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Pain interference and alcohol, nicotine, and cannabis use disorder in a national sample of substance users

Katherine A. McDermott[a,*], Keanan J. Joyner[a], Jahn K. Hakes[b], Sarah A. Okey[a], Jesse R. Cougle[a]

[a] Department of Psychology, Florida State University, Tallahassee, FL, USA
[b] Center for Administrative Records Research and Applications, US Census Bureau, Suitland, MD, USA

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ABSTRACT

Background: Pain interference is associated with substance use, but has yet to be considered as a potential indicator of SUDs among substance users. We sought to examine whether moderate and high pain interference would confer risk for SUDs in ever and weekly users.

Methods: Using data from the National Epidemiologic Survey on Alcohol and Related Conditions, logistic regression analyses were conducted to examine the association between pain interference and concurrent and prospective alcohol and nicotine dependence, as well as concurrent cannabis use disorder. Those with no/low pain were used as the reference group. Gender was examined as a moderator.

Results: Controlling for relevant covariates, moderate pain interference was associated with past year alcohol (odds ratio [OR] = 1.33, 95% CI, 1.16–1.52, $p < .001$) and nicotine (OR = 1.41, 95% CI 1.27–1.56, $p < .001$) dependence among ever users. In prospective analyses, moderate pain interference predicted the development of alcohol (Moderate: OR = 1.56, 95% CI, 1.39–1.75, $p < .001$) and nicotine (OR = 1.37, 95% CI, 1.14–1.65, $p < .001$) dependence. Similar results were found with high pain and for weekly users. Both moderate and high pain interference were associated with past-year occurrence of cannabis use disorder for women but not men. High pain predicted the development of nicotine dependence exclusively among males.

Conclusion: Pain interference may confer risk for the occurrence of cannabis use disorder among female cannabis users and the occurrence and development of alcohol and nicotine dependence among users of both genders. Pain interference may be an important factor to monitor in these populations.

1. Introduction

Given that not all who use substances develop substance use disorders (SUDs; Center for Behavioral Health Statistics and Quality, 2016; Cougle et al., 2016), it is important to examine factors related to the development of SUDs in those already using substances, as well as the prospective progression from substance use to disorder in this population. Research suggests that several factors could be associated with increased likelihood of developing a SUD after initiation of substance use, including gender and comorbid psychiatric conditions (Cougle et al., 2016).

Few studies have examined the role of pain interference in the progression from use to disorder, despite research demonstrating an association between pain and concurrent and prospective substance use (Griffin et al., 2016; Witkiewitz et al., 2015). Pain interference is the self-reported extent to which physical pain impedes daily activities. Witkiewitz and colleagues (2015) reported that, among those with alcohol dependence, the combination of pain interference and intensity was associated both with worse treatment outcomes and with relapse following treatment. Similarly, Larance and colleagues (2016) found that more severe drinking was associated with greater pain interference among those with a pain condition. Use of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Grant et al., 2003) has facilitated the study of pain interference as a predictor of concurrent and prospective development of SUDs. In the NESARC sample, Novak and colleagues (2009, 2016) concluded that both moderate and high pain interference were associated with greater concurrent non-medical pain analgesic use and prospective development of disordered use. Similarly examining the progression from Wave 1 to Wave 2, Barry et al. (2013) found, in bivariate models, that greater pain interference was associated with increased risk of a drug use disorder, as well as increased risk of alcohol use disorder in women. In multivariate models, a relationship between pain interference and nicotine emerged, such that severe pain was associated with greater risk of nicotine dependence in males.

These studies are limited in that they examined the general NESARC

* Corresponding author.
E-mail address: mcdermott@psy.fsu.edu (K.A. McDermott).

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Table 1
Descriptives of Demographic and Psychiatric Characteristics of NESARC (Wave 1) Participants Reporting Any Pain by Past-Year Substance Use Frequency, Substance Dependent/Total – M (Std. Error) or N (%).

