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*Associations between Cannabis Use, Medication Status and Panic-Anxiety Disorder Symptoms
among US Adults*

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May 2019

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ABSTRACT

The existing body of literature focuses on the onset of panic disorders or other side effects as an association with cannabis use, but does little to address how possible concomitant cannabis use affects symptom presentation in already-diagnosed patients. The present project aims to take a closer look at adults with a lifetime history of DSM-5 diagnosed anxiety disorders, their prescribed (non-cannabis) medication use, cannabis use frequency, and associated symptom severity.

In general, we find that cannabis use is associated with higher panic-anxiety symptom severity across panic disorder without agoraphobia, generalized anxiety disorder, and people with combined anxious-distress diagnoses, after controlling for prescription medication status and professional help seeking. However, the difference between users and non-users is often small and not necessarily clinically relevant: only 1 or 2 symptoms. Worth noting is that we found no dose-response relationship for frequency of cannabis use. Being an infrequent user is not significantly different than being a daily user in terms of unique symptom presentation. This means that increasingly higher cannabis use does not necessarily induce increasingly more severe anxiety or distress. Rather, it seems that once an individual's cannabis use crosses over a certain threshold, symptom presentation increases. For some disorders, this is an all-or-none phenomenon; any cannabis use is associated with more severe symptoms than staying abstinent. For others, only daily users present with higher symptoms than non-users. The sole divergence to this conclusion is that panic without agoraphobia patients who use infrequently seem to have more severe symptoms than non-users and daily users.

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Table 1. Sample Description

Characteristic	Panic Disorder Without Agoraphobia (N=1451) N (%)*	Panic Disorder With Agoraphobia (N=362) N (%)*	Social Anxiety Disorder (N=1255) N (%)*	Generalized Anxiety Disorder (N=2708) N (%)*	Total N (%)*
Cannabis use within the last 12 months					
No	1215 (83.85)	284 (78.45)	1024 (81.59)	2285 (84.38)	3948 (84.20)
Yes	234 (16.15)	78 (21.55)	230 (18.33)	420 (15.51)	737 (15.72)
Cannabis use frequency					
No use	1215 (83.74)	284 (78.45)	1024 (81.59)	2285 (84.38)	3948 (84.20)
Monthly/weekly	120 (8.27)	49 (13.54)	133 (10.60)	224 (8.27)	411 (8.77)
Daily/near daily	113 (7.79)	29 (8.01)	95 (7.57)	193 (7.13)	322 (6.87)
Prescription medication for the affected anxiety disorder					
No	608 (41.90)	70 (19.34)	852 (67.89)	2040 (75.33)	2480 (52.89)
Yes	838 (57.75)	290 (80.11)	400 (31.87)	666 (24.59)	2191 (46.73)
Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional					
No	994 (68.50)	162 (44.75)	981 (78.17)	2244 (82.87)	3737 (79.70)
Yes	455 (31.36)	200 (55.25)	274 (21.83)	464 (17.13)	951 (20.28)
Race/ethnicity					
White	962 (66.30)	247 (68.23)	863 (68.76)	1794 (66.25)	3091 (65.92)
Black	208 (14.33)	48 (13.26)	151 (12.03)	413 (15.25)	697 (14.86)
American Indian /Alaska Native	41 (2.83)	16 (4.42)	35 (2.79)	58 (2.14)	107 (2.28)
Asian/ Pacific Islander	25 (1.72)	3 (0.83)	20 (1.59)	75 (2.77)	111 (2.37)
Hispanic (any race)	215 (14.82)	48 (13.26)	186 (14.82)	368 (13.59)	683 (14.57)
Age (years), mean ± SD	43.63±14.56	42.20±13.85	44.04±16.60	47.09±15.54	45.72± 15.93
Age (years) at first use of marijuana, mean ± SD	16.76±5.43	16.04±4.33	16.98±5.45	17.63±5.53	17.40±6.41
Sex					
Female	1042 (71.81)	277 (76.52)	801 (63.82)	1836 (67.80)	3186 (67.95)
Male	409 (28.19)	85 (23.48)	454 (36.18)	872 (32.20)	1503 (32.05)
Education					
Less than high school	212 (14.61)	58 (16.02)	191 (15.22)	346 (12.78)	661 (14.10)
High school graduate	375 (25.84)	104 (28.73)	378 (30.12)	673 (24.85)	1211 (25.83)
At least some college up to a Bachelor's	703 (48.45)	166 (45.86)	572 (45.58)	1279 (47.23)	2220 (47.34)
At least some graduate studies	161 (11.10)	34 (9.39)	114 (9.08)	410 (15.14)	597 (12.73)
Marital status					
Never married	341 (23.50)	103 (28.45)	374 (29.80)	625 (23.08)	1167 (24.89)

Married or living with someone as if married	620 (42.73)	150 (41.44)	511 (40.72)	1149 (42.43)	1983 (42.29)
Widowed	86 (5.93)	17 (4.70)	86 (6.85)	226 (8.35)	354 (7.55)
Separated or divorced	404 (27.84)	92 (25.41)	284 (22.63)	708 (26.14)	1185 (25.27)
Number of comorbidities					
1	935 (64.44)	125 (34.53)	619 (49.32)	1820 (67.21)	3499 (74.62)
2	407 (28.05)	137 (37.85)	427 (34.02)	679 (25.07)	825 (17.59)
3	109 (7.51)	100 (27.62)	209 (16.65)	209 (7.72)	209 (4.46)

*may not add up to 100% due to some missing values or overlap in multiple comorbidities. Also, panic disorder alone and panic disorder with agoraphobia are mutually exclusive diagnoses.

