Original Investigation

Testing the Drug Substitution Switching-Addictions Hypothesis
A Prospective Study in a Nationally Representative Sample

Carlos Blanco, MD, PhD; Mayumi Okuda, MD; Shuai Wang, PhD; Shang-Min Liu, MS; Mark Olfson, MD, MPH

IMPORTANCE Adults who remit from a substance use disorder (SUD) are often thought to be at increased risk for developing another SUD. A greater understanding of the prevalence and risk factors for drug substitution would inform clinical monitoring and management.

OBJECTIVE To determine whether remission from an SUD increases the risk of onset of a new SUD after a 3-year follow-up compared with lack of remission from an SUD and whether sociodemographic characteristics and psychiatric disorders, including personality disorders, independently predict a new-onset SUD.

DESIGN, SETTING, AND PARTICIPANTS A prospective cohort study where data were drawn from a nationally representative sample of 34 653 adults from the National Epidemiologic Survey on Alcohol and Related Conditions. Participants were interviewed twice, 3 years apart (wave 1, 2001-2002; wave 2, 2004-2005).

MAIN OUTCOMES AND MEASURES We compared new-onset SUDs among individuals with at least 1 current SUD at wave 1 who did not remit from any SUDs at wave 2 (n = 3275) and among individuals with at least 1 current SUD at wave 1 who remitted at wave 2 (n = 2741).

RESULTS Approximately one-fifth (n = 2741) of the total sample had developed a new-onset SUD at the wave 2 assessment. Individuals who remitted from 1 SUD during this period were significantly less likely than those who did not remit to develop a new SUD (13.1% vs 27.2%, $P < .001$). Results were robust to sample specification. An exception was that remission from a drug use disorder increased the odds of a new SUD (odds ratio [OR] = 1.46; 95% CI, 1.11-1.92). However, after adjusting for the number of SUDs at baseline, remission from drug use disorders decreased the odds of a new-onset SUD (OR = 0.66; 95% CI, 0.46-0.95) whereas the number of baseline SUDs increased those odds (OR=1.68; 95% CI, 1.43-1.98). Being male, younger in age, never married, having an earlier age at substance use onset, and psychiatric comorbidity significantly increased the odds of a new-onset SUD during the follow-up period.

CONCLUSIONS AND RELEVANCE As compared with those who do not remit from an SUD, remitters have less than half the risk of developing a new SUD. Contrary to clinical lore, achieving remission does not typically lead to drug substitution but rather is associated with a lower risk of new SUD onsets.

Author Affiliations: Department of Psychiatry, Columbia University/New York State Psychiatric Institute, New York.

Corresponding Author: Carlos Blanco, MD, PhD, Department of Psychiatry, Columbia University/New York State Psychiatric Institute, 1051 Riverside Dr, Unit 69, New York, NY 10032 (cb255@columbia.edu).

JAMA Psychiatry. 2014;71(11):1246-1253. doi:10.1001/jamapsychiatry.2014.1206
Published online September 10, 2014.

Substance use disorders (SUDs) are highly prevalent, often comorbid with other psychiatric disorders,[1,2] and are associated with substantial individual suffering and societal cost.[3] Remission from SUDs contributes to short-term and long-term reduction of criminal activity,[4] improved medical status and social functioning,[4] and a higher quality of life.[5]

Adults who recover from an SUD are often thought to be at increased risk for developing another SUD.[6] Drug addiction is commonly viewed as a unitary syndrome with multiple expressions[7] and drug substitution is of clinical concern.[8,9] Yet rigorous empirical support for this clinical concept remains mixed.[8-10] A greater understanding of the prevalence and risk factors for drug substitution would inform clinical monitoring and management.

Most studies on the drug substitution hypothesis have been conducted in clinical samples, constraining the generalizability of their results. To our knowledge, no epidemiological study has examined whether remission of an SUD predicts new onset of another SUD. It is also understudied whether co-occurring psychiatric disorders increase the risk of a new SUD after remission from 1 SUD. The goals of the present study were to help fill these gaps in knowledge using data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). We hypothesized that remission from an SUD would increase the probability of new onset of an SUD and that sociodemographic characteristics and co-occurring psychiatric disorders would constitute independent risk factors for a new-onset SUD.

Methods

Sample

All procedures in this study received full review and approval from the US Census Bureau and US Office of Management and Budget. Participants provided written informed consent. Data were drawn from waves 1 and 2 of the NESARC.[11] The target population of the NESARC was the civilian noninstitutionalized population 18 years and older residing in households and group quarters. Black and Hispanic individuals and adults aged 18 to 24 years were oversampled, with data adjusted for oversampling and household-level and person-level nonresponse. Excluding respondents who were ineligible for the wave 2 interview (eg, deceased), the wave 2 response rate was 86.7%, resulting in 34 653 completed interviews.[11] Sample weights were developed to adjust for wave 2 nonresponse. The mean interval between wave 1 and 2 interviews was 36 (SE = 2.6) months.

We divided the study sample into 2 mutually exclusive groups by SUD status at each wave. The first group comprised all individuals with at least 1 current SUD (within the past 12 months) at wave 1 who did not remit from any SUD at wave 2 (n = 3275), whereas the second group included all individuals with at least 1 current SUD at wave 1 who had remitted at wave 2 (n = 2741).

