Journal of Affective Disorders 148 (2013) 188–195

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The bidirectional relationships between alcohol, cannabis, co-occurring alcohol and cannabis use disorders with major depressive disorder: Results from a national sample

Lauren R. Pacek [a,*], Silvia S. Martins [a,b], Rosa M. Crum [a,c,d]

[a] Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States
[b] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York
[c] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States
[d] Department of Psychiatry and Behavioral Sciences, Johns Hopkins School of Medicine, Baltimore, MD, United States

ARTICLE INFO

Article history:
Received 5 October 2012
Accepted 20 November 2012
Available online 21 December 2012

Keywords:
Cannabis
Alcohol
Abuse
Dependence
Depression
Co-occurring use

ABSTRACT

Introduction: Alcohol use disorders (AUD) and cannabis use disorders (CUD) are common in the United States (US), and are associated with major depressive disorder (MDD). Co-occurring alcohol and cannabis use/use disorders (AUD+CUD), though understudied, have been found to be associated with greater adverse outcomes than alcohol or cannabis use/use disorders alone. There is a paucity of research on the co-occurring relationships of the two disorders with depression.
Methods: Data came from Waves 1 and 2 of the National Epidemiologic Survey of Alcohol and Related Conditions (NESARC), a population-based longitudinal survey of the adult non-institutionalized, civilian population in the US. Logistic regression analyses were used to assess the associations between: 1) baseline AUD, CUD, and co-occurring AUD+CUD with incident MDD at follow-up and 2) baseline MDD with incident AUD, CUD, and co-occurring AUD+CUD at follow-up, adjusted for potential confounding variables.
Results: For Aim 1, most of the AUD and CUD were positively associated with MDD. The strongest associations with incident MDD were observed for cannabis dependence (OR=6.61, CI=1.67–26.21) and co-occurring alcohol and cannabis dependence (OR=2.34, CI=1.23–4.48). For Aim 2, baseline MDD was significantly associated with comparatively fewer cases of incident AUD and CUD but the strongest association was observed for new onset co-occurring alcohol and cannabis dependence (OR=4.51, CI=1.31–15.60).
Limitations: The present study is limited by the potential for social desirability and recall biases.
Discussion: Positive associations between AUD, CUD and MDD were observed bidirectionally. Findings have implications for preventive and treatment programs and initiatives.

1. Introduction

Alcohol and cannabis are among the most commonly used substances in the United States (US). Fifty percent of adults report current frequent drinking, while an additional 14% report current infrequent drinking (Pleis et al., 2009). Additionally, cannabis continues to be the most frequently used illegal substance in the US (Substance Abuse and Mental Health Services Administration (2007)); 4% of the adult population report current cannabis use (Substance Abuse and Mental Health Services Administration, 2007,2008,2009; Compton et al., 2004). Correspondingly, alcohol use disorders and cannabis use disorders (i.e., abuse and/or dependence), are fairly common as well. According to results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the 12-month prevalence of alcohol abuse and dependence were 4.7% and 3.8%, respectively (Grant et al., 2004). Similarly, past-year cannabis abuse was estimated at 1.1%, and past-year dependence at 0.4% (Compton et al., 2004), with cannabis dependence being twice as prevalent as dependence on any other illegal psychoactive substance (Substance Abuse and Mental Health Services Administration, 2009); Anthony and Helzer, 1991; Anthony et al., 1994). Despite the high prevalence of both alcohol and cannabis use, as well as alcohol use disorders (AUD) and cannabis use disorders (CUD) in the general population, sparse research has focused on the co-occurring use of alcohol and cannabis, and even less has examined co-occurring alcohol and cannabis use disorders (AUD+CUD) and subsequent health complications.

Existing research indicates that individuals who use alcohol and cannabis simultaneously experience greater social consequences, higher rates of alcohol dependence, as well as higher rates of

* Corresponding author.
E-mail address: lropelew@jhsph.edu (L.R. Pacek).

0165-0327/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2012.11.059

depression when compared to individuals who use only alcohol or onlycannabis (Midanik et al., 2007). Among college students, those who reported co-occurring alcohol and cannabis use were more likely to report academic problems than were students reporting only alcohol use (Shillington and Clapp, 2001). Additionally, among 250 adult patients with alcohol dependence in inpatient treatment in New York State, US, those who continued to smoke cannabis following treatment were more likely to return to alcohol use following sustained abstinence (Aharonovich et al., 2005). Furthermore, in a cross-sectional study utilizing data from the National Survey on Drug Use and Health (NSDUH), White, African American, and Hispanic participants with co-occurring alcohol and cannabis use disorders were significantly more likely to report having been arrested within the past year, as compared with individuals with an alcohol use disorder only (Pacek et al., 2012). Additionally, African American participants with a co-occurring alcohol and cannabis use disorder were significantly more likely to report having experienced a major depressive episode within the past year as compared to individuals with an alcohol or cannabis use disorder alone (Pacek et al., 2012).