Table 2. Unadjusted association between cannabis use frequency and symptom severity category for each disorder

Disorder	N (total)	Cannabis Use Frequency	Symptom severity category (row %)				Rao-Scott χ^2	p
			0-Mild	Moderate	High	Severe		
Panic Disorder	1215	No use	29.7%	34.2%	21.0%	15.1%	18.6257	0.0048
	120	Monthly or weekly	20.8%	34.7%	22.3%	22.1%		
	113 (1451)	Daily or near daily	22.9%	20.4%	27.4%	29.2%		
Panic Disorder with Agoraphobia	284	No use	27.9%	22.4%	24.5%	23.4%	7.5733	0.2711
	49	Monthly or weekly	20.5%	22.8%	25.2%	31.5%		
	29 (362)	Daily or near daily	8.4%	32.0%	29.7%	29.9%		
Social Anxiety Disorder	1024	No use	24.0%	30.1%	25.2%	20.7%	11.2665	0.0805
	133	Monthly or weekly	22.5%	24.8%	21.9%	30.7%		
	95 (1252)	Daily or near daily	17.1%	22.4%	26.2%	34.3%		
Generalized Anxiety Disorder	2285	No use	71.8%	11.0%	9.1%	8.1%	13.5699	0.0348
	224	Monthly or weekly	62.2%	12.1%	13.5%	12.1%		
	193 (2702)	Daily or near daily	62.9%	12.1%	10.3%	14.7%		
Anxious-Distress Symptoms, a group that comprises of patients with at least one of the above disorders	3948	No use	27.9%	27.2%	22.7%	22.3%	61.4618	<.0001
	411	Monthly or weekly	19.9%	24.5%	24.5%	28.7%		
	322 (4681)	Daily or near daily	13.3%	19.2%	24.7%	42.8%		

Table 3. Unadjusted ordinal logistic regression model for association between cannabis use frequency and increasing levels of symptom severity (zero-mild, moderate, high and severe)

Disorder	Variable	OR (95% CI)	p
Panic Disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.508 (1.011, 2.248)	0.0439
	Daily or near daily	2.058 (1.276, 3.320)	0.0034
Panic Disorder with Agoraphobia	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.515 (0.844, 2.719)	0.1610
	Daily or near daily	1.782 (0.897, 3.539)	0.0976
Social Anxiety Disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.359 (0.884, 2.090)	0.1600
	Daily or near daily	1.808 (1.133, 2.885)	0.0136
Generalized Anxiety Disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.450 (1.072, 1.961)	0.0163
	Daily or near daily	1.954 (1.421, 2.686)	<.0001
Anxious-Distress Symptoms, a group that comprises of patients with at least one of the following: panic disorder without agoraphobia, panic disorder with a agoraphobia, social anxiety disorder, and generalized anxiety disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.488 (1.194, 1.855)	0.0005
	Daily or near daily	2.578 (1.928, 3.448)	<.0001

Table 4. Adjusted ordinal logistic regression model for relationship between cannabis use frequency and increasing symptom severity categories (zero/none, low, moderate, and severe)

Disorder	Variable*	OR (95% CI)	p
Panic Disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.449 (0.977, 2.150)	0.0648
	Daily or near daily	1.694 (1.041, 2.755)	0.0341
	Ever prescribed medicine for disorder		
	No	1.00	---
	Yes	1.504 (1.199, 1.888)	0.0006
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	1.00	---
	Yes	1.531 (1.183, 1.981)	0.0014
	Race/ethnicity		
	White	1.00	---
	Black	1.656 (1.143, 2.399)	0.0082
	Native	1.198 (0.458, 3.136)	0.7097
	Asian	1.035 (0.509, 2.105)	0.9239
	Hispanic	1.567 (1.087, 2.258)	0.0233
	Age	1.504 (1.058, 2.138)	0.0166
	Education		
	Less than high school	1.00	---
	High school or equivalent	0.927 (0.594, 1.446)	0.7357
At least some college	0.731 (0.455, 1.173)	0.1916	
At least some graduate school	0.508 (0.295, 0.876)	0.0153	
Panic Disorder with Agoraphobia	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.063 (0.541, 2.086)	0.8580
	Daily or near daily	1.702 (0.833, 3.478)	0.1416
	Ever prescribed medicine for disorder		
	No	1.00	---
	Yes	2.610 (1.504, 4.529)	0.0009
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	1.00	---
	Yes	1.597 (1.008, 2.531)	0.0464
	Race/ethnicity	1.00	---
	White	2.716 (1.332, 5.539)	0.0068
Black	4.829 (1.370, 17.024)	0.0151	