Assessment

Sociodemographic measures included sex, race/ethnicity, nativity, marital status, education, and family history of SUDs and were measured as categorical variables. Age at the time of the wave 1 interview and age at the onset of substance use were measured as continuous variables.

The Alcohol Use Disorder and Associated Disabilities Interview Schedule *DSM-IV* Version (AUDADIS-IV),[12] a structured diagnostic interview, was used to generate current (12-month) *DSM-IV* SUD diagnoses (ie, abuse and dependence) based on computer algorithms. Extensive AUDADIS-IV questions covered *DSM-IV* abuse and dependence criteria for sedatives, tranquilizers, painkillers, stimulants, cannabis, cocaine/crack (collapsed in this report to increase the stability of estimates), hallucinogens, inhalants/solvents, heroin, alcohol, and nicotine (for this last one, only dependence). Substance use onset was determined by asking respondents the age at which they had at least 1 drink of any kind of alcohol (not counting small tastes or sips), used drugs for the first time, or smoked a first full cigarette. Good to excellent (κ = 0.70-0.91) test-retest reliability and validity of AUDADIS-IV SUD variables have been documented in clinical and general population samples.[12,13]

In waves 1 and 2, mood disorders included *DSM-IV* major depressive disorder, dysthymia, and bipolar disorder. Anxiety disorders included *DSM-IV* panic disorder, social anxiety disorder, specific phobia, and generalized anxiety disorder. The AUDADIS-IV methods to diagnose these disorders are described in detail elsewhere.[14] Past-year and prior-to-past-year diagnoses of attention-deficit/hyperactivity disorder (ADHD) were assessed in wave 2.[15] Personality disorders assessed at wave 1 included avoidant, dependent, obsessive-compulsive, paranoid, schizoid, histrionic, and antisocial personality disorders.[11] Borderline, schizotypal, and narcissistic personality disorders were measured at wave 2. To increase the stability of our estimates and increase statistical power, we grouped personality disorders in the 3 *DSM-IV* clusters. Test-retest reliabilities of AUDADIS-IV personality disorders compare favorably with those obtained in patient samples using semistructured personality interviews.[11] Test-retest reliabilities for AUDADIS-IV mood, anxiety, ADHD, and personality disorders in the general population and clinical settings are fair to good.[11,12]

Remission of an SUD and New-Onset SUD

Individuals were considered to have remitted from an SUD (alcohol abuse/dependence, drug abuse/dependence, or nicotine dependence) by the time of the wave 2 assessment if they met *DSM-IV* criteria for that disorder in wave 1 but not in wave 2. Having a new SUD was defined as having an SUD at wave 2 among individuals who had no lifetime history of that SUD at wave 1. Individuals who met criteria for abuse of 1 substance at wave 1 and criteria for dependence on that substance at wave 2 were considered to have a new-onset SUD, whereas individuals who met criteria for dependence at wave 1 and abuse but not dependence on that substance at wave 2 were not considered to have remitted from dependence on that substance. *Relapse* was defined as a new episode of an SUD at wave

Table 1. Sociodemographic Characteristics of Individuals With and Without Remission of at Least 1 SUD at Wave 2 of the NESARC

Characteristic	Mean (95% CI), %		Odds Ratio (95% CI)
	Remission of at Least 1 SUD (n = 2741)	No Remission (n = 3275)[a]	
Age, y	36.8 (36.1 to 37.5)	39.4 (38.8 to 40.0)	[b]
Age at substance use onset, y	15.1 (14.9 to 15.3)	14.8 (14.7 to 15.0)	[c]
Sex			
Female[a]	39.3 (37.1 to 41.6)	43.0 (40.9 to 45.2)	1.0 (1.0 to 1.0)
Male	60.7 (58.4 to 62.9)	57.0 (54.8 to 59.2)	1.2 (1.0 to 1.3)
Race/ethnicity			
White[a]	74.9 (71.7 to 77.8)	78.5 (75.8 to 81.0)	1.0 (1.0 to 1.0)
Black	9.7 (8.2 to 11.4)	8.3 (7.0 to 9.9)	1.2 (1.0 to 1.5)
Native American	3.5 (2.6 to 4.6)	3.7 (2.8 to 4.9)	1.0 (0.7 to 1.4)
Asian	2.1 (1.4 to 3.2)	1.9 (1.2 to 2.8)	1.2 (0.7 to 1.9)
Hispanic	9.9 (7.9 to 12.3)	7.6 (5.9 to 9.8)	1.4 (1.1 to 1.7)[d]
Born in the United States	92.0 (90.0 to 93.7)	94.9 (93.4 to 96.1)	0.6 (0.5 to 0.8)[d]
Marital status			
Married[a]	51.4 (48.7 to 54.1)	55.2 (53.1 to 57.2)	1.0 (1.0 to 1.0)
Widowed/separated/divorced	16.7 (15.1 to 18.4)	19.8 (18.3 to 21.4)	0.9 (0.8 to 1.1)
Never married	32.0 (29.4 to 34.6)	25.0 (23.1 to 27.1)	1.4 (1.2 to 1.6)[d]
Education			
College[a]	52.3 (49.8 to 54.7)	51.2 (48.9 to 53.4)	1.0 (1.0 to 1.0)
High school	31.8 (29.6 to 34.1)	33.4 (31.4 to 35.4)	0.9 (0.8 to 1.1)
<High school	15.9 (14.1 to 18.0)	15.5 (13.9 to 17.3)	1.0 (0.8 to 1.2)

Abbreviations: NESARC, the National Epidemiologic Survey on Alcohol and Related Conditions; SUD, substance use disorder.

