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Authors

Merlin, Jessica S
Long, Dustin
Becker, William C
et al.

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Marijuana Use is Not Associated with Changes in Opioid Prescriptions or Pain Severity Among People Living with HIV and Chronic Pain

Jessica S. Merlin, MD, PhD[1], **Dustin Long, PhD**[2], **William C. Becker, MD**[3], **Edward R. Cachay, MD**[4], **Katerina A. Christopolous, MD, MPH**[5], **Kasey R. Claborn, PhD**[6], **Heidi M. Crane, MD, MPH**[7], **E. Jennifer Edelman, MD, MHS**[8], **Travis I. Lovejoy, PhD, MPH**[9,10], **W. Christopher Mathews, MD**[4], **Benjamin J. Morasco, PhD**[9,10], **Sonia Napravnik, PhD**[11], **Connall O'Cleirigh, PhD**[12], **Michael S. Saag, MD**[13], **Joanna L. Starrels, MD, MS**[14], **Robert Gross, MD, MSCE**[15], and **Jane M. Liebschutz, MD, MPH**[1]

[1]Center for Research on Healthcare, Divisions of General Internal Medicine and Infectious Diseases, University of Pittsburgh School of Medicine, Pennsylvania; [2]Department of Biostatistics, University of Alabama at Birmingham School of Public Health; [3]Section of General Internal Medicine, Department of Medicine, Yale School of Medicine, New Haven, Connecticut, and VA Connecticut Healthcare System, West Haven; [4]Division of Infectious Diseases, Owen Clinic, and Department of Medicine, University of California at San Diego; [5]Division of HIV, Infectious Diseases, and Global Medicine, Zuckerberg San Francisco General Hospital, University of California, San Francisco; [6]Department of Psychiatry, University of Texas at Austin Dell Medical School; [7]Division of Infectious Disease, Department of Medicine, University of Washington, Seattle; [8]Yale Schools of Medicine and Public Health, New Haven, Connecticut; [9]Department of Psychiatry, Oregon Health & Science University, Portland; [10]Center to Improve Veteran Involvement in Care, VA Portland Health Care System, Oregon; [11]Division of Infectious Diseases, Department of Medicine, University of North Carolina at Chapel Hill; [12]Massachusetts General Hospital/Harvard Medical School, Department of Psychiatry, The Fenway Institute, Boston; [13]Division of Infectious Diseases, Department of Medicine, University of Alabama at Birmingham; [14]Division of General Internal Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York; [15]Division of Infectious Diseases, Department of Medicine, and Department of Biostatistics, Epidemiology & Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia.

Abstract

Background: People living with HIV (PLWH) commonly report marijuana use for chronic pain, though there is limited empirical evidence to support its use. There is hope that marijuana may reduce prescription opioid use. Our objective was to investigate whether marijuana use among PLWH who have chronic pain is associated with changes in pain severity and prescribed opioid use (prescribed opioid initiation and discontinuation).

Correspondence to: J. S. Merlin, Division of General Internal Medicine, University of Pittsburgh School of Medicine, 230 McKee Place, Suite 600, Pittsburgh, PA 15213 (merlinjs@upmc.edu), 215-806-1888.

Methods: Participants completed self-report measures of chronic pain and marijuana use at an index visit and were followed for one year in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS). Self-reported marijuana use was the exposure variable. Outcome variables were changes in pain and initiation or discontinuation of opioids during the study period. The relationship between exposure and outcomes was assessed using generalized linear models for pain and multivariable binary logistic regression models for opioid initiation/discontinuation.

Results: Of 433 PLWH and chronic pain, 28% reported marijuana use in the past 3 months. Median pain severity at the index visit was 6.3/10 (IQR 4.7–8.0). Neither increases nor decreases in marijuana use were associated with changes in pain severity and marijuana use was not associated with either lower odds of opioid initiation or higher odds of opioid discontinuation.

Conclusions: We did not find evidence that marijuana use in PLWH is associated with improved pain outcomes, or reduced opioid prescribing. This suggests that caution is warranted when counseling PLWH about potential benefits of recreational or medical marijuana.

Keywords

Marijuana; opioids; pain; HIV

Introduction

Marijuana use is common, particularly in people living with HIV (PLWH). Prior studies suggest that the prevalence of current marijuana use in PLWH ranges from 20% to 60%[1–7]. In the general population, this number is 8%[8].