Though existing research on co-occurring alcohol and cannabis use disorders is limited to cross-sectional studies, some evidence from both cross-sectional and longitudinal studies exists that describes the relationship between alcohol use disorders and major depressive disorder, as well as between cannabis use and major depressive disorder. Evidence has fairly consistently supported a positive relationship between alcohol use disorders and major depressive disorder. For instance, using data from the National Longitudinal Alcohol Epidemiologic Survey (NLAES), Hasin and Grant (2002) found that prior alcohol dependence increased the risk of current major depressive disorder by more than four-fold among a sample of former drinkers. Additionally, among individuals participating in the first two waves of data in the Epidemiological Catchment Area (ECA) community survey, findings suggested a reciprocal relationship between alcohol dependence and major depressive disorder: alcohol dependence at Wave 1 was associated with an increased risk for development of depression at Wave 2, and similarly, the presence of depression at Wave 1 also was associated with increased risk for the onset of alcohol dependence at Wave 2 (Gilman and Abraham, 2001). Using data from the Christchurch Health and Development Study, a 25-year longitudinal study of a birth cohort of children from New Zealand, Fergusson et al., 2009, through the use of structural equation modeling, suggested that the association between alcohol dependence and depression is best explained by a causal model in which alcohol dependence leads to major depressive disorder. Furthermore, though research has demonstrated positive relationships between both alcohol abuse and alcohol dependence with major depressive disorder, the strongest relationship appears to exist between alcohol dependence and major depressive disorder. For instance, among an earlier population-based sample, Grant and Harford (1995) observed a significant relationship between alcohol abuse, alcohol dependence, and major depressive disorder. However, the observed association between alcohol dependence and depression was approximately twice as strong as the association between alcohol abuse and depression (odds ratio of 3.82 versus 1.69, respectively). Dawson et al. (2005), using data from the NESARC, also found that among non-college student adults aged 18–29 as well as adults aged 30 and older, the association between alcohol dependence and major depressive disorder was much stronger than the association between alcohol abuse and major depressive disorder (age 18–29: odds ratios of 4.5 versus 2.1; age 30+: odds ratios of 3.8 versus 1.5).

Though fairly consistent evidence for the association, and even a purported causal link, between alcohol use disorders and major depressive disorder (MDD) exists, research examining the relationship between cannabis use and use disorders with depression has yielded somewhat more mixed evidence. For instance, Harder et al. (2008) stated that their evidence does not support a causal association between adolescent-onset cannabis use and depression in young adulthood. Conversely, evidence from a population-based study indicates that there is a modest association between early cannabis use and later onset of depression (deGraaf et al., 2010). Furthermore, in a population-based sample, both early- and adult-onset cannabis users were found to have an increased odds of depression compared to individuals who had never smoked cannabis, leading the authors to conclude that cannabis smoking at any age potentially signals a modest increased risk for a depressive episode in adulthood (Fairman and Anthony, 2012). These positive findings are corroborated by reports from a review conducted by Degenhardt et al. (2003). They found that within cohort and well-designed cross-sectional studies in the general population, a modest association was observed between heavy or problematic use of cannabis and depression.

The existing evidence seems to suggest that alcohol and cannabis use, as well as use disorders, when looked at singly are associated with MDD. Yet, two avenues of research remain as of yet unexplored, leading us to assess the following aims: whether the associations between AUD, CUD, and MDD are bidirectional, and whether the co-occurrence of alcohol and cannabis use disorders is associated with even greater risk for the development of MDD than AUD or CUD alone. We also aimed to assess the reverse association between co-occurring AUD and CUD with the incidence of MDD. With respect to the temporal ordering of the relationship between substance use disorders and MDD, three main models have been postulated to explain these associations. The first is known as the precipitation model (McEwan, 2000; Brady and Sinha, 2005), whereby alcohol and/or drug use may trigger psychopathology via neuroadaptation in brain reward pathways that can lead to subsequent development of psychiatric disorders. A second hypothesis is the self-medication model (Quitkin et al., 1972; Conger, 1956; Lader, 1972; Markou et al., 1998), which postulates that psychiatric disorders may cause an increase in alcohol and/or drug use due to their ability to alleviate mental health symptoms. Last, it is possible that a third factor or underlying vulnerability may influence the risk for developing both drug use/use disorders and psychiatric disorders, and may explain the observed association.

In order to further evaluate the association between these substance use disorders and depression; the present study had the following specific aims: 1) to describe the relationship between baseline alcohol, cannabis, and co-occurring alcohol and cannabis use disorders and the development of incident MDD and; 2) to describe the relationship between baseline MDD and the development of incident alcohol, cannabis, and co-occurring alcohol and cannabis use disorders in a population-based, longitudinal sample. Findings from the present study have potential implications for the development and implementation of treatment and prevention intervention efforts. We hypothesize that while AUD and CUD will both be associated with MDD, co-occurring AUD+CUD will be more strongly associated with MDD than either AUD or CUD alone.

2. Methods

2.1. Study population

The NESARC is a population-based longitudinal survey of the adult non-institutionalized, civilian population in the United States conducted by the US Census Bureau under the direction of the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Wave 1 interviews were conducted in 2001–2002 with a sample of 43,093 individuals age 18 and older (Grant et al., 2003). Wave 2 was a three-year prospective follow-up survey

comprised of 34,653 of the Wave 1 respondents, representing a response rate of 86.7% of the eligible respondents (Grant et al., 2009). Trained lay interviewers conducted face-to-face interviews using computer-assisted software. Informed consent was obtained from all participants prior to the interviews. Detailed descriptions of the methodology, sampling, and weighting procedures can be found elsewhere (Grant et al., 2003; Ruan et al., 2008).

For Aim 1 of the present analyses, the study sample was restricted to three subgroups: individuals with lifetime AUD without lifetime CUD at Wave 1 ($N=5934$); individuals with lifetime CUD without lifetime AUD at Wave 1 ($N=395$); and individuals with lifetime co-occurring AUD+CUD at Wave 1 ($N=1475$). Within these AUD, CUD, and AUD+CUD categories, we chose to also look at individuals with lifetime alcohol abuse only, without dependence at Wave 1 ($N=4127$); individuals with lifetime alcohol dependence (with or without abuse) at Wave 1 ($N=1807$); individuals with lifetime cannabis abuse alone, without dependence at Wave 1 ($N=366$); individuals with lifetime cannabis dependence (with or without abuse) at Wave 1 ($N=29$); and individuals with lifetime co-occurring alcohol dependence and cannabis dependence at Wave 1 ($N=146$). The reference group for these analyses was individuals without lifetime AUD, CUD, or AUD+CUD, and without a lifetime history of MDD at Wave 1 ($N=20,845$). An additional criterion for inclusion in all groups was that individuals had to have been followed up at Wave 2.