[a] Reference group.

[b] $t = -6.5$ and $P < .001$.

[c] $t = 2.0$ and $P = .05$.

[d] Results are significant at $P < .05$.

2 among individuals with a lifetime history of the SUD that was in remission at wave 1.

Statistical Analyses

Weighted means, frequencies, and odds ratios (ORs) of sociodemographic correlates and comorbid psychiatric disorders were computed. Odds ratios were considered significant if their 95% CIs did not include 1. Adjusted odds ratios derived from multiple logistic regressions indicated associations of sociodemographic correlates with each specific psychiatric disorder and SUD with a new-onset SUD as the outcome variable. All standard errors and 95% CIs were estimated using SUDAAN to adjust for design characteristics of the survey.[16]

We conducted a series of sensitivity analyses to examine the robustness of results and provide complementary information. To examine whether results were similar across each type of substance, we conducted a logistic regression with remission from nicotine dependence, alcohol use disorders, drug use disorders, and the number of SUDs at baseline as predictors and new onset of an SUD as the outcome. To guard against the possibility that differences between remitters and nonremitters were owing to differences in rates of new onset of nicotine dependence, the most prevalent SUD, we conducted analyses on the new onset of alcohol or drug disorders, excluding nicotine dependence. We also examined whether stratifying by number of SUDs at wave 1 (1 vs multiple SUDs) modified the results. To examine whether among remitters abstinence was associated with lower rates of new-onset SUDs, we conducted a χ^2 trend test comparing abstinent remitters, nonabstinent remitters, and nonremitters. We further examined whether seeking treatment was associated with remission at wave 2 and, if so, whether it was associated with lower rates of a new-onset SUD even after adjusting for the effect of remission. We tested whether the results held when the new onset of an SUD was defined as meeting no *DSM-IV* criteria for that SUD at wave 1 but meeting full *DSM-IV* criteria at wave 2; remission from an SUD was defined as not meeting any *DSM-IV* criteria for that SUD. We further examined whether there were differences between remitters and nonremitters in rates of relapse onto another SUD.

Results

Characteristics of Adults With and Without SUD Remission

Among individuals who did not remit from an SUD, 87.0% had 1 SUD, 11.8% had 2 SUDs, and 1.2% had 3 or more SUDs whereas among individuals who remitted from an SUD, 72.5% had 1 SUD, 19.9% had 2 SUDs, and 7.6% had 3 or more SUDs at baseline ($\chi^2_2 = 68.6$, $P < .001$). Among individuals who remitted, 88.9% remitted from 1 SUD, 8.4% remitted from 2 SUDs, and 2.7% remitted from 3 or more SUDs. The highest percentage of remission was from nicotine dependence (51.2%) followed by alcohol use disorder (42.9%) and drug use disorder (16.5%). The proportion of individuals with 1 SUD who remitted was 41.1% whereas among individuals with 2 or more SUDs, 17.1% remitted from all of them, 46.9% from at least 1 of them, and 36.1% did not remit from any of them.

Table 2. Psychiatric Disorders and Substance Use–Related Characteristics of Individuals With and Without Remission of at Least 1 SUD at Wave 2 of the NESARC

Characteristic	% (95% CI)		Odds Ratio (95% CI)
	Remission of at Least 1 SUD (n = 2741)	No Remission (n = 3275)[a]	
Any Axis I disorder[b]	26.3 (24.1-28.5)	30.9 (28.9-32.9)	0.8 (0.7-0.9)[c]
Any mood disorder	15.9 (14.2-17.7)	17.4 (15.9-19.0)	0.9 (0.8-1.1)
Major depressive disorder	8.7 (7.5-10.1)	10.0 (8.8-11.4)	0.9 (0.7-1.1)
Bipolar	6.5 (5.5-7.8)	7.0 (6.0-8.2)	0.9 (0.7-1.2)
Dysthymia	2.0 (1.5-2.6)	2.2 (1.7-2.9)	0.9 (0.6-1.3)
Any anxiety disorder	17.4 (15.6-19.3)	21.6 (19.8-23.6)	0.8 (0.6-0.9)[c]
Panic	4.3 (3.5-5.2)	5.7 (4.7-6.8)	0.7 (0.6-1.0)
Social anxiety	4.3 (3.4-5.4)	6.1 (5.1-7.2)	0.7 (0.5-0.9)[c]
Specific phobia	10.9 (9.5-12.4)	13.6 (12.0-15.3)	0.8 (0.6-1.0)[c]
Generalized anxiety	3.8 (3.0-4.8)	5.0 (4.2-6.1)	0.7 (0.5-1.0)
ADHD	3.5 (2.6-4.6)	6.6 (5.6-7.7)	0.5 (0.4-0.7)[c]
Any personality disorder	34.3 (31.9-36.7)	41.9 (39.7-44.1)	0.7 (0.6-0.8)[c]
Cluster A	15.1 (13.5-16.9)	20.4 (18.7-22.2)	0.7 (0.6-0.8)[c]
Cluster B	24.3 (22.3-26.4)	29.9 (27.8-32.0)	0.8 (0.7-0.9)[c]
Cluster C	14.3 (12.7-16.1)	17.3 (15.7-19.1)	0.8 (0.7-1.0)
Family history of SUD	51.1 (48.8-53.5)	57.1 (54.9-59.2)	0.8 (0.7-0.9)[c]

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; NESARC, the National Epidemiologic Survey on Alcohol and Related Conditions; SUD, substance use disorder.

