A Longitudinal Investigation of the Role of Self-Medication in the Development of Comorbid Mood and Drug Use Disorders: Findings From the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

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ABSTRACT

Objective: To examine whether self-medication with drugs confers risk of comorbid mood and drug use disorders.

Method: A longitudinal, nationally representative survey was conducted by the National Institute on Alcohol Abuse and Alcoholism. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) assessed *DSM-IV-TR* psychiatric disorders, self-medication, and sociodemographic variables at 2 time points. A total of 34,653 adult, US participants completed both waves of the survey. Wave 1 was conducted between 2001 and 2002, and Wave 2 interviews took place 3 years later (2004–2005). Logistic regression and population attributable fractions were calculated to obtain estimates of the association between self-medication and incident disorders.

Results: Logistic regression analyses revealed that self-medication with drugs conferred a heightened risk of new-onset drug dependence among those with baseline mood disorders (adjusted odds ratio [AOR] = 7.65; 95% CI, 3.70–15.82; $P < .001$) and accounted for over 25% of incident drug dependence disorders among people with mood disorders. Among those with comorbid mood and drug use disorders at baseline, self-medication with drugs was associated with the persistence of drug abuse (AOR = 2.47; 95% CI, 1.34–4.56; $P < .01$), accounting for over one-fifth of the persistence of drug use disorders at 3-year follow-up.

Conclusions: Self-medication with drugs among individuals with mood disorders confers substantial risk of developing incident drug dependence and is associated with the persistence of comorbid mood and drug use disorders. These results clarify a pathway that may lead to the development of mood and drug use disorder comorbidity and indicate an at-risk population, with potential points of intervention for prevention of comorbidity.

J Clin Psychiatry 2012;73(5):e588–e593

Submitted: *August 19, 2011; accepted November 8, 2011 (doi:10.4088/JCP.11m07345).*
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Both mood disorders and substance use disorders occur frequently in the general population, with lifetime prevalence rates of approximately 15%–20%.[1] Individually, each set of disorders is associated with substantial disability, poor quality of life, and ineffective treatment for patients.[2,3] While mood and substance use disorders are common in their own right, they also co-occur frequently in the same individual.[4–7] Approximately 20% of people with an alcohol or drug use disorder have a co-occurring mood disorder, and a similar proportion of individuals with a mood disorder also endorse symptoms of a comorbid substance use disorder.[5] The consequences of such comorbidity are considerable: individuals with 2 (or more) psychiatric conditions often report more severe symptomatology,[8] disability,[9] longer duration of illness,[10] and greater rates of mental health service utilization[11] relative to a noncomorbid cohort.

While much is known about the negative consequences of comorbidity, the underlying cause of mental illness/substance use disorder co-occurrence has received less research attention. One etiologic theory to account for the relationship between mood and substance use disorder comorbidity asserts that a direct causal relationship leads one disorder to predispose an individual to develop a second disorder.[12] The "self-medication," or "tension-reduction" theory,[13] focuses on the use of alcohol or drugs as a method of self-medicating affective symptoms. Historically, this theory has been used to account for the comorbidity found in alcohol use and anxiety disorders[14–18] and is exemplary of such a direct causal relationship. Other authors (eg, Markou et al,[19] Swann[20]) have examined the self-medication theory in the context of mood and substance use disorder comorbidity and have postulated similar underlying neurologic substrates that may help to explain the coalescence of these 2 groups of conditions.

Although a frequently considered hypothesis, there is relatively little known about the use of drugs or prescription medications to self-medicate mood symptoms in population-based samples. Population-based studies are less affected by selection bias that influences clinical samples. Previous studies of the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC) dataset have examined self-medication by using cross-sectional assessments of co-occurring conditions[21–23] and found strong associations of using alcohol and drugs to self-medicate mood disorders with comorbid psychopathology. We aimed to extend these analyses by using longitudinal information from Waves 1 and 2 of the NESARC in order to assess the temporal association of using drugs and prescription medications to self-medicate mood symptoms with the subsequent new onset of drug use disorders. Our primary goal was to assess whether self-medication of affective symptoms with drugs would be associated with an increase in the incidence of drug use disorders over time. We hypothesized that individuals who reported using drugs to self-medicate negative mood symptoms at baseline would be at increased risk for the new development of drug use disorders at the time of the follow-up interview. We further examined whether self-medication is associated with comorbidity among

people without mood and drug use disorders at baseline or with persistence of comorbidity among individuals with both mood and drug use disorders at baseline.