Variable	Alcohol Dependence		Nicotine Dependence		Cannabis Use Disorder	
	Used at Least Once, Dependent/Total	Used Weekly, Dependent/Total	Used at Least Once, Dependent/Total	Used Weekly, Dependent/Total	Used at Least Once, Dependent/Total	Used Weekly, Dependent/Total
Sociodemographic						
Age, in years	31.52/42.68 (0.19)/(0.07)	32.13/43.55 (0.19)/(0.09)	39.66/41.27 (0.14)/(0.10)	39.69/41.34 (0.13)/(0.10)	27.77/29.98 (0.20)/(0.14)	27.50/29.92 (0.18)/(0.13)
Female	519/13,853 (31.8)/(47.4)	399/4646 (29.0)/(36.4)	2570/5156 (46.9)/(41.3)	2544/4801 (47.0)/(42.3)	174/606 (27.7)/(33.7)	104/216 (25.4)/(29.1)
Race						
White	1156/21,648 (83.6)/(86.7)	980/9699 (84.6)/(87.6)	3949/8695 (87.4)/(86.3)	3901/7860 (87.4)/(85.9)	432/1238 (82.5)/(83.0)	277/491 (81.2)/(79.6)
Non-White	327/5231 (16.4)/(13.3)	271/2155 (15.4)/(12.4)	1008/2384 (12.6)/(13.7)	998/2242 (12.6)/(14.1)	126/361 (17.5)/(17.0)	86/177 (18.8)/(20.4)
Personal Income	$23,792/$34,120 (274)/(192)	$24,940/$39,775 (287)/(408)	$25,480/$27,943 (705)/(354)	$25,605/$26,302 (698)/(374)	$19,679/$23,972 (215)/(248)	$19,110/$20,642 (245)/(323)
Marital status						
Married	451/14,236 (33.6)/(62.5)	387/6166 (34.2)/(61.1)	2133/5042 (53.7)/(56.2)	2107/4508 (53.8)/(55.2)	125/422 (26.7)/(31.6)	80/177 (25.6)/(32.5)
Not married	1032/12,643 (66.4)/(37.5)	864/5688 (65.8)/(38.9)	2824/6037 (46.3)/(43.8)	2792/5594 (46.2)/(44.8)	433/1177 (73.3)/(68.4)	283/491 (74.4)/(67.5)
Years of education	12.90/13.67 (0.03)/(0.01)	12.95/13.93 (0.03)/(0.014)	12.57/12.65 (0.023)/(0.015)	12.56/12.51 (0.023)/(0.017)	12.62/12.94 (0.04)/(0.022)	12.44/12.51 (0.05)/(0.04)
Psychiatric						
Past-year diagnoses						
Depressive disorder	368/2533 (24.0)/(8.9)	297/994 (22.3)/(7.8)	1030/1493 (19.7)/(13.0)	1020/1392 (19.8)/(13.4)	152/351 (26.3)/(21.1)	101/158 (26.6)/(23.2)
Bipolar disorder	204/928 (13.2)/(3.4)	163/404 (12.2)/(3.1)	428/567 (8.4)/(5.0)	422/529 (8.3)/(5.1)	90/178 (16.1)/(11.0)	63/87 (17.7)/(14.0)
Personality disorder	593/4386 (39.5)/(16.3)	500/1877 (39.6)/(15.9)	1556/2345 (31.6)/(21.4)	1534/2167 (31.6)/(21.7)	263/586 (48.4)/(37.6)	183/291 (52.5)/(46.2)
Anxiety disorder	337/3232 (24.0)/(11.9)	271/1273 (22.9)/(10.6)	1109/1682 (22.6)/(15.1)	1098/1562 (22.7)/(15.5)	123/330 (24.2)/(21.1)	85/146 (26.2)/(24.2)
Alcohol dependence	−/1483 −/(5.8)	−/1251 −/(11.0)	634/914 (13.6)/(8.9)	627/835 (13.5)/(8.8)	206/426 (39.9)/(29.8)	147/220 (44.2)/(36.4)
Nicotine dependence	634/3869 (45.5)/(15.5)	555/1973 (47.2)/(17.5)	−/4957 −/(46.2)	−/4899 −/(50.1)	283/669 (53.2)/(44.7)	195/324 (57.2)/(52.0)
Drug dependence	131/222 (9.4)/(0.88)	113/152 (9.1)/(1.3)	167/189 (3.4)/(1.8)	166/182 (3.4)/(1.9)	156/180 (27.7)/(11.4)	132/143 (36.3)/(22.6)
Frequency of current substance use						
Weekly use in past year	1251/11,854 (85.4)/(45.1)	–/—/–	4899/10,102 (98.9)/(91.1)	–/– –/–	363/668 (66.1)/(41.6)	–/– –/–
Daily use in past year	275/1861 (18.2)/(7.0)	275/1861 (21.3)/(15.6)	4634/8912 (93.9)/(81.2)	4634/8912 (95.0)/(89.0)	137/226 (23.7)/(14.3)	137/226 (35.8)/(34.4)
Current use of other substances						
Cocaine	107/209 (8.2)/(0.83)	100/163 (8.7)/(1.5)	111/166 (2.3)/(1.6)	109/152 (2.3)/(1.6)	84/160 (16.6)/(11.0)	69/110 (20.9)/(19.2)
Amphetamines/Stimulants	81/171 (6.0)/(0.69)	71/123 (6.1)/(1.1)	118/156 (2.5)/(1.5)	117/149 (2.5)/(1.6)	64/123 (12.2)/(8.0)	51/76 (15.5)/(12.7)
Initiation of substance use (in years)						
Alcohol	16.80/19.39 (0.05)/(0.022)	16.66/18.87 (0.05)/(0.028)	17.95/18.33 (0.05)/(0.03)	17.95/18.35 (0.04)/(0.03)	16.33/16.50 (0.06)/(0.04)	16.11/16.16 (0.08)/(0.07)
Nicotine	14.54/15.98 (0.05)/(0.019)	14.56/15.83 (0.05)/(0.028)	15.27/15.83 (0.04)/(0.024)	15.27/15.80 (0.04)/(0.024)	14.07/14.33 (0.09)/(0.07)	13.93/14.11 (0.13)/(0.08)
Cannabis	16.61/17.93 (0.08)/(0.025)	16.60/18.00 (0.09)/(0.03)	16.86/17.08 (0.04)/(0.03)	16.86/17.04 (0.04)/(0.03)	15.96/16.49 (0.04)/(0.04)	15.67/15.83 (0.05)/(0.05)
Heroin	21.14/21.36 (N/A)/(N/A)	21.15/20.96 (N/A)/(N/A)	22.51/22.16 (N/A)/(N/A)	22.51/22.15 (N/A)/(N/A)	22.54/20.90 (N/A)/(N/A)	23.87/22.12 (N/A)/(N/A)
Opioids	19.86/22.91 (0.14)/(0.05)	20.02/22.91 (0.14)/(0.11)	21.70/21.94 (0.14)/(0.11)	21.69/21.90 (0.14)/(0.11)	19.00/19.81 (0.09)/(0.08)	19.42/19.87 (0.09)/(0.08)
Amphetamines/Stimulants	18.59/18.93 (0.18)/(0.08)	18.84/19.09 (0.21)/(0.10)	18.53/18.73 (0.10)/(0.09)	18.51/18.69 (0.10)/(0.09)	18.03/18.55 (0.16)/(0.11)	18.17/18.61 (0.23)/(0.12)
Cocaine	21.06/21.60 (0.07)/(0.05)	20.98/21.75 (0.05)/(0.07)	21.27/21.41 (0.11)/(0.08)	21.23/21.41 (0.11)/(0.09)	20.55/21.03 (0.13)/(0.10)	20.47/20.72 (0.18)/(0.09)
Pain Interference						
Moderate Pain	125/1826 (7.9)/(6.6)	106/801 (8.1)/(6.6)	471/891 (9.3)/(7.8)	465/826 (9.3)/(7.9)	34/122 (7.7)/(7.8)	21/49 (7.6)/(7.4)
High/Severe Pain	181/2717 (11.8)/(9.6)	153/1127 (11.3)/(8.8)	879/1688 (16.8)/(14.5)	874/1588 (16.9)/(15.0)	66/195 (11.0)/(12.6)	40/83 (10.9)/(13.0)
Sample size (Dependent/Total) in Wave 1	1483/26,879	1251/11,854	4957/11,079	4899/10,102	558/1599	363/668
Sample size (Dependent/Total) for ADHD in Wave 2	1172/22,205	982/9682	4015/8879	3971/8092	442/1275	287/519