[a] Reference group.

[b] Any Axis I disorder does not include an SUD.

[c] Results are significant at $P < .05$.

Table 3. Types of New-Onset SUDs Among Individuals With and Without Remission of at Least 1 SUD at Wave 2 of the NESARC

SUD Type	% (95% CI)		Odds Ratio (95% CI)
	Remission of at Least 1 SUD (n = 2741)	No Remission (n = 3275)[a]	
Alcohol use disorder	7.6 (6.5-8.9)	19.2 (17.4-21.2)	0.3 (0.3-0.4)[b]
Cannabis use disorder	1.9 (1.3-2.7)	4.7 (3.9-5.8)	0.4 (0.3-0.6)[b]
Nicotine dependence	3.5 (2.7-4.5)	3.9 (3.1-4.8)	0.9 (0.6-1.3)
Opioid/heroin use disorder	1.1 (0.7-1.6)	2.6 (1.9-3.6)	0.4 (0.2-0.7)[b]
Cocaine use disorder	0.8 (0.5-1.4)	2.2 (1.6-3.1)	0.4 (0.2-0.7)[b]
Other drug use disorders	1.3 (0.9-2.0)	2.4 (1.8-3.1)	0.6 (0.3-0.9)[b]

Abbreviation: SUD, substance use disorder.

[a] Reference group.

[b] Results are significant at $P < .05$.

Individuals who remitted from an SUD were significantly younger than those who did not remit (**Table 1**). Age at onset of substance use did not differ between those who remitted and those who did not. As compared with their nonremitting counterparts, individuals who remitted from an SUD were significantly more likely to be Hispanic and have never married and were significantly less likely to be born in the United States.

Individuals who remitted from at least 1 SUD had lower odds than those who did not remit of having an Axis I disorder specifically including an anxiety disorder, social anxiety disorder, specific phobia, ADHD, and clusters A and B personality disorders. They also had lower odds of having a family history of SUDs (**Table 2**).

New-Onset SUD

Approximately one-fifth (20.8%) of the total study sample had a new-onset SUD (n = 1215). Individuals with an SUD remission were more likely than those with no lifetime history of SUD (13.1% vs 10.8%, $P = .01$) to have a new-onset SUD at wave 2 but not more likely than those with a lifetime but no current history of having an SUD (13.1% vs 12.6%, $P = .60$) to have such a new onset. By contrast, compared with individuals who did not remit from an SUD, a significantly smaller proportion of those with an SUD remission had a new-onset SUD (13.1% vs 27.2%, $P < .001$).

In univariate analyses, remission from nicotine dependence or an alcohol use disorder was associated with a lower odds (OR = 0.46; 95% CI, 0.37-0.57 and OR = 0.28; 95% CI, 0.21-0.38, respectively) of having a new-onset SUD, whereas remitting from a drug use disorder increased the odds (OR = 1.46, 95% CI, 1.11-1.92). However, after adjusting for the number of SUDs at baseline, remission from nicotine dependence (OR = 0.38; 95% CI, 0.31-0.48), an alcohol use disorder (OR = 0.23; 95% CI, 0.17-0.32), or a drug use disorder (OR = 0.66; 95% CI, 0.46-0.95) all decreased the odds of a new-onset SUD, whereas the number of SUDs at baseline increased the odds (OR = 1.68; 95% CI = 1.43-1.98).

Results were robust to sample specification. When nicotine dependence was excluded, remitters continued to have lower rates of a new-onset SUD than nonremitters (8.7% vs 43.3%, $P < .001$). Stratifying by the number of SUDs yielded a

Table 4. SUD Status, Sociodemographic, Psychiatric Disorders, and Substance Use-Related Characteristics of Individuals With New-Onset SUD at Wave 2 of the NESARC