A secondary objective of the study was to examine whether self-medication of subthreshold mood symptoms among people with drug use disorders at baseline predicted incident mood disorders. On the basis of previous cross-sectional studies showing a high prevalence of self-medication in mood disorders,[21] we hypothesized that this behavior would be associated with higher rates of comorbid mental illness.

Clinical Points

- Using drugs to self-medicate mood symptoms increases a person's risk of developing drug dependency within 3 years.
- Self-medication accounts for one-quarter of new cases of drug dependence among people with mood disorders.

METHOD

Sample

The NESARC is a longitudinal, nationally representative survey conducted by the National Institute of Alcohol Abuse and Alcoholism. Wave 1 of the NESARC occurred between 2001 and 2002 and consisted of a total of 43,093 respondents from the US adult, noninstitutionalized population. Wave 2 of the NESARC was carried out between 2004 and 2005 and yielded a sample of 34,653 respondents who had also taken part in Wave 1. The overall response rate was 70.2%. The sampling frame of the NESARC was based on the US Bureau of the Census Supplementary Survey data and has been described in detail elsewhere.[24] Respondents were contacted in writing, informed of the nature of the survey and its potential uses, ensured of confidentiality, and told that participation was voluntary. The ethics protocol for the NESARC was reviewed and approved by the US Census Bureau and the US Office of Management and Budget. Data were weighted to account for sampling biases and to ensure representativeness of the US population based on the 2000 Census. Additional information about the NESARC sampling design and methodology is available elsewhere.[25]

Measures

Sociodemographic variables. Eight sociodemographic variables were assessed at Wave 1 of the NESARC. These included gender, annual household income, ethnicity, age, region of residence, marital status, education, and urban status. Annual income was divided into 4 categories ($0–$19,999; $20,000–$34,999; $35,000–$59,999; and $60,000+), as were ethnicity (white, black, Native American or Asian, and Latino or Hispanic), age (18–29, 30–44, 45–64, and 65+ years), and region (Northeast, Midwest, South, and West). Marital status was classified into one of the following categories: (1) married/cohabitating, (2) divorced/separated/widowed, or (3) never married. Education was categorized as (1) less than high school, (2) high school, and (3) some college or higher. Urban status classified participants into either (1) urban or (2) rural groups.

Assessment of mental disorders. The Alcohol Use Disorders and Associated Disabilities Interview Schedule IV (AUDADIS-IV)[26] generated diagnoses in accordance with the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*).[27] The reliability and validity of the AUDADIS-IV ranges from good to excellent across diagnoses.[28] Lifetime and past-year diagnoses consisted of mood (dysthymia, mania, hypomania, and depression), anxiety (panic disorder, social phobia, specific phobia, and generalized anxiety disorder), and substance use disorders (alcohol and drug abuse and dependence). Specific medicines or drugs inquired about included sedatives (eg, sleeping pills, barbiturates, chloral hydrate), tranquilizers (eg, benzodiazepines), opioid painkillers (eg, codeine, meperidine), amphetamines (eg, Benzedrine, Methadrine), cannabis, and cocaine. Lifetime diagnoses also included personality disorders (paranoid, schizoid, schizotypal, antisocial, borderline, histrionic, narcissistic, avoidant, dependent, and obsessive-compulsive). In order to receive a particular diagnosis, participants had to endorse the minimum number of symptoms in accordance with *DSM-IV-TR*. The Wave 1 interview measured presence of Axis I disorders at any point in the lifetime as well as within the past year. Interviews at Wave 2 measured presence of Axis I disorders in the past year and at any point in the 3-year interval between surveys. New-onset disorders were defined by excluding those who met criteria for the disorder at any point in their lifetime (at Wave 1 interview) and by including those who met criteria for the disorder in the 3-year interval preceding Wave 2. For the aggregate "any" incident disorder categories, those who met criteria for any 1 of the individual disorders assessed at baseline (for example, any of the 4 mood disorders) were excluded.

Self-medication. Self-medicating behavior was assessed at the Wave 1 survey within 4 different mood disorder categories. Participants who endorsed a minimum number of mood symptoms were asked if at any time in the past they had used drugs for the purpose of ameliorating mood symptoms. For example, the following item was used to assess self-medication of depressive symptoms:

> Did you ever take any medicines or drugs on your own, that is, without a prescription or in greater amounts, or more often or longer than prescribed to help improve your mood or to make yourself feel better when you felt sad, blue, depressed, or down/didn't care about or enjoy things?