Note: N's represent unweighted counts. Means are weighted to be representative of the U.S. population. N/A = not available because too few non-self-representing strata were present to allow estimation of statistic.

sample as a whole, rather than those who are already using but have yet to develop a disorder. Yet substance users, particularly regular users, are most at risk for developing an SUD, with rates of dependence higher among regular users than those who have ever used (Cougle et al., 2016). Thus, it is particularly important to examine risk factors for SUDs in this population. It is unclear whether pain interference is associated with risk of SUDs in those who are already using, particularly those who are using regularly. It is possible that regular substance use already captures increased risk for an SUD, such that the presence of pain interference adds little predictive ability. Alternatively, the presence of increased pain interference in regular users could signify more likelihood of presenting with or developing a SUD, perhaps because of a need to use the substance continuously to cope with pain or emotional difficulties resulting from pain (Moitra et al., 2015; Parkerson and Asmundson, 2016).

The association between pain interference and substance use may also differ by substance. Previous studies in the NESARC sample have generally collapsed across drug categories when examining the association between pain interference and drug dependence (Barry et al., 2012, 2013). However, substances differ in the extent to which use confers risk for dependence (Cougle et al., 2016). Use of cannabis or alcohol, for example, is associated with lower risk of dependence compared to use of nicotine. Therefore, it is possible that the presence of pain may add predictive ability that frequency of alcohol or cannabis use alone cannot account for. Furthermore, substances differ in the extent to which they are societally endorsed as analgesics. In particular, cannabis is increasingly seen as a viable alternative to other analgesics (Degenhardt et al., 2015; Haroutounian et al., 2016). Understanding the association between pain interference and cannabis use disorder is especially relevant given the increased use of medicinal cannabis in the treatment of pain (Compton et al., 2017).