For Aim 2 of the present analyses, the sample was restricted to individuals with lifetime MDD at Wave 1 who did not have a lifetime diagnosis of AUD, CUD, or co-occurring AUD+CUD ($N=3320$). The reference group for these analyses was individuals without lifetime AUD, CUD, or AUD+CUD, and without a lifetime history of MDD at Wave 1 ($N=20,845$). Similar to Aim 1, an additional criterion for inclusion in the analyses for Wave 2 was that individuals had to have been followed up at Wave 2.

2.2. Measures

Lifetime alcohol and cannabis abuse and dependence were assessed at Wave 1, and incident alcohol and cannabis abuse and dependence were assessed at Wave 2 using the Alcohol Use Disorders and Associated Disabilities Interview Schedule-DSM IV Version (AUDADIS-IV). The AUDADIS was administered through a structured computer-assisted personal interview (CAPI) (Grant et al., 2003). The AUDADIS is a fully structured diagnostic interview that is designed for use by lay interviewers. It assesses alcohol and other drug consumption data as well as selected Axis I and II psychiatric disorders via criteria presented in the Diagnostic and Statistical Manual, Fourth Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 1994). This instrument was also used to assess lifetime prevalence of other drug use disorders (i.e., heroin, other opioids, cocaine, and hallucinogen use disorders). Other lifetime drug use disorders were assessed as

Table 1
Baseline characteristics of individuals with alcohol (AUD) and/or cannabis use disorders (CUD), in the sample to assess incident major depressive disorder, NESARC, 2001-05.

	Reference group[a] $n=20,845$ n (wt%[e])	AUD[b] $n=5,943$ *n* (wt%)	CUD[c] $n=395$ *n* (wt%)	AUD+CUD[d] $n=1,475$ *n* (wt%)
Characteristics				
Sex				
Male	7486 (41.84)	4008 (71.86)*	219 (59.92)*	1053 (75.47)*
Female	13,359 (58.16)	1926 (28.14)	176 (40.08)	422 (24.53)
Age				
18–29	3945 (21.28)	1004 (19.24)*	138 (41.28)*	375 (29.09)*
30–39	4030 (18.09)	1413 (23.57)	90 (20.20)	403 (27.10)
40–54	5498 (26.62)	1894 (31.47)	146 (33.84)	618 (39.40)
55+	7372 (34.02)	1623 (25.72)	21 (4.67)	79 (4.41)
Marital status				
Married/living together	11,205 (63.79)	3555 (68.61)*	191 (57.45)*	756 (59.26)*
Not married	9640 (36.21)	2,379 (31.39)	204 (42.55)	719 (40.74)
Race/ethnicity				
White	10,904 (66.00)	4040 (78.83)*	230 (70.53)	1017 (78.31)*
Black	4609 (13.08)	850 (7.82)	90 (13.52)	211 (9.04)
Hispanic	4309 (13.46)	847 (9.13)	64 (11.57)	190 (7.63)
Other	1023 (7.46)	197 (4.22)	11 (4.38)	57 (5.02)
Education				
< 12 years	3878 (16.15)	774 (11.71)*	62 (16.81)	141 (10.26)*
12 years	6234 (30.29)	1580 (27.07)	119 (30.56)	417 (28.59)
> 12 years	10,733 (53.56)	3,580 (61.23)	214 (52.62)	917 (61.15)
Income				
< $20,000	5429 (20.86)	1006 (14.14)*	85 (18.83)	243 (15.23)*
$20,000–$49,999	7589 (35.58)	1984 (32.14)	144 (34.25)	505 (32.47)
$50,000–$79,999	4121 (22.10)	1442 (25.54)	87 (24.72)	355 (24.42)
$80,000	3706 (21.45)	1502 (28.18)	79 (22.20)	372 (27.87)
Family history of depression				
No	15,668 (74.29)	3833 (63.86)*	206 (53.48)*	805 (53.54)*
Yes	5177 (25.71)	2101 (36.14)	189 (46.52)	670 (46.46)

* Statistically significant difference ($p < 0.05$) relative to the reference group.
[a] Reference group is made up of individuals without lifetime alcohol use disorders, cannabis use disorders, or major depressive disorder.
[b] AUD=alcohol use disorders; alcohol abuse and/or dependence.
[c] CUD=cannabis use disorders; cannabis abuse and/or dependence.
[d] AUD+CUD=co-occurring alcohol and cannabis use disorders; alcohol and cannabis abuse and/or dependence.
[e] wt%=weighted percentage.

Table 2
Baseline characteristics of individuals with alcohol and/or cannabis use disorders, separately for abuse, and dependence with or without abuse categories, in the sample to assess incident major depressive disorder, NESARC, 2001–05.