	Native	3.588 (1.259, 10.231)	0.0176
	Asian	1.763 (0.866, 3.588)	0.1158
	Hispanic		
	Education		
	Less than high school	1.00	---
	High school or equivalent	0.649 (0.343, 1.229)	0.1809
	At least some college	0.449 (0.236, 0.853)	0.0153
	At least some graduate school	0.212 (0.085, 0.524)	0.0011
Social Anxiety Disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.317 (0.853, 2.031)	0.2111
	Daily or near daily	1.535 (0.958, 2.457)	0.0741
	Ever prescribed medicine for disorder		
	No	1.00	---
	Yes	2.269 (1.626, 3.165)	<.0001
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	1.00	---
	Yes	1.510 (1.114, 2.046)	0.0084
	Education		
	Less than high school	1.00	---
	High school or equivalent	0.799 (0.465, 1.372)	0.4120
	At least some college	0.604 (0.401, 0.909)	0.0163
At least some graduate school	0.365 (0.229, 0.582)	<.0001	
Generalized Anxiety Disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.218 (0.898, 1.653)	0.2023
	Daily or near daily	1.434 (1.042, 1.972)	0.0271
	Ever prescribed medicine for disorder		
	No	1.00	---
	Yes	1.760 (1.453, 2.132)	<.0001
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	1.00	---
	Yes	2.543 (1.889, 3.422)	<.0001
	Age	0.982 (0.976, 0.988)	<.0001
	Education	1.00	---
	Less than high school	1.103 (0.839, 1.450)	0.4774
	High school or equivalent	0.771 (0.608, 0.978)	0.0324
At least some college	0.658 (0.497, 0.872)	0.0039	

		At least some graduate school	
Anxious-Distress Symptoms, a group that comprises of patients with at least one of the following: panic disorder without agoraphobia, panic disorder with a agoraphobia, social anxiety disorder, and generalized anxiety disorder	Cannabis use frequency		
	No use	1.00	---
	Monthly or weekly	1.297 (1.022, 1.645)	0.0325
	Daily or near daily	2.090 (1.510, 2.894)	<.0001
	Ever prescribed medicine for disorder		
	No	1.00	---
	Yes	2.101 (1.787, 2.471)	<.0001
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	1.00	---
	Yes	3.416 (2.860, 4.080)	<.0001
	Race/ethnicity		
	White	1.00	---
	Black	1.193 (0.972, 1.464)	0.0906
	Native	1.642 (1.095, 2.461)	0.0168
	Asian	1.432 (1.017, 2.017)	0.0400
	Hispanic	0.988 (0.831, 1.174)	0.8855
	Age	0.989 (0.984, 0.993)	<.0001
	Gender		
	Female	1.00	---
	Male	0.844 (0.736, 0.967)	0.0152
	Education		
	Less than high school	1.00	---
	High school or equivalent	1.026 (0.824, 1.279)	0.8144
At least some college	0.714 (0.571, 0.894)	0.0036	
At least some graduate school	0.517 (0.387, 0.691)	<.0001	

*controlling variables were omitted from the final model via backwards selection if they did not significantly contribute to prediction value ($p < (\alpha = .05)$).

Table 5. Unadjusted multiple linear regression model for relationship between ln(past year symptom count) and cannabis use frequency

Disorder	Variable	Adjusted β (SE)	p
Panic Disorder	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.077 (0.043)	0.0785
	Daily or near daily	0.059 (0.030)	0.0559
Panic Disorder with Agoraphobia	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.060 (0.029)	0.0459
	Daily or near daily	0.084 (0.030)	0.0065
Social Anxiety Disorder	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.048 (0.043)	0.2641
	Daily or near daily	0.095 (0.048)	0.0500
Generalized Anxiety Disorder	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.062 (0.022)	0.0050
	Daily or near daily	0.103 (0.020)	<.0001
Anxious-Distress Symptoms, a group that comprises of patients with at least one of the following: panic disorder without agoraphobia, panic disorder with a agoraphobia, social anxiety disorder, and generalized anxiety disorder	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.308 (0.097)	0.0019
	Daily or near daily	0.715 (0.121)	<.0001

Table 6. Adjusted multiple linear regression model for relationship between ln(past year symptom count) and cannabis use frequency (N= 4689)