A final consideration is whether gender may influence the association between pain interference and SUDs in regular substance users. In some populations, women tend to report greater pain interference (Kenzik et al., 2015; Przekop et al., 2015). Using the NESARC, Barry et al. (2012) found that greater pain interference was significantly associated with less cannabis use in women but not men. Barry and colleagues (2013) also found that the association between severe pain interference and new onset of alcohol or nicotine dependence was stronger in men than in women. Their analyses were conducted on the sample as a whole (regardless of their substance use history) rather than those who had ever used or used regularly; it is unclear whether similar findings would emerge among those who were currently using. Because women tend to have a shorter timeline between the onset of use and entry into SUD treatment (Hernandez-Avila et al., 2004) it is possible that female users in particular are a considerably different population compared to the general population.

Utilizing the NESARC, the present study examined associations between past-month pain interference and concurrent (Wave 1) and prospective (Wave 2) prevalence of substance dependence/SUD among those who had ever used and those who were using substances weekly at Wave 1. We hypothesized that pain interference would be associated with increased incidence of alcohol and nicotine dependence and cannabis use disorder and prospective risk of alcohol and nicotine dependence. In addition, we examined whether gender was a moderating factor in these associations among ever users in particular. Mirroring previous findings, we hypothesized that the association between pain interference and SUDs would be stronger for men than women.

2. Materials and methods

2.1. Sample and procedures

The present study examined participants of Wave 1 and Wave 2 of the National Institute on Alcohol Abuse and Alcoholism's (NIAAA) NESARC (Grant et al., 2003, 2007), a nationally-representative sample of the non-institutionalized adult U.S. population. Wave 1 was collected from 2001 to 2002 and aimed to assess past year and lifetime prevalence of alcohol use disorders and related conditions. The completed data were adjusted based on the 2000 Census to be representative of the national population in terms of age, region, sex, ethnicity, and race. Wave 2 follow-up data were then collected in 2004–2005, with 34,653 responding from the original Wave 1 sample of 43,093. Wave 2 solely assessed the entire period since the Wave 1 interview, separating out information from the year prior to the Wave 2 interview in particular. There were no significant differences between respondents and non-respondents on sociodemographic or clinical variables. Descriptive information for the sample used in the present analyses – i.e., those reporting no/low, moderate, or high pain interference – is presented in Table 1.

2.2. Measures

2.2.1. Diagnostic assessment

Psychiatric disorders were assessed using NIAAA's Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV (AUDADIS-IV; Grant et al., 2001). Disorders assessed with this structured diagnostic interview include substance use, mood, personality, and anxiety disorders. In the present study, past year and prospective alcohol and nicotine dependence, as well as past-year cannabis use disorder served as the outcome variables, controlling for past-year mood disorder, personality disorder, and anxiety disorder. Because there were too few cases of cannabis dependence to ensure adequate power, cannabis use disorder was used as an outcome in all cannabis analyses (Hasin et al., 2011).

2.2.2. Pain interference

Pain interference was measured using the following single item, "During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?" taken from the SF-12 health-related quality of life scale (Ware et al., 1996). Consistent with prior research, participants were grouped into three categories: no/low pain interference, moderate pain interference, and high pain interference (Barry et al., 2013).

2.3. Statistical analyses

All analyses were conducted with Statistical Analysis Software (SAS), version 9.4 [TS1M3], copyright © 2015 SAS Institute Inc. Analyses were completed using SAS's PROC SURVEYLOGISTIC procedure. Logistic regressions were utilized to assess whether pain interference at Wave 1 was associated with concurrent (Wave 1) and prospective (Wave 2) substance dependence (0 = not dependent, 1 = dependent) or cannabis use disorder (0 = no SUD, 1 = SUD). Bivariate analyses were conducted first, followed by multivariate analyses, controlling for the following covariates assessed at Wave 1: age, income, marital status, gender, race, years of education, and past-year depressive disorder, bipolar disorder, personality disorder, and anxiety disorder. Alcohol and nicotine analyses also controlled for past-year drug dependence. Moderate and high pain interference were examined in separate regressions. Regressions were conducted separately for past-year ever users (i.e., those who had used the substance at least once in the past year at Wave 1) and past-year weekly users. Prospective analyses predicting Wave 2 substance dependence excluded those who were already dependent on the substance at Wave 1 in order to assess for new onset of substance dependence. For all regressions, odds ratios (ORs) are presented, along with 95% Confidence Intervals (CIs). An OR is considered significant if the CI does not include one. For all ORs, the no/low pain group served as the reference group.

Differential effects of pain interference on risk of substance dependence/SUD between genders were examined (e.g., testing if there were differences *between genders* in the size of the differences *between pain*

Table 2
Pain interference and Risk of Past-Year Substance Dependence/SUD by Past-Year Substance Use Frequency.