	Reference group[a] *n*=20,845	Alcohol abuse *n*=4,127	Alcohol dependence *n*=1,807	Marijuana abuse n=366	Marijuana dependence *n*=29	Alcohol dependence+ Marijuana dependence *n*=146
	n (wt%[b])	n (wt%)	*n* (wt%)	*n* (wt%)	*n* (wt%)	*n* (wt%)
Characteristics						
Sex						
Male	7486 (41.84)	2786 (71.56) *	1222 (72.55) *	203 (59.96) *	16 (59.35)	109 (82.07) *
Female	13,359 (58.16)	1341 (28.44)	585 (27.45)	163 (40.04)	13 (40.65)	37 (17.93)
Age						
18–29	3945 (21.28)	536 (14.53)*	468 (29.68) *	126 (40.63) *	12 (49.88) *	66 (49.10) *
30–39	4030 (18.09)	949 (22.59)	464 (25.73)	80 (19.10)	10 (34.88)	38 (27.82)
40–54	5498 (26.62)	1382 (33.30)	512 (27.40)	193 (35.25)	7 (15.24)	37 (22.06)
55+	7372 (34.02)	1260 (29.58)	363 (17.19)	21 (5.03)	0 (0.00)	5 (1.01)
Marital status						
Married/living together	11,205 (63.79)	2602 (72.52) *	953 (59.94) *	177 (57.59)	14 (55.62)	63 (48.86) *
Not married	9640 (36.21)	1525 (27.48)	854 (40.06)	189 (42.41)	15 (44.38)	83 (51.14)
Race/Ethnicity						
White	10,904 (66.00)	2862 (80.07) *	1178 (76.08) *	216 (70.44)	14 (71.77)	99 (77.16)
Black	4609 (13.08)	568 (7.49)	282 (8.55)	79 (13.01)	11 (20.28)	27 (8.59)
Hispanic	4309 (13.46)	568 (8.49)	279 (10.54)	61 (11.91)	3 (7.03)	13 (8.41)
Other	1023 (7.46)	129 (3.95)	68 (4.83)	10 (4.64)	1 (0.92)	7 (5.84)
Education						
< 12 years	3878 (16.15)	534 (11.53) *	240 (12.11)*	57 (15.43)	5 (35.09)	23 (14.33)
12 years	6234 (30.29)	1086 (26.92)	494 (27.39)	112 (31.42)	7 (19.20)	45 (32.01)
> 12 years	10,733 (53.56)	2,507 (61.55)	1,073 (60.50)	197 (53.15)	17 (45.71)	78 (53.67)
Income						
< $20,000	5429 (20.86)	635 (12.38) *	371 (17.03) *	81 (19.37)	4 (11.74)	33 (20.05)
$20,000-$49,999	7589 (35.58)	1388 (31.60)	596 (33.31)	130 (32.61)	14 (56.03)	61 (42.38)
$50,000-$79,999	4121 (22.10)	998 (25.21)	444 (26.27)	81 (25.24)	6 (17.86)	30 (21.86)
$80,000	3706 (21.45)	1106 (30.35)	396 (23.39)	74 (22.79)	5 (14.37)	22 (15.89)
Family history of depression						
No	15,668 (74.29)	2761 (67.13)*	1,072 (56.62) *	192 (54.92) *	14 (34.36) *	45 (29.31) *
Yes	5177 (25.71)	1366 (32.87)	735 (43.38)	174 (45.08)	15 (65.64)	101 (70.69)

* Statistically significant difference ($p < 0.05$) relative to the Reference Group.
[a] Reference group is made up of individuals without lifetime alcohol use disorders, cannabis use disorders, or major depressive disorder.
[b] wt%=weighted percentage.

a dichotomous variable (yes/no). Lifetime primary (i.e., not substance-induced or due to general medical conditions) MDD was assessed at Wave 1 and incident MDD was assessed at Wave 2, also using the AUDADIS-IV. Participants were also questioned as to whether a variety of blood relatives (i.e., mother, father, brother(s), sister(s), children, etc.) had ever had depression. A composite variable was then created to assess whether any first-degree relatives had a history of depression (yes/no).

Sociodemographic characteristics of sex, age, marital status, race/ethnicity, educational attainment, and income were assessed at Wave 1. Sex and marital status (married versus unmarried) were assessed as dichotomous variables, while all other variables were categorical (See Tables 1 and 2 for categories).

2.3. Statistical analyses

Two sets of analyses were conducted in the present manuscript. For both aims, descriptive statistics were calculated and chi-square(χ^2) tests were used to assess differences between individuals with AUD, CUD, and AUD+CUD, as well as alcohol abuse, alcohol dependence, cannabis abuse, cannabis dependence, and alcohol dependence plus cannabis dependence (in the case of Aim 1), as well as to assess differences between individuals with baseline MDD as compared to those without MDD (in the case of Aim 2). For Aim 1, the association between baseline substance use disorders and the development of incident MDD at Wave 2 was assessed. Because we were examining incidence of MDD in Aim 1, baseline cases of MDD were excluded. For Aim 2, we explored the relationship between baseline lifetime MDD and development of incident substance use disorders at Wave 2. For aim 2, baseline AUD and CUD were excluded in order to examine the new onset of these substance use disorders among those with and without MDD. To achieve the statistical goals of both Aims 1 and 2, bivariate and multivariate logistic regression analyses were completed. Results are presented via weighted proportions (wt%), odds ratios (ORs), and adjusted odds ratios (aORs). Selection of control variables in the multivariate models was based on a combination of p-values of < 0.05 in the bivariate analyses, as well as *a priori* theory, and prior studies in the literature. All analyses were conducted in STATA 12 (StataCorp (2007)). We used Taylor series estimation methods (STATA "svy" commands) to obtain proper standard error estimates for the cross-tabulations and logistic regression analyses and to account for the complex survey design of the NESARC.

3. Results

3.1. Descriptive statistics

3.1.1. AUD and CUD with incident MDD

Descriptive statistics for participants included in Aim 1 can be found in Tables 1 and 2. Relative to those without alcohol, cannabis or major depressive disorders,, individuals with lifetime baseline AUD ($p < 0.001$), CUD ($p < 0.001$) and AUD+CUD ($p < 0.001$) were all significantly more likely to be male.

