Dr. Blanco conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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