Responses to self-medication questions were coded as either yes or no. Participants who answered no to the self-medication question were set as the reference category in logistic regression analyses. Individuals who engaged in self-medication only with alcohol were excluded from the analyses.

Statistical Analyses

Suitable statistical weights were applied to ensure representativeness of the NESARC data. Because of the complex sampling design of the NESARC, SUDAAN's Taylor Series Linearization was utilized in the calculation of standard error estimates.[29] Cross-tabulation and frequency calculations were conducted to determine descriptive information on sociodemographic and incident mental disorder variables for the entire NESARC sample. Prevalence was estimated for individuals who used any drugs in the past year and reported self-medication at Wave 1. Descriptive statistics and population attributable fractions were calculated and multiple logistic regression analyses were performed in order to obtain information on self-medication within each subpopulation of interest. In each regression analysis, self-medication was set as the dependent variable, and models were adjusted for sociodemographic characteristics and Wave 1 lifetime comorbidity (Axes I and II disorders).

First, among those diagnosed with any lifetime mood disorder at Wave 1, regression analyses were conducted to examine the impact of self-medication with drugs on incident drug use disorders. The 2 drug use disorders (drug abuse and dependence) were examined in separate analyses, as was a summary variable ("any drug use disorder"). The proportion of incident disorders that could be attributed to self-medication within mood disorders was calculated by using population attributable fractions.

Second, among those diagnosed with a lifetime drug use disorder at Wave 1, regression analyses were conducted to examine the impact of self-medication with drugs on incident mood disorders. Among those with drug use disorders at baseline, separate models were tested with each individual incident mood disorder as an independent variable. An "any incident mood disorder" model was also tested. Population attributable fractions were calculated to determine the proportion of incident mood disorders that were attributable to self-medication with drugs among those with lifetime drug use disorders at baseline.

Among participants at baseline who had both mood and drug use disorders in the past year, the effect of self-medication with drugs on the persistence of each disorder was calculated with logistic regression analyses. Similar regression and population attributable fraction analyses were also performed within the population of individuals who did not meet criteria for a mood or drug use disorder at Wave 1 in order to determine the effect of self-medication with drugs on the development of either incident drug use disorders or mood disorders. Cross-tabulation analyses were performed to determine the frequency of use of each specific drug at Wave 1 and the frequency of dependence by drug type at Wave 2 among individuals who self-medicated their mood symptoms and later became dependent on drugs.

RESULTS

Table 1 presents information on sociodemographic characteristics in the total NESARC sample. Approximately 2.0% of the Wave 2 sample met criteria for new-onset drug use disorders (1.1% for incident drug abuse and 0.8% for incident drug dependence).

Table 1. Wave 1 Sociodemographic Characteristics and Wave 2 Incident Drug Use and Mood Disorders Among the Entire NESARC Sample (N = 34,653)

Variable	n (%)[a]
Gender	
Male	14,564 (47.9)
Female	20,089 (52.1)
Age, y	
18–29	6,719 (21.8)
30–44	11,013 (30.9)
45–64	10,917 (31.1)
65+	6,004 (16.2)
Ethnicity	
White	20,174 (70.9)
Black	6,577 (11.0)
American Indian/Alaskan	580 (2.2)
Asian/Hawaiian	966 (4.3)
Hispanic	6,356 (11.6)
Marital status	
Married/cohabitating	18,413 (63.1)
Widowed/separated/divorced	8,564 (16.5)
Never married	7,676 (20.5)
Region	
Northwest	6,444 (19.7)
Midwest	7,540 (23.1)
South	12,833 (35.2)
West	7,836 (22.0)
Income	
$0–$19,999	8,959 (20.3)
$20,000–$34,999	7,309 (19.6)
$35,000–$59,999	8,812 (26.3)
$60,000+	9,573 (33.8)
Education	
Less than high school	5,744 (14.6)
High school	9,955 (29.0)
Some college or more	18,954 (56.3)
Urbanicity	
Urban	11,672 (28.9)
Rural	22,981 (71.1)
Incident disorders	
Major depression	1,807 (6.1)
Dysthymia	353 (1.1)
Bipolar I disorder	672 (1.9)
Bipolar II disorder	188 (0.5)
Any mood disorder	2,019 (7.0)
Drug abuse	322 (1.1)
Drug dependence	264 (0.8)
Any drug use disorder	586 (2.0)

[a]Percentages are weighted to account for sampling biases.
Abbreviation: NESARC = Nationally Epidemiologic Survey on Alcohol and Related Conditions.