Variable	Alcohol Dependence		Nicotine Dependence		Cannabis Use Disorder	
	Used at Least Once, OR (95% CI)	Used Weekly, OR (95% CI)	Used at Least Once, OR (95% CI)	Used Weekly, OR (95% CI)	Used at Least Once, OR (95% CI)	Used Weekly, OR (95% CI)
'Bivariate						
Moderate pain interference	1.27 (1.12–1.44)***	1.32 (1.17–1.51)***	1.58 (1.42–1.75)***	1.57 (1.42–1.74)***	0.94 (0.76–1.15)	0.99 (0.74–1.32)
High pain interference	1.30 (1.15–1.47)***	1.41 (1.24–1.61)***	1.47 (1.36–1.59)***	1.40 (1.29–1.52)***	0.79 (0.66–0.95)*	0.66 (0.54–0.80)***
Multivariate						
Moderate pain interference	1.33 (1.16–1.52)***	1.34 (1.14–1.57)***	1.41 (1.27–1.56)***	1.45 (1.31–1.60)***	0.89 (0.72–1.11)	1.03 (0.72–1.47)
High pain interference	1.23 (1.07–1.40)**	1.31 (1.12–1.53)**	1.26 (1.15–1.37)***	1.24 (1.13–1.36)***	0.79 (0.61–1.03)	0.99 (0.71–1.39)
Number reporting past–month pain interference at Wave 1[a] (Number of dependent/Total)	1483/26,879 (5.83%)	1251/11,854 (11.0%)	4957/11,079 (46.2%)	4899/10,102 (50.1%)	558/1599 (35.6%)	363/668 (56.5%)
No/low	1177/22, 336 (5.58%)	992/9926 (10.5%)	3607/8500 (44.0%)	3560/7688 (48.0%)	458/1282 (36.3%)	302/536 (57.8%)
Moderate	125/1826 (6.98%)	106/801 (13.5%)	471/891 (55.3%)	465/826 (59.2%)	34/122 (34.8%)	21/49 (57.5%)
High	181/2717 (7.13%)	153/1127 (14.2%)	879/1688 (53.5%)	874/1588 (56.4%)	66/195 (31.1%)	40/83 (47.5%)

Notes: For both moderate and high pain interference, no/low pain interference was used as the reference group. All multivariate analyses controlled for the following covariates (assessed at Wave 1): age, income, marital status, gender, race, years of education, and past-year depressive disorder, bipolar disorder, personality disorder, and anxiety disorder. Alcohol and nicotine analyses also controlled for past-year drug dependence. Prevalence rates of dependence/disorder are based on weighted proportions.
*p < .05, **p < .01, ***p < .001.
Abbreviation: OR = odds ratio.
[a]These values reflect weighted counts and means.

interference groups). A significant interaction OR indicates that the strength of the association between pain interference and substance dependence/SUD differs by gender. Gender moderation was examined in ever users for analyses predicting both concurrent and prospective dependence (the latter only for alcohol and nicotine, due to limited power for the cannabis analyses). Weekly users were excluded from these analyses due to limited power. ORs for the risk of dependence/SUD associated with pain were calculated separately for each gender, with persons with no/low pain used as the reference group.

3. Results

Table 2 summarizes the effects of pain interference on risk of substance dependence/SUD in the past year at Wave 1. Moderate pain interference significantly heightened risk of a past-year alcohol and nicotine dependence diagnosis in past year ever (PY-ever) and past-year weekly (PY-weekly) users in both univariate and multivariate models. Both PY-ever and PY-weekly alcohol and nicotine users who experienced high pain interference showed the same pattern of heightened risk for alcohol dependence as described for those with moderate pain interference in both univariate and multivariate models. High pain interference, but not moderate pain interference, significantly lowered risk of a past-year cannabis use disorder diagnosis in PY-ever and weekly users. However, this association was not significant when controlling for relevant demographic and clinical variables.

Table 3 summarizes the effects of pain interference on prospective risk of development of substance dependence outcomes for alcohol and nicotine in logistic regressions. There were too few new cases of cannabis use disorder with moderate (ever: N = 15, weekly: N = 6) or high (ever: N = 16, weekly: N = 9) pain interference to include cannabis in prospective analyses. For PY-ever and PY-weekly alcohol and nicotine users in both bivariate and multivariate models, individuals reporting either moderate or high pain interference at Wave 1 demonstrated increased risk of developing a substance use disorder in the following year for both alcohol and nicotine. The one exception was for the bivariate analysis of the effect of high pain interference on likelihood of prospective alcohol dependence for PY-ever alcohol users, for which there was no significant association.