Characteristic	New Onset of SUD (n = 1215)	
	Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)[a]
Age, y	[b]	1.0 (1.0-1.0)[d]
Age at substance use onset, y	[c]	1.0 (1.0-1.0)
SUD status		
No remission	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Remission	0.4 (0.3-0.5)[d]	0.3 (0.3-0.4)[d]
Sex		
Female	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Male	1.7 (1.5-2.0)[d]	1.6 (1.4-2.0)[d]
Race/ethnicity		
White	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Black	1.1 (0.9-1.4)	1.2 (0.9-1.5)
Native American	1.1 (0.7-1.9)	1.4 (0.8-2.4)
Asian	2.1 (1.2-3.9)	2.1 (1.1-4.0)
Hispanic	1.4 (1.1-1.8)[d]	1.2 (1.0-1.6)[d]
Born in the United States	1.1 (0.8-1.6)[d]	1.4 (1.0-2.0)
Marital status		
Married	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Widowed/separated/divorced	1.0 (0.8-1.2)	1.1 (0.9-1.4)
Never married	2.2 (1.8-2.7)[d]	1.4 (1.1-1.7)[d]
Education		
College	1.0 (1.0-1.0)	1.0 (1.0-1.0)
High school	0.9 (0.8-1.1)	1.0 (0.8-1.2)
<High school	0.8 (0.7-1.1)	0.9 (0.7-1.1)
Any Axis I disorder[e]	1.0 (0.8-1.2)	NA[f]
Any mood disorder	1.1 (0.9-1.3)	NA[f]
Major depressive	1.2 (0.9-1.5)	1.2 (0.9-1.7)
Bipolar	0.9 (0.7-1.3)	0.7 (0.4-1.0)
Dysthymia	0.9 (0.5-1.5)	0.9 (0.5-1.5)
Any anxiety disorder	0.9 (0.8-1.2)	NA[f]
Panic	1.0 (0.7-1.5)	1.1 (0.7-1.6)
Social anxiety	1.1 (0.8-1.5)	1.1 (0.7-1.6)
Specific phobia	1.0 (0.7-1.3)	1.0 (0.7-1.3)
Generalized anxiety	1.0 (0.7-1.4)	0.9 (0.6-1.5)
ADHD	1.6 (1.1-2.2)[d]	1.0 (0.7-1.5)
Any personality disorder	1.6 (1.4-1.9)[d]	NA[f]
Cluster A	1.4 (1.1-1.7)[d]	1.1 (0.8-1.4)
Cluster B	2.0 (1.6-2.4)[d]	1.6 (1.3-2.0)[d]
Cluster C	1.1 (0.9-1.4)	1.0 (0.8-1.3)
Family history of SUD	0.8 (0.7-1.0)	0.9 (0.8-1.1)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; NA, not applicable; SUD, substance use disorder.

[a] Mutually adjusted for other variables in the Table.

[b] $t = -11.6$ and $P < .001$.

[c] $t = -4.1$ and $P < .001$.

[d] Results are significant at $P < .05$.

[e] Any Axis I disorder does not include SUDs.

[f] Not entered in the model to avoid multicollinearity with the disorders included in that category.

similar pattern of results. Remitters who had only 1 SUD at baseline were less likely than nonremitters to have a new SUD at wave 2 (10.0% vs 24.3%, $P < .001$). Remitters with multiple SUDs at baseline were less likely to have a new-onset SUD at wave 2 than nonremitters with multiple SUDs (21.4% vs 46.3%, $P < .001$).

Individuals who sought treatment between waves 1 and 2 were significantly more likely to remit than those who did not (36.8% vs 19.2%, $P < .001$). Furthermore, after adjusting for remission status (ie, remission vs nonremission), individuals who sought treatment had lower odds of a new-onset SUD at wave 2 (OR = 0.31; 95% CI, 0.22-0.43). The probability of a new-onset SUD was lowest for abstinent remitters (12.4%), intermediate for nonabstinent remitters (15.2%), and highest for nonremitters (27.2%; linear $\chi^2_1 = 30.9$, $P < .001$).

When remission was defined as not meeting any *DSM-IV* criteria, remitters were still less likely than nonremitters to have a new-onset SUD at wave 2 (13.0% vs 23.3%, $P < .001$). Remitters were also less likely than nonremitters to have a new-onset SUD when new onset was defined as meeting no *DSM-IV* criteria for that SUD at baseline but meeting full *DSM-IV* criteria for the new SUD at wave 2 (5.6% vs 10.3%, $P < .001$). Furthermore, individuals with remission from 1 SUD were less than half as likely as nonremitters to relapse to another SUD at wave 2 (2.6% vs 4.3%, $P = .006$).

When considering the substances separately, individuals with an SUD remission were significantly less likely than those with no SUD remission to have a new-onset alcohol use disorder, cannabis use disorder, opioid use disorder, cocaine use disorder, and other drug disorder whereas there was no significant difference in the new onset of nicotine dependence (**Table 3**).

Predictors of a New Onset SUD

The odds of a new-onset SUD were lower for individuals who remitted from a SUD than for those who did not (**Table 4**). Being younger at the time of the survey and a younger age at onset of substance use increased the likelihood of having a new-onset SUD. In the unadjusted analyses, the odds of onset of a new SUD were greater for men, Asian individuals, Hispanic individuals, and those who were never married. The odds of onset of a new SUD were also greater for individuals with ADHD and cluster A and cluster B personality disorders.

After adjusting for sociodemographic characteristics and psychiatric comorbidity, the odds of a new-onset SUD remained significantly greater for men, Asian individuals, individuals who were never married, and those with a cluster B personality disorder. The odds of a new-onset SUD remained significantly lower for those who had remitted from a SUD.

Discussion

In a large nationally representative sample of adults with SUDs, approximately 1 in 5 had developed a new-onset SUD during the course at the 3-year follow-up. Contrary to our first hypothesis, individuals who remitted from 1 SUD at wave 2 were significantly less likely than those who did not

remit to develop a new SUD. These results were robust to sample specification, including exclusion of nicotine dependence, stratification by number of SUDs, and alternative definitions of remission and new-onset SUDs. We also found that men who were younger and/or never married as well as individuals with early-onset substance use and co-occurring psychiatric disorders were all at increased risk of developing a new SUD at wave 2.