Cross-tabulations were calculated among those with mood disorders and substance use to determine frequency of self-medication. Among individuals with a mood disorder who used any drugs in the past year, 38.1% reported self-medication with drugs. Among individuals at Wave 1 who had a comorbid mood and drug use disorder, 34.2% reported self-medication with drugs.

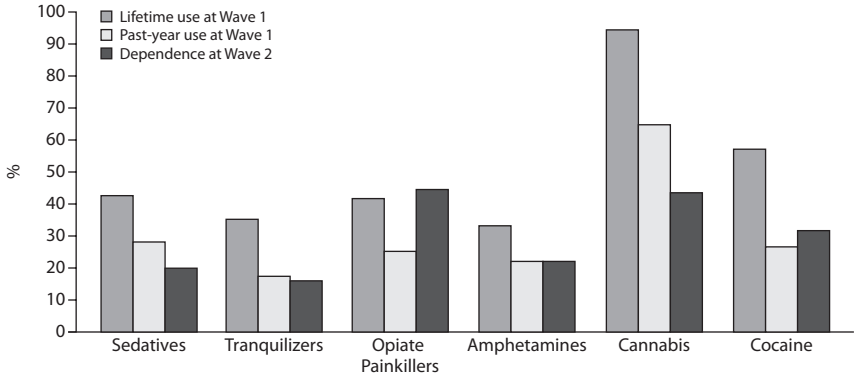
Table 2 presents frequency distributions, adjusted odds ratios, and population attributable fractions of incident drug use disorders among participants with any lifetime mood disorder (Table 2—top half) and among those with any lifetime mood disorder who engage in self-medication with drugs (Table 2—bottom half). Regression analyses

Table 2. Incident Drug Use Disorders Among Those With a History of Any Lifetime Mood Disorder at Baseline (Wave 1), Broken Down by Self-Medication Status[a]

		Any Lifetime Mood Disorder			
			Yes (n = 7,082)[b]		
Disorder	n	No (n = 27,571) n (%)[c]	n (%)	Adjusted Odds Ratio[d] (95% CI)	Population Attributable Fraction, % (95% CI)
Drug abuse	322	234 (1.0)	88 (1.5)	1.96 (1.51–2.56)***	1.4 (0.8–2.3)
Drug dependence	264	166 (0.7)	98 (1.6)	2.06 (1.42–3.01)***	1.7 (0.7–3.1)
Any drug use disorder	586	400 (1.6)	186 (3.0)	1.93 (1.53–2.42)***	2.7 (1.6–4.1)
		Self-Medication of Lifetime Mood Disorder with Drugs[a]			
			Yes (n = 546)		
		No (n = 5,428) n (%)	n (%)	Adjusted Odds Ratio (95% CI)	Population Attributable Fraction, % (95% CI)
Drug abuse	67	65 (1.4)	2 (0.5)	…	…
Drug dependence	74	49 (1.1)	25 (5.2)	7.65 (3.70–15.82)***	25.7 (12.3–43.5)
Any drug use disorder	141	114 (2.5)	27 (5.6)	4.11 (2.33–7.25)***	14.8 (6.9–25.9)

[a]Only those patients who met criteria for any lifetime mood disorder at Wave 1 and did not meet criteria for the substance use disorder in question were included in these analyses.
[b]7,082 respondents met criteria for lifetime mood disorder at Wave 1. The bottom half of the table presents analyses of those that engaged in self-medication with drugs (and excluded those who used alcohol exclusively to self-medicate [n = 1,108]).
[c]Percentages are weighted (for example, among those who met criteria for baseline mood disorder, 1.5% developed incident drug abuse) to account for sampling biases.
[d]Odds ratios were adjusted for the following sociodemographic variables: gender, age, income, marital status, education level, ethnicity, region, and urban status as well as any lifetime psychiatric disorder at Wave 1.
***$P < .001$.