Disorder	Variable	Adjusted β (SE)	p
Panic Disorder	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.051 (0.025)	0.0431
	Daily or near daily	0.036 (0.041)	0.3824
	Ever prescribed medicine for disorder		
	No	Reference	---
	Yes	0.081 (0.016)	<.0001
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	Reference	---
	Yes	0.070 (0.017)	<.0001
	Race/ethnicity		
	White	Reference	---
	Black	0.071 (0.024)	0.0047
	Native	0.061 (0.066)	0.3555
	Asian	0.020 (0.045)	0.6641
	Hispanic	0.068 (0.024)	0.0064
	Age	-0.002 (0.001)	0.0015
	Education		
	Less than high school	Reference	---
	High school or equivalent	-0.028 (0.025)	0.2504
At least some college	-0.061 (0.025)	0.0167	
At least some graduate school	-0.104 (0.030)	0.0006	
Panic Disorder with Agoraphobia	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.026 (0.031)	0.4084
	Daily or near daily	0.064 (0.028)	0.0246
	Ever prescribed medicine for disorder		
	No	Reference	---
	Yes	0.026 (0.031)	<.0001
	Race/ethnicity		
	White	Reference	---
	Black	0.067 (0.042)	0.1186
	Native	0.103 (0.045)	0.0238
	Asian	0.143 (0.103)	0.1705
	Hispanic	0.033 (0.034)	0.3347
	Education		
Less than high school	-0.035 (0.034)	0.3077	
High school or equivalent	-0.086 (0.031)	0.0073	

	At least some college	-0.180 (0.047)	0.0002
	At least some graduate school		
Social Anxiety Disorder	Cannabis use frequency		
	No use	Reference	
	Monthly or weekly	0.025 (0.034)	0.4745
	Daily or near daily	0.051 (0.037)	0.1702
	Ever prescribed medicine for disorder		
	No	Reference	---
	Yes	0.130 (0.025)	<.0001
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	Reference	---
	Yes	0.068 (0.024)	0.0059
	Education		
	Less than high school	Reference	---
	High school or equivalent	-0.062 (0.038)	0.1019
	At least some college	-0.112 (0.031)	0.0006
At least some graduate school	-0.181 (0.037)	<.0001	
Generalized Anxiety Disorder	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.055 (0.021)	0.0096
	Daily or near daily	0.082 (0.020)	<.0001
	Ever prescribed medicine for disorder		
	No	Reference	---
	Yes	0.092 (0.013)	<.0001
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	Reference	---
	Yes	0.134 (0.019)	<.0001
	Race/ethnicity		
	White	Reference	---
	Black	0.029 (0.016)	0.0768
	Native	0.056 (0.040)	0.1600
	Asian	0.071 (0.035)	0.0464
	Hispanic	0.030 (0.018)	0.0917
	Education		
	Less than high school	Reference	---
	High school or equivalent	0.024 (0.023)	0.2932
At least some college	-0.012 (0.020)	0.5389	
At least some graduate school	-0.042 (0.025)	0.1001	

Anxious-Distress Symptoms, a group that comprises of patients with at least one of the following: panic disorder without agoraphobia, panic disorder with a agoraphobia, social anxiety disorder, and generalized anxiety disorder	Cannabis use frequency		
	No use	Reference	---
	Monthly or weekly	0.083 (0.033)	0.0138
	Daily or near daily	0.193 (0.045)	<.0001
	Ever prescribed medicine for disorder		
	No	Reference	---
	Yes	0.245 (0.024)	<.0001
	Sought help from a private physician, psychiatrist, psychologist, social worker, or any other professional		
	No	Reference	---
	Yes	0.375 (0.027)	<.0001
	Race/ethnicity		
	White	Reference	---
	Black	0.059 (0.029)	0.0490
	Native	0.180 (0.052)	0.0007
	Asian	0.089 (0.046)	0.0568
	Hispanic	0.001 (0.026)	0.9890
	Age	-0.004 (0.001)	<.0001
	Education		
	Less than high school	Reference	---
	High school or equivalent	-0.013 (0.034)	0.7112
	At least some college	-0.119 (0.034)	0.0005
At least some graduate school	-0.216 (0.042)	<.0001	

*controlling variables were omitted from the final model via backwards selection if they did not significantly contribute to prediction value ($p < (\alpha = .05)$).

BACKGROUND & RATIONALE

Self-medication for existing anxiety and mood disorders is quite common in adults (Bolton 2009). Cannabis is a popular drug of choice for relief from a variety of conditions including migraines, everyday stresses and sleeping difficulties resulting from insomnia as well as both disordered and non-disordered or “common” anxiety (Ogborne 2000; Bonn-Miller et al., 2007; Buckner et al., 2008). According to a review by Wittchen et. al. (2007), a number of prospective studies have shown that the presence of highly symptomatic anxiety disorders in adolescence significantly predicts cannabis use later in adulthood.

While people report reduced anxiety as their primary motivation for using cannabis, paradoxically, acute anxiety is the most common adverse effect of cannabis use. When taken in high doses, [(>5 mg oral D9-tetrahydrocannabinol (D9-THC) for a man of average weight)], cannabis can cause intense fear, anxiety, panic and phobic attacks (Hall and Solowij, 1998; Thomas, 1993; Tournier et al., 2003). This conflict in evidence may be mediated by the observation that the side effects of cannabis appear to be dose-dependent. For example, low doses of the cannabinoid receptor agonists, nabilone (Onaivi et al., 1990) and D9-THC (Berrendero and Maldonado, 2002) have anxiolytic-like effects in laboratory rodents, whereas higher doses produce anxiogenic behaviour and activate the hypothalamic–pituitary–adrenocortical axis (Berrendero and Maldonado, 2002; Giuliani et al., 2000; Viveros et al., 2005). This necessitates a closer look at the potential therapeutic effects of cannabis self-medication through the lens of frequency and dose of use.