Individuals who remitted from an SUD had less than half the risk of developing a new SUD than those who did not remit from any SUD. In univariate analyses, remission from drug use disorders was associated with increased odds of a new-onset SUD. However, after adjusting for the number of SUDs at baseline, remission from a drug use disorder was associated with decreased odds of a new-onset SUD. Our findings help reconcile clinical lore about drug substitution with apparently contradictory findings from previous research.[8-10] They also converge with earlier findings in stressing the role of previous psychopathology in the course of SUDs.[17-20] Taken together, our findings indicate that remission of an SUD is not associated with an increase but rather with a dramatic decrease in the risk of a new-onset SUD or relapse onto a previously remitted SUD.

Several mechanisms may contribute to the protective effects of SUD remission from new-onset SUDs. Remission may decrease external or interpersonal precipitants of drug use, such as drug-related cues and contact with drug-using peers, which often lead to relapses. Coping strategies, skills, and motivation of individuals who remit from an SUD may also protect them from the onset of a new SUD.[21,22] Furthermore, remission from an SUD even if the person does not achieve abstinence can decrease the drug-associated behavioral disinhibition, which might otherwise facilitate use of additional substances.[23] Remission from an SUD also decreases the possibility of pharmacological[24] or acute psychological synergistic effects[25,26] with other substances, perhaps making them less reinforcing. In addition, some pharmacological and psychological treatments may be efficacious for more than 1 drug and may thereby reduce the risk of drug substitution.[27] Consistent with these findings, receiving treatment for an SUD was associated with increased probability of remission and with decreased odds of a new-onset SUD.

In accord with our second hypothesis and with earlier published work, we report a higher incidence of SUDs among men,[28] unmarried individuals,[28] and those who were younger at the onset of substance use.[29] Age-related differences in the excitability and sensitivity of the midbrain dopaminergic system[30] and age-specific vulnerabilities related to the level of maturation and substance use patterns in young individuals may contribute to a greater risk for the development of SUDs in adolescents.[29]

Several psychiatric disorders and SUDs are also marked by impulsivity[31,32] and impaired behavioral control[33] and thus may share genetic susceptibility or other common etiological factors with new-onset SUDs.[34,35] Individuals with psychiatric disorders and comorbid SUDs may have a heavier load of risk fac1tors or familial influences.[36,37] Psychoactive substances may be used to alleviate adverse emotional states (self-medication).[38-42] Psychiatric disorders may also contribute to social and interpersonal contexts, such as increasing the odds of generating stressful events[43] and reducing their social networks[44] that facilitate the new onset of SUDs.[17]

Exposure to other substances, even among individuals who achieve remission from 1 SUD, may increase the risk of a new-onset SUD or relapse.[19,45] This pattern highlights the importance of abstaining from any substance use for individuals in remission of an SUD.[46,47] Addictive substances engage a set of common molecular mechanisms involved in associative learning, including stimulation of dopamine D_1 receptors, activation of the signal transduction pathways, altered gene expression, and synaptic rearrangements.[48] Substance use may increase substance memories that can manifest in substance cravings[48] and activation of reward circuitry, increasing the risk for another SUD.[49] It can also lead to epigenetic changes that increase cross-addiction vulnerability,[50] particularly given the complex interactions among receptors for different psychoactive substances.[51]

Our study has several limitations. First, information was based on self-reporting and did not include objective measures of substance use, such as urinalysis. Second, to limit subject burden, the comorbidity assessments, although extensive, did not include all Axis I or Axis II diagnoses. Third, the follow-up period was limited to 3 years. Therefore, individuals in remission at wave 2 may have experienced future relapses.[19,45]

Conclusions

Contrary to a common clinical perception, remission from an SUD decreases rather than increases the risk of onset of another SUD. Psychiatric comorbidity and the use of other substances increase the risk of new-onset SUDs. Achieving remission from 1 SUD and abstaining from substance use may have the added clinical benefit of helping to prevent the onset of new SUDs.

ARTICLE INFORMATION

Submitted for Publication: December 30, 2014; final revision received April 28, 2014; accepted April 28, 2014.

Published Online: September 10, 2014. doi:10.1001/jamapsychiatry.2014.1206.

Author Contributions: Dr Wang and Ms Liu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Blanco, Okuda, Olfson.
Acquisition, analysis, or interpretation of data: Blanco, Wang, Liu.
Drafting of the manuscript: Blanco, Okuda.
Critical revision of the manuscript for important intellectual content: Okuda, Wang, Liu, Olfson.
Statistical analysis: Blanco, Wang, Liu.
Obtained funding: Blanco.
Administrative, technical, or material support: Blanco.

Conflict of Interest Disclosures: None reported.

Funding/Support: This manuscript was supported by grants DA019606, DA023200, MH0760551, and MH082773 from the National Institutes of Health, grant U18 HS021112 from the Agency for Health Care Research and Quality, and the New York State Psychiatric Institute.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of any of the sponsoring organizations, agencies, or the US government.