Figure 1. Types of Drugs Used at Wave 1 of the NESARC and the Categories of Drug Dependence at Wave 2 Among Individuals With Baseline Mood Disorders Who Endorsed Self-Medication at Wave 1 and Subsequently Developed Drug Dependence at Wave 2 (n = 25)



Abbreviation: NESARC = National Epidemiologic Survey on Alcohol and Related Conditions.

revealed that, among those with mood disorders at baseline, the risk of incident drug abuse and drug dependence was increased approximately 2-fold relative to those without a lifetime mood disorder at baseline. Among individuals who met criteria for a baseline mood disorder and reported self-medication with drugs, 5.6% developed an incident drug use disorder. Regression analyses revealed that self-medication with drugs among those with mood disorders at baseline was associated with a substantially increased odds of incident drug dependence (adjusted odds ratio [AOR] = 7.65; 95% CI, 3.70–15.82; $P < .001$), independent of the effects of sociodemographic factors and comorbid psychiatric illness. One-quarter of new-onset drug dependence disorders were attributable to self-medication.

Figure 1 displays the types of drugs used at Wave 1 (both lifetime and past year) and the categories of drug dependence at Wave 2 among individuals with baseline mood disorders who endorsed self-medication with drugs at Wave 1 and subsequently developed drug dependence at Wave 2. When examined by drug class, the highest rates of dependence were observed for cannabis (43.7%) and opioid dependence (44.7%). Cannabis was commonly used by people who self-medicated mood symptoms at Wave 1; 94% had used cannabis at some point in their lifetime, with almost two-thirds (65%) using it within the past year. There were also high rates of prescription drug use among those who self-medicate, with almost half of them using sedatives and opioid painkillers in their lifetime. Interestingly, for amphetamines, cocaine, and, in particular, opioid painkillers, a relatively large proportion of those who reported lifetime or past-year use of these substances at Wave 1 later went on to develop dependence at Wave 2.

Among those with drug use disorders at baseline who reported using drugs to self-medicate lifetime subthreshold mood symptoms, the prevalence of incident mood disorders ranged from 1.8% (dysthymic disorder) to 5.5% (bipolar I disorder). Regression analyses revealed that self-medication with drugs was not significantly associated with any new-onset mood disorders meeting *DSM-IV-TR* criteria.

Table 3 presents frequency distributions, adjusted odds ratios, and population attributable fractions of persistent drug use disorders at Wave 2 among those with lifetime comorbid mood and drug use disorders at baseline who reported self-medication with drugs. Among those with comorbid mood and drug use disorders at baseline, self-medication with drugs was associated with both the persistence of drug abuse (AOR = 2.47; 95% CI, 1.34–4.56; $P < .01$) and the persistence of any drug use disorder (AOR = 2.02; 95% CI, 1.46–2.80; $P < .001$). Population attributable fraction results suggest that self-medication accounted for over one-fifth of the persistence of drug use disorders at 3-year follow-up. Self-medication was not associated with the persistence of mood disorders among those with comorbidity at baseline.

Table 3. Persistence of Drug Use Disorders at Wave 2 Among Those With Lifetime Comorbid Mood and Drug Use Disorders at Baseline (Wave 1)[a]

		Self-Medication With Drugs			
		No	Yes		
Persistence of Wave 2 Disorder	n	n (%)[b]	n (%)	Adjusted Odds Ratio[c] (95% CI)	Population Attributable Fraction, % (95% CI)
Drug abuse	85	54 (7.3)	31 (18.3)	2.47 (1.34–4.56)**	21.2 (5.9 to 39.4)
Drug dependence	73	28 (13.6)	45 (16.2)	1.12 (0.63–1.99)	1.9 (−6.4 to 13.8)
Any drug use disorder	247	120 (13.0)	127 (26.3)	2.02 (1.46–2.80)***	21.2 (10.8 to 32.1)

[a]In each regression analysis, the baseline population included those with mood disorders and the persistent drug use disorder of interest. For example, for persistent drug abuse, the baseline population consisted of those who met lifetime criteria for any mood disorder and for drug abuse.
[b]Percentages are weighted column percents. For example, 7.3% of those who did not self-medicate (and met criteria for comorbid mood and drug abuse disorders) continued to meet drug abuse criteria at follow-up.
[c]Odds ratios were adjusted for the following sociodemographic variables: gender, age, income, marital status, education level, ethnicity, region, and urban status as well as any lifetime psychiatric disorder at Wave 1.
**$P < .01$; ***$P < .001$.