Furthermore, the existing body of literature seems to focus on the onset of panic disorders or other side effects as an association with cannabis use, but does little to address how possible concomitant cannabis use affects symptom presentation in already-diagnosed patients. There is currently little known about how cannabis interacts with prescription medication in symptom

abation. The present project aims to take a closer look at adults with a history of DSM-5 diagnosed panic, social anxiety, or generalized anxiety disorder, their prescribed (non-cannabis) medication use, cannabis use status, and associated symptom severity. For example: does self-medication with cannabis in lieu of prescribed medication abate symptoms? If a person is already taking anxiety medication, does simultaneously using cannabis have even greater symptom reduction than using prescriptions alone? Or does it have no additional benefit? We are hoping to compare symptom presentation of groups of people based on cannabis use status while controlling for prescribed medication status. Additionally, we investigate the plausibility of a frequency-response relationship of symptom severity in conjunction with frequency of cannabis use.

METHODS

Survey Instrument

The National Epidemiologic Survey on Alcohol and Related Conditions-III (NESARC-III) was sponsored, designed and directed by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). The NESARC-III is cross-sectional, based on a nationally representative sample of the civilian population of the United States.

The NESARC-III contains data from a well-characterized population sample, containing demographic data as well as various information such as lifetime and past 12 month history of chronic diseases/disorders/disabilities, substance use attitudes, and self-reports of symptoms. Data on cannabis use and frequency is available for both lifetime and past year use. Particular focus will be put on patients who have current (within the past year) active diagnoses and their current symptoms, as their experiences may be more salient and more accurately reported while completing the NESARC-3 survey. All patients are non-institutionalized adults ages 18 years and over residing in the US.

Full survey methodology can be found on the [NIH website](#).

Study Population

In total, 36,309 adults were captured with the NESARC-III survey. In this study, I focused on 4,689 individuals who had a lifetime history of DSM-5 diagnosed anxiety-related disorders, including panic disorder without agoraphobia (n= 1451), panic disorder with agoraphobia (n=362), social anxiety disorder (n=1255), and generalized anxiety disorder (n= 2708) in the US. Of this anxiety-related subset, 825 individuals had a lifetime history of 2 or more of the disorders of interest.

Measures

Independent Variables

Cannabis Use. The primary independent variable of interest is current (defined as past-year) use of cannabis. Past year cannabis use was assessed by the NESARC-III questions that ask “Have you ever used cannabis?” and if so, “Have you used cannabis within the last 12 months?”. Based off of these questions, past year cannabis use is coded as “Yes”, “No”, or “Missing”.

A variable for cannabis use frequency was also derived from a NESARC-III question that asked, “How often do you use cannabis?”. The original question had 13 response levels, ranging from never to daily. We chose to collapse these levels into 3: never, monthly or weekly, daily or more days than not. The reasoning behind these new categorizations is that 1.) a large proportion of people choose not to use cannabis or choose not to reveal their usage out of stigma and 2.) daily or near daily users may have an additional motive for cannabis usage, implying that they are more likely to be using it as a coping mechanism or self-medication, whereas recreational users likely are not reliant on continuous use for symptom management.

Medication status. The medication status variable reflects whether or not a patient has ever been prescribed medication for their specific panic-anxiety disorder by a physician.

Possible confounders. There remains a possibility that having more than 1 panic-anxiety disorder may non-linearly increase the magnitude of symptom presentation. To address this, we looked at comorbidity, creating a variable that captured how many conditions (1-3 out of panic disorder without agoraphobia, panic disorder with agoraphobia, social anxiety disorder, and general anxiety disorder) an individual met lifetime for.

Additionally, it is common practice for patients suffering from panic-anxiety symptoms to manage their symptoms with talk therapy with or without medication. Although the NESARC-III survey does not specifically address psychotherapy in its probing for each disorder, we attempt to control for this by creating a variable that reflects whether or not a patient has sought help for their condition from a private physician, psychiatrist, psychologist, social worker, or any other professional.

Demographics. We included the following demographic variables: age, sex, race, marital status, and educational attainment.

Age was left as its original continuous variable.

Race was included as a categorical variable, with its levels being: White, Black, Native-American, Asian, and Hispanic.

Marital status was collapsed from its original categorical variable, to include 4 levels: Never Married, Married/Common-Law Marriage, Separated/Divorced and Widowed.

Educational attainment was collapsed from its original 14 level variable into a 4 level ordinal categorical variable, categorized as less than high school, high school or equivalent, some college up to a bachelor's, or at least some graduate school.