Table 4 presents analyses of the moderating effect of gender on associations between pain interference and incidence of SUD diagnosis. Female alcohol users with moderate pain interference were significantly less likely to show increased incidence of alcohol dependence compared to males. Analysis of ORs by gender revealed that moderate pain interference was associated with past-year alcohol dependence among men but not women. Female cannabis users with moderate and high pain interference were significantly more likely to show increased incidence of cannabis use disorder compared to males. Analysis of ORs by gender revealed that this was both due to increased occurrence of cannabis use disorder among women and decreased occurrence of cannabis use disorder among men associated with both moderate and high pain interference.

Although there were no further interactions, analyses of ORs by gender demonstrated that in multivariate analyses, high pain was associated with increased incidence of past-year alcohol dependence in men but not women, whereas in bivariate analyses, high pain was associated with increased incidence of past-year alcohol dependence in both genders. Thus, covariates appeared to have accounted for more of the association between high pain interference and past-year alcohol dependence in women compared to men.

Regarding prospective analyses, high pain interference was associated with the prospective occurrence of nicotine dependence among men but not women. No other significant gender interactions were found in prospective analyses. For both men and women, moderate pain was associated with the onset of nicotine dependence. For women but not men, high pain was associated with increased risk of alcohol dependence in both bivariate and multivariate analyses. In bivariate analyses, moderate pain was associated with increased risk of developing alcohol dependence for males only; however, in multivariate analyses moderate pain was associated with increased risk of alcohol dependence onset in both genders.

4. Discussion

The present study assessed the association between pain interference and risk of past-year and prospective SUDs among those already using substances in a nationally representative sample. Among those who had any use of the substance at Wave 1, greater pain interference was largely associated with greater likelihood of past-year and prospective alcohol and nicotine dependence. These findings were robust to the inclusion of covariates. Results were similar across ever and weekly users.

Multiple studies have shown an association between pain

Table 3
Pain Interference and Prospective Risk of Substance Dependence (Wave 2) Onset by Past-Year (Wave 1) Substance Use Frequency.

Variable	Alcohol		Nicotine	
	Used at Least Once, OR (95% CI)	Used Weekly, OR (95% CI)	Used at Least Once, OR (95% CI)	Used Weekly, OR (95% CI)
Bivariate				
Moderate pain interference	1.22 (1.08–1.37)**	1.32 (1.18–1.48)***	1.40 (1.16–1.68)***	1.43 (1.18–1.73)***
High pain interference	1.11 (0.96–1.28)	1.23 (1.07–1.40)**	1.37 (1.24–1.52)***	1.28 (1.14–1.43)***
Multivariate				
Moderate pain interference	1.56 (1.39–1.75)***	1.58 (1.42–1.75)***	1.37 (1.14–1.65)**	1.44 (1.19–1.76)***
High pain interference	1.24 (1.08–1.43)**	1.30 (1.13–1.49)***	1.34 (1.21–1.49)***	1.29 (1.15–1.45)***
Number reporting pain interference at Wave 2[a](Number of dependent/Total)	820/21,033 (4.00%)	506/8700 (5.81%)	1411/4864 (29.3%)	1359/4121 (33.4%)
No/low	668/17,551 (3.91%)	409/7358 (5.60%)	1086/3907 (28.0%)	1045/3287 (32.2%)
Moderate	62/1443 (4.70%)	40/579 (7.25%)	114/333 (35.2%)	110/285 (40.4%)
High	90/2039 (4.31%)	57/763 (6.78%)	211/624 (34.8%)	204/549 (37.7%)

Notes: For both moderate and high pain interference, no/low pain interference was used as the reference group. The regression sample was limited to those who were non-dependent users at Wave 1. All multivariate analyses controlled for the following covariates (assessed at Wave 1): age, income, marital status, gender, race, years of education, and past-year depressive disorder, bipolar disorder, personality disorder, anxiety disorder, and past-year drug dependence. Prevalence rates of dependence/disorder are based on weighted proportions.
*p < .05, **p < .01, ***p < .001.
Abbreviation: OR = odds ratio.
[a]These values reflect weighted counts and means.

interference and concurrent (Larance et al., 2016; Novak et al., 2009; Witkiewitz et al., 2015) and prospective (Barry et al., 2013; Novak et al., 2016) SUDs. In particular, Barry and colleagues (2013) demonstrated that greater pain interference at NESARC Wave 1 was associated with the development of a substance use disorder at Wave 2, particularly alcohol abuse/dependence in women and drug abuse/dependence in both genders. Our findings in those already using substances diverge somewhat from those of Barry et al. (2013). For example, they did not find a bivariate association between pain interference and the prospective development of nicotine dependence, nor did they see a multivariate association between pain interference and the development of alcohol abuse/dependence. Furthermore, the present findings suggest that pain interference may confer risk for the development of alcohol dependence in users of both genders, whereas it may only confer risk for women in the general population (Barry et al., 2013). These discrepancies suggest that pain interference is valuable to consider as a risk factor for SUDs, but may have differential effects in substance users compared to the population as a whole. It is of note that we found largely similar results across alcohol and nicotine, despite previously observed differences in dependence risk for these drugs (Cougle et al., 2016) and the greater frequency of use of nicotine relative to alcohol in the present sample. These similar findings suggest that pain interference confers risk for substance dependence regardless of substance dose, though more research is needed to examine dose of substances in response to pain on a proximal level.