DISCUSSION

To our knowledge, the present study is the first to longitudinally demonstrate the role of self-medication with drugs in the genesis of incident drug use disorder comorbidity among people with mood disorders in a representative sample of the US population. Although previous studies have demonstrated an association between substance use and mood disorders,[4–7] the factors that mediate this relationship have been examined less frequently. The results of this study are novel in that self-medication is identified as a factor that underscores the risk of developing a comorbid disorder in specific populations. Self-medication has been generally overlooked in the area of mood disorders, yet appears to be a common behavior with significant negative consequences. Our findings may have important clinical implications for patient assessment and could provide a target for treatment efforts to prevent future substance use disorder comorbidity.

The findings from this study indicate that, among individuals with a mood disorder at baseline who use drugs to self-medicate their symptoms, the odds of developing a new-onset drug use disorder within the next 3 years increased up to 7-fold, relative to those with mood disorders who do not self-medicate. Over 25% of incident drug dependence diagnoses were found to be attributable to self-medication in this population. The control of numerous confounding effects and longitudinal design of this study provide new evidence in support of the self-medication hypothesis and suggest a potentially causative role in the etiology of mood and drug use disorder comorbidity. Furthermore, the strength of the association and high population attributable fraction value for incident drug dependence emphasize the importance of self-medication in comorbidity development. Our findings thus support the notion that self-medication is a behavior that magnifies the risk of developing comorbid drug use and mood conditions.

The results of this study give us important clues as to the types of drugs utilized by those with mood disorders to self-medicate their affective symptoms, as well as the addictive potential of various substances. Cannabis is used commonly by those with mood disorders who engage in self-medication, prior to the development of a drug use disorder. Almost half of the people who develop subsequent drug dependence become dependent on cannabis. Cannabis use in this population may be a double-edged sword: the potential of cannabis to exert antidepressant effects has been examined by some authors (eg, Gruber et al[30]), as has the notion that heavy cannabis use exacerbates, rather than ameliorates, depressive symptoms.[31] Another important observation is that many of the incident drug dependence diagnoses among people who self-medicate are for prescription drugs. This finding suggests that physicians need to carefully assess and follow their mood disorder patients who self-medicate, since there is a high risk of developing dependence to commonly prescribed psychotropics and painkillers.

There are several limitations to this study that warrant mentioning. First, only 1 explanatory mechanism (self-medication) was examined to elucidate the development of mood and drug use disorder comorbidity. Other possible mechanisms, including hereditary and shared etiologic factors, may also play a role. Second, self-medication assessments were retrospective and, thus, subject to recall bias. We were unable to objectively study the temporal relationship between negative mood states and subsequent drug consumption and therefore cannot be certain that substance use was directly related to mood symptoms. Third, a lack of experimental design precludes us from making definitive statements in regard to causality. Although the Bradford Hill criteria[32] of plausibility and coherence are met by the current study design, there are other elements for establishing causality that are not addressed herein. Fourth, certain populations (eg, those currently residing in institutional settings) were excluded from the NESARC survey, and our results may therefore not generalize to these individuals. Finally, the amount of substances used for self-medication and frequency of self-medication were not assessed in the NESARC survey. Future studies in this area should strive to mitigate these limitations and focus on possible interventions that address self-medication of affective symptoms, with the aim of preventing subsequent psychiatric comorbidity.

In conclusion, the results of this study support the notion that self-medication with drugs among individuals with mood disorders confers substantial risk of developing incident drug dependence. Cannabis in particular is a drug on which people frequently become dependent when self-medicating mood symptoms. These results clarify a pathway that may lead to the development of mood and drug use disorder comorbidity and indicate to clinicians an at-risk

population. Careful inquiry about self-medication would appear warranted, as early detection and intervention could prevent persistent mood and drug use disorder comorbidity for individual patients and reduce the overall public health burden of these commonly co-occurring mental health conditions.

Drug names: meperidine (Demerol).

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Potential conflicts of interest: None reported.

Funding/support: This work was generously supported by grants/awards from the National Institute on Alcohol Abuse and Alcoholism (AA016346) to Dr Crum, the National Institute of Drug Abuse (DA030460) to Dr Mojtabai, the Manitoba Health Research Chair to Dr Sareen, the Manitoba Health Research Council Establishment Award and Canadian Institutes of Health Research New Investigator Award (#113589) to Dr Bolton, and the Social Sciences and Humanities Research Council to Ms Robinson.

Additional information: The original data set for the National Epidemiologic Survey on Alcohol and Related conditions (NESARC) is available from the National Institute on Alcohol Abuse and Alcoholism (http://www.niaaa.nih.gov).

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