Similarly, individuals with alcohol abuse ($p<0.001$), alcohol dependence ($p<0.001$), cannabis abuse ($p<0.001$), and co-occurring alcohol dependence and cannabis dependence ($p<0.001$) were significantly more likely to be male than participants in the reference group. In terms of age, differences between the reference group and all substance use disorder groups were observed. Individuals with AUD ($p<0.001$) and alcohol abuse ($p<0.001$) were more likely than the reference group to be married or living with a partner as if married, while individuals with CUD ($p=0.045$), AUD+CUD ($p=0.003$), alcohol dependence ($p=0.010$), and co-occurring alcohol dependence and cannabis dependence ($p=0.002$) were all less likely to be married as compared to the reference. Differences from the reference group on the basis of race were observed for individuals with AUD ($p<0.001$), AUD+CUD ($p<0.001$), alcohol abuse ($p<0.001$), and alcohol dependence ($p<0.001$). Individuals with AUD ($p<0.001$), AUD+CUD ($p<0.001$), alcohol abuse ($p<0.001$), and alcohol dependence ($p<0.001$) differed from the reference group on the basis of educational attainment, with these substance disorder groups appearing more likely to have achieved greater than 12 years of education. Differences from the reference group were also observed for individuals with AUD ($p<0.001$), AUD+CUD ($p<0.001$), alcohol abuse ($p<0.001$), and alcohol dependence ($p<0.001$) on the basis of income. Additionally, individuals in all of the study groups were significantly more likely to have a family history of depression as compared to the reference group.

3.1.2. MDD with incident AUD and CUD

Individuals with baseline MDD were more likely to be female ($p<0.001$), younger ($p<0.001$), and unmarried ($p<0.001$) as compared to individuals without baseline MDD (Table 3). A greater proportion of individuals with MDD reported being White ($p<0.001$) and had attained more than 12 years of education ($p=0.002$) as compared to those without MDD. Differences were also observed on the basis of income between the two groups ($p=0.015$). Individuals with MDD were also significantly more likely than those without MDD to report other lifetime drug use disorders ($p<0.001$).

Table 3
Baseline characteristics of individuals without a prior history of AUD or CUD, by baseline MDD[a] status in the sample to assess incident AUD [d] and/or CUD [e], NESARC, 2001–2005.

	BaselineMDD		
	Absent (*n*=20,845) *n* (wt% [b])	**Present (*n*=3,320) *n* (wt%)**	
Characteristics			
Sex			
Male	7486 (41.84)	655 (23.22)	$p<0.0001$
Female	13,359 (58.16)	2665 (76.78)	
Age			
18–29	3945 (21.28)	666 (22.37)	$p<0.0001$
30–39	4030 (18.09)	696 (18.94)	
40–54	5498 (26.62)	1028 (32.82)	
55+	7372 (34.02)	900 (25.87)	
Marital status			
Married/living together	11,205 (63.79)	1561 (57.84)	$p<0.0001$
Not married	9640 (36.21)	1759 (42.16)	
Race			
White	10,904 (66.00)	2037 (75.04)	$p<0.0001$
Black	4609 (13.08)	543 (9.05)	
Hispanic	4309 (13.46)	599 (9.57)	
Other	1023 (7.46)	141 (6.34)	
Education			
<12 years	3878 (16.15)	556 (14.73)	$p=0.0017$
12 years	6234 (30.29)	907 (27.37)	
>12 years	10,733 (53.56)	1857 (57.90)	
Income			
<$20,000	5429 (20.86)	961 (24.03)	$p=0.0105$
$20,000-$49,999	7589 (35.58)	1201 (34.25)	
$50,000-$79,999	4121 (22.10)	643 (22.18)	
$80,000	3706 (21.45)	515 (19.55)	
Other drug use disorders [c]			
No	20,776 (99.71)	3273 (98.59)	$p<0.0001$
Yes	67 (0.29)	46 (1.41)	

[a] MDD=Major depressive disorder.
[b] wt%=weighted percentage.
[c] Includes heroin, other opioids, cocaine, and hallucinogen use disorders.
[d] AUD=alcohol use disorder.
[e] CUD=cannabis use disorder.

3.2. Multivariable analyses

3.2.1. AUD and CUD with incident MDD

In unadjusted analyses, individuals with alcohol dependence were significantly more likely than those without AUD or CUD to develop incident depression (OR=1.54, CI=1.25–1.90) (Table 4). Individuals with CUD as a whole were approximately twice as likely as individuals without AUD or CUD to develop depression at Wave 2 (OR=2.02, CI=1.35–3.04). When separating CUD into abuse and dependence, participants with cannabis abuse were more likely to develop incident depression than individuals without AUD or CUD (OR=1.68, CI=1.13–2.50), as were participants with cannabis dependence (OR=8.39, CI=2.15–32.76). Additionally, individuals with co-occurring AUD+CUD (OR=1.43, CI=1.15–1.78), as well as those with co-occurring alcohol and cannabis dependence (OR=2.64, CI=1.45–4.80) were more likely than individuals without AUD or CUD to develop incident depression at Wave 2.

In adjusted analyses, individuals with AUD were 1.35 times more likely than those without AUD or CUD to develop incident depression (aOR=1.35, CI=1.15–1.60). Additionally, the association between alcohol dependence and incident depression remained significant in the adjusted model (aOR=1.75, CI=1.40–2.19). The relationships between CUD (aOR=1.78, CI=1.17–2.71) and cannabis dependence (aOR=6.61, CI=1.67–26.21) with incident depression also remained statistically significant, while the relationship between cannabis abuse (aOR=1.49, CI=0.99–2.26) and depression attenuated to the point of non-significance in the adjusted model. Furthermore, in the adjusted model, the relationships between co-occurring AUD+CUD (aOR=1.54, CI=1.20–1.98) and co-occurring alcohol and cannabis dependence (aOR=2.34, CI=1.23–4.48) with incident depression remained statistically significant.