Similar to previous NESARC findings, gender moderated some of the associations between pain interference and alcohol and nicotine dependence among ever users. A cross-sectional observation shows that the risk for alcohol dependence associated with moderate pain interference was greater for men relative to women. It is possible that men are more likely than women to use alcohol to cope with moderate amounts of pain rather than seeking professional help or other forms of support (Unruh et al., 1999). Women tend to report greater pain and reactivity to pain than men (Przekop et al., 2015; Sherman et al., 2017), which may be related to their willingness to disclose such information. Alcohol use in particular may be a more societally acceptable coping mechanism for men, and there is some evidence to suggest that men are more likely than women to use alcohol to cope with pain (Riley and King, 2009). In addition, the association between high pain interference and the development of nicotine dependence was greater in men compared to women, which mirrored findings from Barry et al. (2013) in the general NESARC population. These gender discrepancies may have emerged in moderate pain for alcohol and high pain for nicotine due to differences in the analgesic properties of these substances.

In contrast to previous NESARC studies examining drug dependence generally (Barry et al., 2013), we looked at the association between pain interference and cannabis use disorder specifically. This is important, given that pain interference has previously been associated with less cannabis use in Wave 1 of the NESARC sample (Barry et al., 2012). Our results regarding cannabis differed somewhat from the alcohol and nicotine findings. In particular, men showed reduced risk of past-year cannabis use disorder when concurrent moderate or high pain were present. By contrast, moderate and high pain were associated with increased incidence of cannabis use disorder for women. This result diverges from Barry and colleagues' (2012) finding that greater pain interference was associated with less likelihood of cannabis use in women but not men. There may be differential effects of pain interference in those already using cannabis versus the population in general, and there may be discrepancies based on likelihood of any use versus likelihood of cannabis use disorder. Women with pain may be less likely to try cannabis for the first time. However, there is evidence to suggest that women may experience lesser analgesic effects of cannabis relative to men (Cooper and Haney, 2016), which suggests that women who are already using cannabis may use increased amounts to cope with pain.

There are limitations to the present study that necessitate consideration. First, we were underpowered to detect effects in some of the cannabis use disorder analyses. In addition, this study was limited in the assessment of outcome at a single time point, which did not allow for an examination of the proximal effect of pain interference on substance use, nor an examination of mediating factors such as reasons for using substances. Future research should examine reasons for use, including coping with pain and the negative emotional effects of pain. Investigating reasons for use is particularly relevant for cannabis, as there may be differences between use for medicinal vs. recreational purposes, as well as whether the cannabis is prescribed to treat pain specifically. As of yet, the extent to which medicinal use of cannabis confers greater or lower risk for the development of cannabis use problems is unclear (Loflin et al., 2017). Future research should examine the association between pain interference and the development of cannabis use disorder prospectively, taking into account reasons for use and the impact of legal vs. illegal use on substance use disorder development. It may also be useful to examine societal trends in the perception of cannabis use and whether these impact frequency of use

Table 4
Odds Ratios for the Interaction of Pain Interference and Gender in the Prediction of Past-Year and Prospective Risk of Substance Dependence/Substance Use Disorder Onset for Wave 1 Past-Year Ever Users.