Additional Contributions: The National Epidemiologic Survey on Alcohol and Related Conditions was sponsored by the National Institute on Alcohol Abuse and Alcoholism and was funded in part by the Intramural Program at the National Institute on Alcohol Abuse and Alcoholism.

REFERENCES

1. Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. *Arch Gen Psychiatry*. 2007;64(5):566-576.

2. Blanco C, Krueger RF, Hasin DS, et al. Mapping common psychiatric disorders: structure and predictive validity in the national epidemiologic survey on alcohol and related conditions. *JAMA Psychiatry*. 2013;70(2):199-208.

3. Rubio JM, Olfson M, Pérez-Fuentes G, Garcia-Toro M, Wang S, Blanco C. Effect of first episode axis I disorders on quality of life. *J Nerv Ment Dis*. 2014;202(4):271-274.

4. Hser YI, Hoffman V, Grella CE, Anglin MD. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry*. 2001;58(5):503-508.

5. Rubio JM, Olfson M, Villegas L, Pérez-Fuentes G, Wang S, Blanco C. Quality of life following remission of mental disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2013;74(5):e445-e450.

6. Sussman S, Black DS. Substitute addiction: a concern for researchers and practitioners. *J Drug Educ*. 2008;38(2):167-180.

7. Kendler KS, Jacobson KC, Prescott CA, Neale MC. Specificity of genetic and environmental risk factors for use and abuse/dependence of cannabis, cocaine, hallucinogens, sedatives, stimulants, and opiates in male twins. *Am J Psychiatry*. 2003;160(4):687-695.

8. Peters EN, Hughes JR. Daily marijuana users with past alcohol problems increase alcohol consumption during marijuana abstinence. *Drug Alcohol Depend*. 2010;106(2-3):111-118.

9. Haylett SA, Stephenson GM, Lefever RM. Covariation in addictive behaviours: a study of addictive orientations using the Shorter PROMIS Questionnaire. *Addict Behav*. 2004;29(1):61-71.

10. Maremmani I, Pani PP, Mellini A, et al. Alcohol and cocaine use and abuse among opioid addicts engaged in a methadone maintenance treatment program. *J Addict Dis*. 2007;26(1):61-70.

11. Ruan WJ, Goldstein RB, Chou SP, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of new psychiatric diagnostic modules and risk factors in a general population sample. *Drug Alcohol Depend*. 2008;92(1-3):27-36.

12. Grant BF, Dawson DA, Stinson FS, Chou PS, Kay W, Pickering R. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV): reliability of alcohol consumption, tobacco use, family history of depression and psychiatric diagnostic modules in a general population sample. *Drug Alcohol Depend*. 2003;71(1):7-16.

13. Cottler LB, Grant BF, Blaine J, et al. Concordance of DSM-IV alcohol and drug use disorder criteria and diagnoses as measured by AUDADIS-ADR, CIDI, and SCAN. *Drug Alcohol Depend*. 1997;47(3):195-205.

14. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry*. 2005;62(10):1097-1106.

15. Bernardi S, Faraone SV, Cortese S, et al. The lifetime impact of attention deficit hyperactivity disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Psychol Med*. 2012;42(4):875-887.

16. Research Triangle Institute. *Software for Survey Data Analysis (SUDAAN) Language Manual, Release 10.0*. Research Triangle Park, NC: Research Triangle Institute; 2008.

17. Lopez-Quintero C, Pérez de los Cobos J, Hasin DS, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2011;115(1-2):120-130.

18. Lopez-Quintero C, Hasin DS, de Los Cobos JP, et al. Probability and predictors of remission from life-time nicotine, alcohol, cannabis or cocaine dependence: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Addiction*. 2011;106(3):657-669.

19. Flórez-Salamanca L, Secades-Villa R, Budney AJ, García-Rodríguez O, Wang S, Blanco C. Probability and predictors of cannabis use disorders relapse: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2013;132(1-2):127-133.

20. Hasin D, Fenton MC, Skodol A, et al. Personality disorders and the 3-year course of alcohol, drug, and nicotine use disorders. *Arch Gen Psychiatry*. 2011;68(11):1158-1167.

21. Breslau N, Peterson E, Schultz L, Andreski P, Chilcoat H. Are smokers with alcohol disorders less likely to quit? *Am J Public Health*. 1996;86(7):985-990.

22. Agosti V, Levin FR. Does remission from alcohol and drug use disorders increase the likelihood of smoking cessation among nicotine dependent young adults? *Soc Psychiatry Psychiatr Epidemiol*. 2009;44(2):120-124.

23. Fillmore MT. Drug abuse as a problem of impaired control: current approaches and findings. *Behav Cogn Neurosci Rev*. 2003;2(3):179-197.

24. Bradberry CW, Lee T, Jatlow P. Rapid induction of behavioral and neurochemical tolerance to cocaethylene, a model compound for agonist therapy of cocaine dependence. *Psychopharmacology (Berl)*. 1999;146(1):87-92.

25. Conway KP, Kane RJ, Ball SA, Poling JC, Rounsaville BJ. Personality, substance of choice, and polysubstance involvement among substance dependent patients. *Drug Alcohol Depend*. 2003;71(1):65-75.

26. Goodwin RD, Kim JH, Weinberger AH, Taha F, Galea S, Martins SS. Symptoms of alcohol dependence and smoking initiation and persistence: a longitudinal study among US adults. *Drug Alcohol Depend*. 2013;133(2):718-723.