Dependent Variables

Symptom severity. Under a separate section for each disorder, the NESARC-III survey asks questions akin to “Do you have an intense fear of using public transportation?” and “Do you often feel detached from things around you?” in an effort to measure how symptomatic the respondents are during a specified time period. These questions are directly referenced from the DSM-5 diagnostic criteria for their respective disorders (American Psychiatric Association, 2013). We define “current symptoms” as any symptom occurring within the past year (last 12 months). First, within each disorder, for this time period, we tallied up the number of symptom questions to which patients responded “Yes”; “No” responses did not contribute to the count, and “Missing” responses were few enough in number to be safely excluded without fear of disproportionality or bias. This symptom count variable is treated as continuous when used for linear regression modeling (see “Data Analysis”). A composite version of this variable was created by simply summing up all symptom tallies for all disorders of interest; this all-encompassing symptom severity variable is meant to allow us to assess symptom presentation for all patients within our panic-anxiety population, regardless of formal DSM-5 diagnosis. This is done to account for the fact that while an individual can be clinically diagnosed with one disorder, they may still experience some symptoms that are associated with another, to a lesser extent (e.g., someone with a generalized anxiety diagnosis can still experience panic attacks, but not to the magnitude that they would also meet panic disorder DSM-5 criteria).

Secondly, we converted our symptom count variables to reflect an ordinal categorization of severity for use in chi-square and ordinal logistic regression (see “Data Analysis”). The ordinal symptom severity variables all have 4 levels: none-mild, moderate, high, and severe

based on quartiles. The count distribution was divided into quartiles to populate the none-mild, moderate, high and severe levels respectively.

Data Analysis

χ^2 Tests

As part of exploratory analysis, unadjusted χ^2 tests were performed for each disorder, as well as the entire sample of people who have any of the 4 disorders, looking for possible bivariate associations between symptom severity categories (zero/none, low, moderate, high and severe) and factors of interest. Bivariate analysis was also undertaken between symptom severity category and categorical demographic variables or other confounders.

Ordinal Logistic Regression

Due to the ordinal nature of the symptom severity levels (i.e., zero/none, low, moderate, high and severe), we investigated the predictive power of cannabis use frequency and medication status via ordinal logistic regression. In addition, other possible predictor variables and possible confounders were added into the adjusted model.

Multiple Linear Regression

We ensured that all symptom severity counts were normally distributed by transforming all of them into their natural logarithms.

The original symptom severity variables turned out to have counts high enough for them to be treated as continuous variables. Due to concerns that turning a continuous variable into a categorical one would abolish some of the nuance of the data, we decided to build both unadjusted and adjusted models to predict symptom severity based on a number of independent variables.

Statistical Plan

I began by using descriptive statistics to summarize the characteristics of the sample, both overall and by disorder. Then, I started looking for possible bivariate associations between frequency of cannabis use and symptom severity for each disorder (as well as the whole anxious-distress subset, for individuals who have a lifetime history of at least 1 of the 4 disorders of interest) using a chi square test.

Subsequently, I used two modeling approaches:

1.) For a 4-level ordinal outcome (the levels of symptom severity ranging from “none-mild” to “severe”), I used ordinal logistic regression. Both the unadjusted and adjusted odds ratios and their respective 95% confidence intervals were calculated. Multivariable models adjusted for prescription medication status, whether or not an individual sought professional help within the last 12 months, age, gender, race, and educational status.

2.) For a continuous symptom score, I used linear regression. Given skewed, non-normal distributions for some of the disorder-specific scores, I transformed my symptoms scores to their natural logarithms. Again, multivariable models adjusted for prescription medication status, whether or not an individual sought professional help within the last 12 months, age, gender, race, and educational status.

All analyses were performed using SURVEY procedures in SAS to account for the multistage probability sample survey design and weighting. Unweighted N’s are presented throughout.

RESULTS

Sample Description

Overall, 15.72% of patients have used cannabis in some form during the last 12 months (see Table 1). Among the disorders, panic disorder with agoraphobia patients have the highest proportion of cannabis users, at 21.55%.

Across disorders, the proportions of people with a history of prescription medication use range from panic disorder with agoraphobia patients with the highest at 80.11% to generalized anxiety disorder patients with the lowest at 24.59%.

Additionally, the majority of our study population is female. Across all panic-anxiety disorders, 63.82% to 76.52% of patients are female.

Interestingly, people who are diagnosed with panic disorder with agoraphobia are more likely to also be diagnosed with the other disorders of interest (save panic disorder alone); 27.62% of this patient group has a lifetime history of both social anxiety and generalized anxiety.

χ^2 test for association between cannabis use and symptom severity categories

Increasing frequency of cannabis use is associated with increasing symptom severity, although not statistically significant for panic disorder with agoraphobia and social anxiety disorder and marginally significant at $p < 0.10$ for panic disorder without agoraphobia, generalized anxiety disorder, and the combined patient pool for all disorders of interest (see Table 2).

Unadjusted ordinal logistic regression model for association between cannabis use frequency and increasing levels of symptom severity

Consistent with findings in Table 2, we find that increasing frequency of cannabis use is associated with increasing odds of more severity symptom level ($p < .05$) for all disorders except panic disorder with agoraphobia (see Table 3). However, we do see one discrepancy: now, social

anxiety patients who use cannabis on a daily or near daily basis have 1.808 times the odds of higher symptom presentation as people who are abstinent ($p=0.0136$).