		Alcohol Dependence OR (95% CI)		Nicotine Dependence OR (95% CI)		Cannabis Use Disorder OR (95% CI)
		Past-Year	Prospective	Past-Year	Prospective	Past-Year
Bivariate						
Moderate pain interference	Increase in dependence/use disorder for females with pain	0.97 (0.80, 1.17)	1.10 (0.90, 1.36)	1.61 (1.43, 1.80)***	1.32 (1.04, 1.66)*	1.44 (1.03, 2.02)*
	Increase in dependence/use disorder for males with pain	1.54 (1.29, 1.83)***	1.37 (1.16, 1.62)***	1.49 (1.29, 1.73)***	1.43 (1.13, 1.81)**	0.77 (0.60, 1.00)
	Gender interaction in risk for dependence/disorder (Comparison of females to males)	0.63 (0.47, 0.83)**	0.81 (0.61, 1.07)	1.08 (0.91, 1.27)	0.92 (0.68, 1.25)	1.86 (1.21, 2.87)**
High pain interference	Increase in dependence/use disorder for females with pain	1.34 (1.13, 1.60)**	1.28 (1.08, 1.51)**	1.40 (1.23, 1.60)***	1.04 (0.88, 1.23)	1.86 (1.48, 2.33)***
	Increase in dependence/use disorder for males with pain	1.32 (1.12, 1.55)**	1.04 (0.84, 1.28)	1.45 (1.29, 1.63)***	1.62 (1.38, 1.92)***	0.51 (0.41, 0.64)***
	Gender interaction in risk for dependence/disorder (Comparison of females to males)	1.02 (0.80, 1.29)	1.23 (0.94, 1.61)	0.97 (0.80, 1.17)	0.64 (0.49, 0.84)**	3.65 (2.73, 4.90)***
Multivariate						
Moderate pain interference	Increase in dependence/use disorder for females with pain	0.87 (0.74, 1.02)	1.32 (1.09, 1.61)**	1.47 (1.31, 1.65)***	1.31 (1.03, 1.67)*	1.51 (1.12, 2.04)**
	Increase in dependence/use disorder for males with pain	1.67 (1.37, 2.05)***	1.74 (1.46, 2.06)***	1.36 (1.18, 1.58)***	1.41 (1.12, 1.78)**	0.66 (0.50, 0.88)**
	Gender interaction in risk for dependence/disorder (Comparison of females to males)	0.52 (0.39, 0.69)***	0.76 (0.57, 1.02)	1.08 (0.91, 1.28)	0.93 (0.69, 1.26)	2.30 (1.51, 3.50)***
High pain interference	Increase in dependence/use disorder for females with pain	1.14 (0.96, 1.34)	1.38 (1.17, 1.64)***	1.21 (1.05, 1.41)*	1.03 (0.88, 1.22)	2.12 (1.69, 2.66)***
	Increase in dependence/use disorder for males with pain	1.28 (1.06, 1.55)*	1.15 (0.93, 1.42)	1.29 (1.14, 1.47)***	1.62 (1.37, 1.92)***	0.47 (0.36, 0.63)***
	Gender interaction in risk for dependence/disorder (Comparison of females to males)	0.89 (0.69, 1.14)	1.21 (0.92, 1.59)	0.94 (0.76, 1.15)	0.64 (0.49, 0.83)**	4.47 (3.27, 6.12)***

Notes: For both moderate and high pain interference, no/low pain interference was used as the reference group. All multivariate analyses controlled for the following covariates (assessed at Wave 1): age, income, marital status, gender, race, years of education, and past-year depressive disorder, bipolar disorder, personality disorder, and anxiety disorder. Alcohol and nicotine analyses also controlled for past-year drug dependence.
*p < .05, **p < .01, ***p < .001.
Abbreviation: OR = odds ratio.
[a]These values reflect unadjusted counts and means.

for analgesia compared to other substances. The present study was also limited in its assessment of pain as pain interference in the past month, rather than a full assessment regarding sources and time course of pain. This is particularly important to examine given the discrepancies in opioid use and frequency between those with chronic versus acute pain. Although, in the present sample, the average age of opioid initiation was greater than that for alcohol, nicotine, and cannabis, it may be in some cases that analgesic substance use occurs primarily following failed opioid use. Research should examine whether non-opioid substance dependence emerges more frequently in those for whom opioids have failed to provide adequate analgesia. Further, it would be beneficial to reexamine these study findings in subsequent years, especially given recent novel trends in substance use, including the proliferation of synthetic cannabinoids and fentanyl, as well as the use of electronic cigarettes. Finally, this study was limited in its assessment of concurrent psychiatric diagnoses, particularly Attention Deficit Hyperactivity Disorder, which was not assessed at Wave 1, despite its association with prescribed stimulant use, which may have influenced use of other substances measured here. Future research should examine whether use of concurrent substances, including stimulant medication, impacts the association between pain and the development of SUDs.

The present investigation suggests that among those using substances, the presence of pain interference may increase vulnerability for the occurrence and development of SUDs. Our findings indicate that pain interference may be an important factor to monitor in alcohol and nicotine users in particular, as well as female cannabis users. The fact that pain interference is predictive of substance dependence even in regular users already at higher risk of developing dependence suggests it is of clinical significance.

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Contributors

Katherine McDermott wrote multiple sections of the manuscript. Keanan Joyner contributed to the interpretation of the findings and wrote the results section. Jahn Hakes performed all data analyses, aided in interpretation of the results, and edited the manuscript. Sarah Okey performed literature searches and contributed to the writing of the discussion. Jesse Cougle conceived of the research question and directed the interpretation of results and writing of the manuscript. All authors approved of the final article.

Conflict of interest

No conflict declared.

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