27. Rösner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev*. 2010;(12):CD001867.

28. De Graaf R, Bijl RV, Ravelli A, Smit F, Vollebergh WA. Predictors of first incidence of *DSM-III-R* psychiatric disorders in the general population: findings from the Netherlands Mental Health Survey and Incidence Study. *Acta Psychiatr Scand*. 2002;106(4):303-313.

29. Grant BF, Stinson FS, Harford TC. Age at onset of alcohol use and *DSM-IV* alcohol abuse and dependence: a 12-year follow-up. *J Subst Abuse*. 2001;13(4):493-504.

30. Placzek AN, Zhang TA, Dani JA. Age dependent nicotinic influences over dopamine neuron synaptic plasticity. *Biochem Pharmacol*. 2009;78(7):686-692.

31. Lappalainen J, Long JC, Eggert M, et al. Linkage of antisocial alcoholism to the serotonin 5-HT1B receptor gene in 2 populations. *Arch Gen Psychiatry*. 1998;55(11):989-994.

32. Chamorro J, Bernardi S, Potenza MN, et al. Impulsivity in the general population: a national study. *J Psychiatr Res*. 2012;46(8):994-1001.

33. Taylor J. Substance use disorders and cluster B personality disorders: physiological, cognitive, and environmental correlates in a college sample. *Am J Drug Alcohol Abuse*. 2005;31(3):515-535.

34. Li MD, Burmeister M. New insights into the genetics of addiction. *Nat Rev Genet*. 2009;10(4):225-231.

35. Blanco C, Rafful C, Wall MM, Ridenour TA, Wang S, Kendler KS. Towards a comprehensive developmental model of cannabis use disorders. *Addiction*. 2014;109(2):284-294.

36. Sugaya L, Hasin DS, Olfson M, Lin KH, Grant BF, Blanco C. Child physical abuse and adult mental health: a national study. *J Trauma Stress*. 2012;25(4):384-392.

37. Verhagen M, van der Meij A, Franke B, et al. Familiality of major depressive disorder and patterns of lifetime comorbidity: the NEMESIS and GenMood studies. a comparison of three samples. *Eur Arch Psychiatry Clin Neurosci*. 2008;258(8):505-512.

38. Blanco C, Alegría AA, Liu SM, et al. Differences among major depressive disorder with and without co-occurring substance use disorders and substance-induced depressive disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2012;73(6):865-873.

39. Magidson JF, Liu SM, Lejuez CW, Blanco C. Comparison of the course of substance use disorders among individuals with and without generalized anxiety disorder in a nationally representative sample. *J Psychiatr Res*. 2012;46(5):659-666.

40. Magidson JF, Wang S, Lejuez CW, Iza M, Blanco C. Prospective study of substance-induced and independent major depressive disorder among individuals with substance use disorders in a nationally representative sample. *Depress Anxiety*. 2013;30(6):538-545.

41. Khantzian EJ. The self-medication hypothesis of addictive disorders: focus on heroin and cocaine dependence. *Am J Psychiatry*. 1985;142(11):1259-1264.

42. Crum RM, Mojtabai R, Lazareck S, et al. A prospective assessment of reports of drinking to self-medicate mood symptoms with the incidence and persistence of alcohol dependence. *JAMA Psychiatry*. 2013;70(7):718-726.

43. Hammen C. Stress generation in depression: reflections on origins, research, and future directions. *J Clin Psychol*. 2006;62(9):1065-1082.

44. Kendler KS, Prescott CA. *Genes, Environment and Psychopathology.* New York, NY: The Guildford Press; 2006.

45. García-Rodríguez O, Secades-Villa R, Flórez-Salamanca L, Okuda M, Liu SM, Blanco C. Probability and predictors of relapse to smoking: results of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *Drug Alcohol Depend*. 2013;132(3):479-485.

46. Brigham GS, Schroeder G, Schindler E. Addressing smoking in community drug abuse treatment programs: practical and policy considerations. *J Psychoactive Drugs*. 2007;39(4):435-441.

47. Lindsay JA, Stotts AL, Green CE, Herin DV, Schmitz JM. Cocaine dependence and concurrent marijuana use: a comparison of clinical characteristics. *Am J Drug Alcohol Abuse*. 2009;35(3):193-198.

48. Nestler EJ. Common molecular and cellular substrates of addiction and memory. *Neurobiol Learn Mem*. 2002;78(3):637-647.

49. Bauco P, Wise RA. Potentiation of lateral hypothalamic and midline mesencephalic brain stimulation reinforcement by nicotine: examination of repeated treatment. *J Pharmacol Exp Ther*. 1994;271(1):294-301.

50. Aguilar-Valles A, Vaissière T, Griggs EM, et al. Methamphetamine-associated memory is regulated by a writer and an eraser of permissive histone methylation. *Biol Psychiatry*. 2014;76(1):57-65.

51. Sim-Selley LJ, Cassidy MP, Sparta A, Zachariou V, Nestler EJ, Selley DE. Effect of ΔFosB overexpression on opioid and cannabinoid receptor-mediated signaling in the nucleus accumbens. *Neuropharmacology*. 2011;61(8):1470-1476.