3.2.2. MDD with incident AUD and CUD

In the unadjusted model, individuals with baseline depression were less likely than those without depression to develop incident alcohol abuse (OR=0.69, CI=0.52–0.93) (Table 5). Conversely, individuals with baseline depression were significantly more likely than those without baseline depression to develop incident alcohol dependence (OR=1.39, CI=1.02–1.90). Additionally, positive relationships were observed between baseline depression and CUD (OR=2.01, CI=1.09–3.68) as well as with cannabis abuse (OR=2.67, CI=1.35–5.28). Furthermore, individuals with baseline depression were more likely to develop co-occurring alcohol and cannabis dependence than were those without baseline depression (OR=5.23, CI=1.28–21.34).

In the adjusted model, the relationship between baseline depression and incident alcohol dependence retained statistical significance (aOR=1.47, CI=1.06–2.03). Additionally, individuals with baseline depression were significantly more likely to develop CUD (aOR=2.28, CI=1.28–4.05) as well as cannabis abuse (aOR=2.96, CI=1.55–5.65)

Table 4
Unadjusted and adjusted odds ratios and 95% confidence intervals depicting the relationship between baseline alcohol use disorder, cannabis use disorder, and co-occurring alcohol and cannabis use disorder withincident major depressive disorder.

Incident major depressive disorder		
Substance use disorder at baseline	**Unadjusted**	**Adjusted** [f]
	OR[a] **(95% CI** [b]**)**	**aOR** [a] **(95% CI)**
AUD [c]	1.07 (0.98–1.25)	1.35 (1.15–1.60)*
Alcohol abuse	0.86 (0.72–1.05)	1.14 (0.94–1.38)
Alcohol dependence	1.54 (1.25–1.90)*	1.75 (1.40–2.19)*
CUD [d]	2.02 (1.35–3.04)*	1.78 (1.17–2.71)*
Cannabis abuse	1.68 (1.13–2.50)*	1.49 (0.99–2.26)
Cannabis dependence	8.39 (2.15–32.76)*	6.61 (1.67–26.21)*
Co-occurring use disorders		
AUD+CUD [e]	1.43 (1.15–1.78)*	1.54 (1.20–1.98)*
Alcohol dependence+Cannabis dependence	2.64 (1.45–4.80)*	2.34 (1.23–4.48)*

Note: In all cases, the reference group is comprised of individuals without AUD, CUD, or MDD at baseline.
* $p < 0.05$.
[a] OR=odds ratio, aOR=adjusted odds ratio.
[b] CI=confidence interval.
[c] AUD=alcohol use disorder; alcohol abuse or alcohol dependence.
[d] CUD=cannabis use disorder; cannabis abuse or cannabis dependence.
[e] AUD+CUD=co-occurring alcohol and cannabis use disorder; alcohol and cannabis abuse and/or dependence.
[f] Adjusted for sex, age, marital status, race, income, education, and family history of depression.

Table 5
Unadjusted and adjusted odds ratios and 95% confidence intervals depicting the relationship between baseline depression and incident alcohol use disorder, cannabis use disorder and co-occurring alcohol and cannabis use disorder.

Incident AUD and CUD		
Specific substance use disorder at follow-up	**Unadjusted**	**Adjusted**[a]
	OR (95% CI)	**aOR**[e] **(95% CI)**[f]
AUD [b]	0.96 (0.77–1.21)	1.04 (0.82–1.32)
Alcohol abuse	0.69 (0.52–0.93)*	0.76 (0.56–1.02)
Alcohol dependence	1.39 (1.02–1.90)*	1.47 (1.06–2.03)*
CUD[c]	2.01 (1.09–3.68)*	2.28 (1.28–4.05)*
Cannabis abuse	2.67 (1.35–5.28)*	2.96 (1.55–5.65)*
Cannabis dependence	0.65 (0.19–2.28)	0.77 (0.22–2.64)
Co-occurring use disorders		
AUD+CUD [d]	1.50 (0.70–3.22)	1.51 (0.70–3.23)
Alcohol dependence+Cannabis dependence	5.23 (1.28–21.34)*	4.51 (1.31–15.60)*

Note: In all cases, the reference group is individuals without AUD, CUD, or MDD at baseline.
* $p < 0.05$.
[a] Adjusted for sex, age, marital status, race, income, education, and other drug use disorders.
[b] AUD=alcohol use disorder; alcohol abuse or alcohol dependence.
[c] CUD=cannabis use disorder; cannabis abuse or cannabis dependence.
[d] AUD+CUD=co-occurring alcohol and cannabis use disorder; alcohol and cannabis abuse and/or dependence.
[e] OR=odds ratio, aOR=adjusted odds ratio.
[f] CI=confidence interval.

than were individuals with-out baseline depression. Furthermore, individuals with baseline depression were significantly more likely than those without depression to develop incident co-occurring alcohol and cannabis dependence (aOR=4.51, CI=1.31–15.60).

4. Discussion

Positive and statistically significant bidirectional associations between AUD, CUD, and MDD were observed. Among individuals with AUDs alone, those with either alcohol abuse or dependence were significantly more likely to develop MDD. When separating the AUD classification into two categories (i.e., those with alcohol abuse only and those with alcohol dependence with or without abuse), it became apparent that individuals with alcohol dependence with or without abuse were driving the relationship. In fact, the relationship for individuals with alcohol abuse alone did not meet criteria for statistical significance. This finding is similar to one reported by Grant and Harford (1995) as well as Dawson et al. (2005), who observed that the association between alcohol use

disorders and MDD was much stronger for individuals with alcohol dependence than for individuals with alcohol abuse. It would also appear that in the present sample, for those with comorbid MDD and alcohol dependence, it was more common for MDD to precede the development of alcohol dependence. This finding is somewhat contradictory when taking into account previous research by Fergusson et al., 2009, among a sample of individuals aged 17–25, who reported that the association between AUD and MDD was best explained by a causal model in which AUD led to MDD, as opposed to a model in which MDD leads to AUD (i.e., a self-medication model). This discrepancy may have arisen due to differences between statistical methods utilized (i.e., logistic regression versus structural equation modeling), as well as differences between the two study samples (i.e., NESARC versus the Christchurch Health and Development Study).