Adjusted ordinal logistic regression model for relationship between cannabis use frequency and increasing levels of symptom severity

There is no significant difference in the odds of being in a higher level of panic with agoraphobia, or social anxiety symptom severity between patients who use cannabis at any frequency and non-users (see Table 4; all $p>(\alpha=.05)$).

GAD patients who use cannabis more days than not have higher odds of having a higher level of symptom severity than non-cannabis users, given that all of the other variables remain constant. Surprisingly, the same is not true for infrequent cannabis consumers; GAD patients who intake cannabis on weekly or monthly basis do not have a significantly different odds of higher symptom severity than non-users ($p=0.2023$). Similar results were found for panic disorder without agoraphobia patients, for which regular users have higher symptom severity ($p=0.0341$) compared to abstinent patients. Yet, infrequent cannabis users do not have significantly different odds of higher panic disorder severity ($p=0.0648$).

In an effort to look at anxiety-distress symptoms in general, non-specific to any disorder and not contingent on a person's fulfillment of all of the DSM-5 criteria for diagnosis, we combined all of the disorders into one patient population. We found similar results in that a cannabis user of any frequency has increased anxious-distress symptom severity compared to non-users, given all of the other variables in the model are held constant ($p< 0.0001$).

There appear to be some confounding, complex underlying relationships between prescription medication status, age, race, and education that simultaneously account for differences in symptom severity. People have been prescribed medication and those who have

sought professional help for their disorder show increased symptom severity compared to those who did not. Consistent across all disorder-specific analyses, educational attainment seems to be a major contributor in particular. Beyond high school, people who have pursued higher education, be it in baccalaureate or graduate studies, have lower odds of presenting with higher levels or buckets of anxious-distress symptoms than non-high school graduates (all $p < (\alpha = .05)$). Specifically, graduate students have the lowest odds of higher symptom severity.

The proportional odds assumption was not met for any of the ordinal logistic tests described above. The Score Tests for the Proportional Odds Assumption were highly significant, which indicates that the cumulative logit model might not adequately fit the data. In addition, concerns that categorizing the symptom presentation tallies (which have high enough counts to possibly be considered continuous) into arbitrary buckets might remove the nuance of patient responses prompted us to fit a multiple linear regression model.

Unadjusted multiple linear regression model for relationship between past year symptom count and cannabis use frequency

Generally, we found a similar pattern of results found when symptom severity is modeled as a continuous outcome; increasing frequency of use is associated with higher symptom presentation (see Table 5). However, one major difference is that the added nuance has now allowed us to see a significant difference in symptom severity among all levels of cannabis use within the panic disorder without agoraphobia population. Additionally, panic disorder without agoraphobia patients now display no difference in symptom severity, regardless of level of cannabis use.

Adjusted multiple linear regression model for relationship between past year symptom count and cannabis use frequency

In general, the adjusted model shows the same pattern of significance as the unadjusted model; higher frequency of cannabis use is associated with higher symptom presentation across all disorders except for social anxiety (see Table 6). This is seen most robustly for generalized anxiety disorder.

Pure panic disorder patients who partake in cannabis on a weekly or monthly basis have a 5.2% more symptoms on average than those who are abstinent, holding all other variables constant ($e^{\beta} = 1.052$). Unexpectedly, daily or near daily users do not have a significantly different mean symptom count than those who are abstinent.

In contrast, the exact opposite results for cannabis frequency levels hold true for patients who have a history of panic disorder with agoraphobia.

Similar results were found when we looked at our entire patient population as a whole, regardless of which of the 4 conditions of interest any individual was affected by. Those who consumed cannabis on a daily or nearly daily basis presented with 21.3% more symptoms on average compared to those who are abstinent ($e^{\beta} = 1.213$) after controlling for confounders. Again, after adjustment, patients whose cannabis intake varies from once weekly or monthly had symptom severities that were on average 8.6% higher compared to non-cannabis users ($e^{\beta} = 1.06$).

The importance of prescription medication status, seeking help from professionals, and educational attainment is evident. Not only are they significant predictors of symptom severity, but they also modulate cannabis use's predictive value across all disorders. This is especially true in the case of social anxiety disorder, as all of cannabis use frequency's effect on symptom count

has been mitigated after controlling for confounders. Sufferers of social anxiety do not have significantly different mean symptom counts, regardless of cannabis use frequency.

As for educational attainment, people who choose to pursue higher learning after high school, on average, have fewer anxious-distress symptoms than people who did not graduate from high school.