Among individuals with CUDs alone, an interesting pattern emerged. When examining whether baseline CUDs precede the development of MDD, individuals with either cannabis abuse or dependence, individuals with cannabis abuse alone, and individuals with cannabis dependence with or without abuse were all significantly more likely to develop MDD at follow-up than were individuals without AUD or CUD. As described previously, it is possible that cannabis use may affect neurotransmitter systems in the brain in such a way that produces depressive symptomatology (Degenhardt et al., 2003). Additionally, it is possible that cannabis use/use disorders may indirectly predispose individuals to MDD by altering and impairing an individual's capacity for psychological coping mechanisms. When examining whether baseline MDD preceded the development of incident CUD, however, findings were less consistent. Participants with MDD were between two and three times more likely than those without MDD to develop CUD, as well as cannabis abuse alone. The relationship between baseline MDD and incident cannabis dependence alone at follow-up, albeit not statistically significant, was inverse, indicating that participants with baseline MDD may be less likely to develop cannabis dependence at follow up. One explanation for this unanticipated finding is that frequency of cannabis use may have decreased and problems remitted among these participants between Waves 1 and 2, thus resulting in these individuals not continuing to meet criteria for cannabis dependence. However, *post hoc* analyses revealed that frequency of cannabis use did not decrease, and in fact did not differ significantly, between Waves 1 and 2 among these participants. An alternate explanation might be that utilization of drug treatment during the interim between Waves 1 and 2 among individuals with baseline MDD may have accounted for the negative association with incident cannabis dependence at Wave 2, thus leading to the impression that MDD is potentially protective of cannabis dependence. Indeed, *post hoc* analyses indicate that approximately 33% of this subpopulation reported utilizing drug and/or alcohol treatment programs during the time between Waves 1 and 2.

When it comes to co-occurring use disorders, individuals with AUD+CUD and co-occurring alcohol dependence and cannabis dependence were both significantly more likely to develop incident MDD at follow-up. Consistent with our hypothesis, the individuals with co-occurring use disorders had the strongest association with MDD, as compared to those with AUD alone or CUD alone, although not when compared to individual abuse/dependence categories. Additionally, individuals with baseline MDD were approximately four and a half times more likely to develop co-occurring alcohol dependence and cannabis dependence, representing a stronger relationship than for any of the other AUD, CUD, or abuse/dependence categories. Thus, it would appear that individuals with co-occurring use disorders are at greater risk of developing incident MDD, and individuals with MDD are at greater risk of developing incident co-occurring use disorders.

The present study has several limitations that should be noted. First, all information was collected from participants via self-report, which is associated with the potential for social desirability or reporting bias. Additionally, some of the data collected is subject to recall bias, given that some information pertains to lifetime conditions. Inspite of these limitations, the present study possesses a number of strengths that should be identified as well. The present study makes use of a large, population-based, longitudinal data set. Thus, findings from the present study have greater potential generalizability, and possible selection biases are reduced. Furthermore, due to the prospective nature of the data set, there is greater potential for making inferences regarding the possible causal nature of relationships observed in this study.

Findings from this study illustrate the bidirectional associations between single and co-occurring alcohol and cannabis use disorders and MDD. Given the bidirectional nature of the relationships observed in this analysis, it is possible that there is a common cause, or causes, of both AUD/CUD/AUD+CUD and MDD, rather than substance use disorders being a precursor or predictor of MDD, or multiple etiological pathways occur. Ultimately, future research is warranted in this area to further elucidate these relationships. Regardless, in light of the highly comorbid nature of AUD, CUD, both singly and in combination with MDD, as well as the potential for substance use disorders to influence the development of MDD, and vice versa, these findings have implications for the development and implementation of preventive interventions and treatment initiatives. Specifically, integrated substance use and depression treatment programs may be indicated for individuals already exhibiting signs and symptoms of both disorders. Furthermore, preventive efforts targeting depressive symptomatology for individuals with existing AUD and/or CUD may also be warranted, as would preventive interventions targeting AUD and/or CUD for individuals with prevalent MDD.

Role of funding source

This research was funded by grants F31 DA033873 (P.I., Pacek), R03 DA023434 (P.I., Martins), and R01 AA016346 (P.I., Crum).

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgments

The data reported herein come from the 2001–2002 Wave 1 and 2004–2005 Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) that was funded by the National Institute of Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health (NIH), with supplemental support from the National Institute on Drug Abuse (NIDA). Fieldwork was conducted by the US Bureau of the Census. Data were obtained from the NESARC public use files.

References

Aharonovich, E., Liu, X., Samet, S., Nunes, E., Waxman, R., Hasin, D., 2005. Postdischarge cannabis use and its relationship to cocaine, alcohol, and heroin use: a prospective study. The American Journal of Psychiatry 162, 1507–1514.

Anthony, J.C., Helzer, J.E. (Eds.), 1991. Psychiatric Disorders in America. Free Press, New York, NY.

Anthony, J.C., Warner, L.A., Kessler, R.C., 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substance, and inhalants: basic findings from the National Comorbidity Survey. Comparative epidemiology of dependence on tobacco, alcohol, controlled substance, and inhalants: basic findings from the National Comorbidity Survey. Experimental and Clinical Psychopharmacology 2, 224–268.

American Psychiatric Association, 1994.*Diagnostic and Statistical Manual of Mental Disorders.*4th ed. Washington, DC: APA.

Brady, K.T., Sinha, R., 2005. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. The American Journal of Psychiatry 162, 1483–1493.

Compton, W.M., Grant, B.F., Colliver, J.D., Glantz, M.D., Stinson, F.S., 2004. Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. JAMA : The Journal of the American Medical Association 291 (17), 2114–2121.