DISCUSSION

In general, we find that cannabis use is associated with higher panic-anxiety symptom severity across panic disorder without agoraphobia, generalized anxiety disorder, and people with combined anxious-distress diagnoses after controlling for prescription medication status and professional help seeking. Worth noting is that we found no dose-response relationship for frequency of cannabis use. Being an infrequent user (defined as once monthly or weekly) is not significantly different than being a daily user in terms of unique symptom presentation. This means that increasingly higher cannabis use does not necessarily induce increasingly more severe anxiety or distress. Rather, it seems that once an individual's cannabis use crosses over a certain threshold, symptom presentation increases. For some disorders, this is an all-or-none phenomenon; any cannabis use is associated with more severe symptoms than staying abstinent. For others, only daily users present with higher symptoms than non-users. The sole divergence to this conclusion is that panic without agoraphobia patients who use infrequently seem to have more severe symptoms than non-users and daily users.

Although cannabis is still registered as a Schedule 1 drug federally, a wave of state initiatives has decriminalized the drug in large swathes of the country, increasing the proportion of recreational users due to ease of access. Former restrictions limited the user pool to medicinal users to some degree, based on effectiveness of enforcement in certain regions. With the current

upswing of recreational marijuana legalization in the United States, new legislation will expand access to cannabis to a wider population.

This will usher in more widespread implications for public health, particularly because up to 33.7% of the population is affected by an anxiety disorder during their lifetime (Bandelow, 2013). Panic disorder with or without agoraphobia, social anxiety disorder, and generalized anxiety disorder are the most prevalent anxiety disorders and are associated with immense health care costs. Due to the high burden of disease, many of these patients choose to self-medicate using cannabis. We found that cannabis use resonates with higher symptom presentation, regardless of frequency. However, we see from the parameter coefficients that the difference between users and non-users is often small and not necessarily clinically relevant: only 1 or 2 symptoms. Although this provides some insight if we define symptom severity as the number of unique symptom presentations, we should also consider the magnitude of impact these additional one or two symptoms may have on patients' quality of life. For example, how life-changing is it if you develop sweaty palms? How about compared to developing excessive fear of social situations? However, barring the most extreme symptoms, cannabis use does not seem to cause excessive harm to the point of drastically reduced functioning. In fact, based off the distribution tables and the fact that more symptomatic patients are more likely to seek help or use prescription medication, it seems entirely possible that the same patients would try to self-medicate using cannabis in an attempt to mitigate some of the more debilitating symptoms.

Contrary to current literature, age is not a major contributing factor for higher symptom presentation for any of the 4 anxiety disorders besides panic disorder, for which our patient population skews slightly young (Patton et. al., 2002). As cannabis policy reform moves forward, one of the greatest concerns legislators and parents have is that legalization will increase

cannabis use among young people, and in particular, initiate adolescent users who would not otherwise have used cannabis. In fact, even legal states such as Colorado and Massachusetts have an age threshold of 21 (down from previous restrictions of at least 25 years old for medical marijuana registration eligibility). However, the *raison d'être* for this is rooted, in large part, in moralistic apprehensions rather than health-related ones. In addition to the null results seen in the present paper, regular cannabis use that begins in adolescence and continues throughout young adulthood appears to produce cognitive impairment but the mechanism and reversibility of the impairment is unclear (Hall, 2015).

As cannabis legislation becomes more permissive, either by lowering the age limit or expanding access, it is our hope that this will lift some of the restrictions on scientific investigations, allowing deeper clarity into the relationship between cannabis and health effects. Directions for future work include further comparisons of how anxious-distress symptoms severity presents in states with and without permissive cannabis legislation. Additionally, regular cannabis use has previously been associated with higher risks of developing chronic bronchitis, as well as higher risks of myocardial infarction in middle-aged adults (Hall, 2015). However, these effects may also be explained by tobacco use, for which cannabis use has long been difficult to disentangle from, as most smokers partake in both. Due to the incredibly varied methods of cannabis consumption (eg. extract vape, oils, regular flower), it may become possible to isolate or remove confounding factors (eg. minimize the confounding effect of physical combustion or smoke by studying only tobacco chewers and cannabis extract vapers). Given any health revelations that elucidate the health risks of cannabis relative to tobacco, this may in turn, allow us to revisit or revise tobacco laws when compared to cannabis laws and vice versa.

A major limitation of this analysis lies in the cross-sectional nature of the NESARC-III survey. Patient responses are captured from a snapshot in time, rather than longitudinally. Of course, this means that a comparison of prior symptoms to current symptoms may be flawed, as prior symptoms are self-reported after possibly years of lag, resulting in memory bias. Additionally, this raises concerns about the actual chronological causality of effects from our “treatments”, medication status and cannabis use; how can we ascertain if more severe symptom presentation causes people to seek out medication or self-medicate with cannabis or if cannabis induces more severe symptoms?

Another potential pitfall is that within the survey definition of “cannabis use”, there is no differentiation between THC, which may be anxiety-inducing in high doses and CBD, which may be anxiolytic. This might confound some of the patient responses regarding anxiety symptoms.

Due to both the social stigma and possible legal ramifications of admitting to cannabis use in more conservative states, it is possible that our sample has underreported cannabis use. However, this bias is likely to only inflate the population of non-users and equally affect reported cannabis use across all other frequencies; social and legal ramifications usually do not differentiate based on magnitude of consumption.

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