Conger, J.J., 1956. Alcoholism: theory, problem and challenge. II. Reinforcement theory and the dynamics of alcoholism. Quarterly Journal of Studies on Alcohol 17, 296–305.

Dawson, D.A., Grant, B.F., Stinson, F.S., Chou, P.S., 2005. Psychopathology associated with drinking and alcohol use disorders in the college and general adult populations. Drug and Alcohol Dependence Journal 77, 139–150.

Degenhardt, L., Hall, W., Lynskey, M., 2003. Exploring the association between cannabis use and depression. Addiction 98, 1493–1504.

deGraaf, R., Radovanovic, M., van Laar, M., Fairman, B., Degenhardt, L., Aguilar-Gaxiola, S., Bruffaerts, R., de Girolamo, G., Fayyad, J., Gureje, O., Haro, J.M., Huang, Y., Kostychenko, S., L QUOTE épine, J.-P., Matchinger, H., Mora, M.E.M., Neumark, Y., Ormel, J., Posada-Villa, J., Stein, D.J., Tachimori, H., Wells, J.E., Anthony, J.C., 2010. Early cannabis use and estimated risk of later onset of depression spells: epidemiologic evidence from the population-based World Health Organization World Mental Health Survey Initiative. American Journal of Epidemiology 172 (2), 149–159.

Fairman, B.J., Anthony, A.C., 2012. Are early-onset cannabis smokers at an increased risk of depression spells? Journal of Affective Disorders 138, 54–62.

Fergusson, D.M., Boden, J.M., Horwood, L.J., 2009. Tests of causal links between alcohol abuse or dependence and major depression. Archives of General Psychiatry 66 (3), 260–266.

Gilman, S.E., Abraham, H.D., 2001. A longitudinal study of the order of onset of alcohol dependence and major depression. Drug and Alcohol Dependence 63, 277–286.

Grant, B.F., Dawson, D.A., Stinson, F.S., Chou, S.P., Dufour, M.C., Pickering, R.P., 2004. The 12-month prevalence and trends in DSM-IV alcohol abuse and dependence: United States, 1991–1992 and 2001–2002. Drug and Alcohol Dependence 74, 223–234.

Grant, B.F., Harford, T.C., 1995. Comorbidity between DSM-IV alcohol use disorders and major depression: results of a national survey. Drug and Alcohol Dependence 39, 197–206.

Grant, B.F., Dawson, D.A., Stinson, F.S., Chou, PS., Kay, W., Pickering, R., 2003. 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 and Alcohol Dependence 71, 7–16.

Grant, B.F., Goldstein, R.B., Chou, S.P., Huang, B., Stinson, F.S., Dawson, D.A., Saha, T.D., Smith, S.M., Pulay, A.J., Pickering, R.P., Ruan, W.J., Compton, W.M., 2009. Sociodemographic and psychopathologic predictors of first incidence of DSM-IV substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. Molecular Psychiatry 14, 1051–1066.

Harder, V.S., Stuart, E.A., Anthony, J.C., 2008. Adolescent cannabis problems and young adult depression: male-female stratified propensity score analyses. American Journal of Epidemiology 168 (6), 592–601.

Hasin, D.S., Grant, B.F., 2002. Major depression in 6050 former drinkers: association with past alcohol dependence. Archives of General Psychiatry 59, 794–800.

Lader, M., 1972. The nature of anxiety. British Journal of Psychiatry 121, 481–491.

Markou, A., Kosten, T.R., Koob, G.F., 1998. Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 18, 135–174.

McEwan, B.S., 2000. Allostasis and allostatic load: implications for neuropsychopharmacology. Neuropsychopharmacology 22, 108–124.

Midanik, L.T., Tam, T.W., Weisner, C., 2007. Concurrent and simultaneous drug and alcohol use: results of the 2000 National Alcohol Survey. Drug and Alcohol Dependence 90 (1), 72–80.

Pacek, L.R., Malcolm, R.J., Martins, S.S., 2012. Race/ethnicity differences between alcohol, marijuana and co-occurring alcohol and Marijuana use disorders and their association with public health and social problems using a national sample. The American Journal on Addictions 21, 435–444.

Pleis, J.R., Lucas, J.W., Ward, B.W., 2009. Summary health statistics for U.S. adults: National Health Interview Survey, 2008. National Center for Health Statistics. Vital and Health Statistics 10, 242.

Quitkin, F.M., Rifkin, A., Kaplan, J., Klein, D.F., 1972. Phobic anxiety syndrome complicated by drug dependence and addiction. A treatable form of drug abuse. Archives of General Psychiatry 27 (2), 159–162.

Ruan, W.J., Goldstein, R.B., Chou, S.P., Smith, S.M., Saha, T.D., Pickering, R.P., Dawson, D.A., Huang, B., Stinson, F.S., Grant, B.F., 2008. 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 and Alcohol Dependence 92, 27–36.

Shillington, A.M., Clapp, J.D., 2001. Substance use problems reported by college students: combined marijuana and alcohol use versus alcohol-only use. Substance Use and Misuse 36 (5), 663–672.

StataCorp, 2007. Stata Statistical Software: Release 10.0. Stata Corporation, College Station, TX.

Substance Abuse and Mental Health Services Administration, 2007. *Results from the 2006 National Survey on Drug Use and Health: National Findings*. Rockville, MD: Office of Applied Studies, Substance Abuse and Mental Health Services.

Substance Abuse and Mental Health Services Administration, 2008.*Results from the 2007 National Survey on Drug Use and Health: National Findings*. Rockville, MD: Office of Applied Studies, Substance Abuse and Mental Health Services.

Substance Abuse and Mental Health Services Administration, 2009. *Results from the 2008 National Survey on Drug Use and Health: National Findings*. Rockville, MD:Office of Applied Studies, Substance Abuse and Mental Health Services.