Discussions with patients about marijuana have taken on more urgency in HIV primary care over the past several years as over half of states have moved to legalize medical marijuana, which is likely to increase use. Furthermore, at least 27 states have designated HIV seropositivity as a qualifying diagnosis for medical marijuana certification[9]. Although experimental trials that substantiate specific benefits are lacking, commonly reported reasons for marijuana use in PLWH include pain relief, as well as other symptoms such as nausea and anorexia[10]. Additionally, chronic pain is common in PLWH, with prevalence estimates ranging from 25% to 85% depending on the cohort studied[11,12], and is the most common reason why people seek treatment with medical marijuana[13]. However, recent systematic reviews have highlighted the limited evidence base for medical marijuana in treating pain and other symptoms in the general population, and specifically in PLWH[14–16]. Another common perception includes a belief that marijuana may allow patients prescribed long-term opioid therapy (LTOT) for chronic pain to reduce their opioid use. Ecological studies in the general population[17] and one study in PLWH support this possibility[18].

With this background, HIV clinicians need empirically based findings to guide patients regarding marijuana use. Additionally, clinicians are faced with the tension between state laws naming HIV as a qualifying diagnosis for medical marijuana and the limited evidence base. Recent studies suggest that the lay public has generally positive views of the benefits of medical marijuana and views risks as minimal[19]. Given the limited evidence base, providers may be influenced by the layperson’s view of marijuana. Since clinical trials

studying the effects of medical marijuana are hampered by federal classification of marijuana as a schedule I substance, observational data must be relied on to advance our understanding of the impact of marijuana on health outcomes.

We investigated whether recreational marijuana use among PLWH who have chronic pain is associated with two clinically important chronic pain-related outcomes: changes in pain severity and prescribed opioid use (prescribed opioid initiation and discontinuation). We first asked whether a change in marijuana use over time predicted a change in pain severity, hypothesizing that an increase in marijuana use would be associated with decreased pain and a decrease in marijuana use would be associated with an increase in pain severity. We then asked whether baseline marijuana use would be associated with lower opioid prescribing. We hypothesized that baseline marijuana use would be associated with lower rates of initiation and higher rates of discontinuation of prescribed opioids.

Methods

Setting, Study Population, and Data Collection

This study is an analysis of data from a large, ongoing national prospective cohort study of chronic pain and HIV outcomes embedded within the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS)[20]. CNICS sites are patient-centered medical homes for PLWH, meaning that they provide primary and specialty care for PLWH including mental health treatment and social services. The majority of patients from CNICS sites (typically >85%) are enrolled in the cohort. CNICS collects demographic and clinical data at routine clinic visits, including laboratory tests, visit data, and prescribed medications from the electronic medical record. Additionally, as part of routine clinical care appointments, participants complete in-person Patient Reported Outcome (PRO) measures on a computer or tablet on a variety of social and behavioral domains approximately every 4 to 6 months[21].

The CNICS clinical assessment of PROs includes the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)[22], which collects self-report of “non-medical” marijuana use over the past 3 months. The possible categories are no current use, use 1–2 times in the past 3 months, monthly, weekly, or daily. Pain instruments were added to the CNICS clinical assessment between July 2015 and July 2016, providing 12 months of data from which to study chronic pain in this cohort[12]. The following five CNICS sites included the Pain instruments and contributed data to this analysis: Fenway Health in Boston, the University of Alabama at Birmingham (UAB), University of California, San Diego (UCSD), University of North Carolina (UNC), and University of Washington (UW). At the time of this study, marijuana was legal recreationally in Washington (since 2012), medically in Washington (1998) and California (1996), and illegal in all other sites. Pain instruments included the Brief Chronic Pain Questionnaire (BCPQ). The BCPQ asks whether participants have pain that has lasted for more than 3 months, and the severity of their pain (none, very mild, mild, moderate, severe, very severe)[23]. Participants who reported at least “moderate” pain for at least 3 months were classified as “chronic pain”[12] and also received the three-item PEG to assess pain severity. This instrument assesses pain intensity (P), interference with enjoyment of life (E), and interference with general activity (G) on a scale of 0–10 for each item[24]. Participants with at least moderate chronic pain were also asked to

complete the following question: “Check everywhere you have had pain for at least 3 months: numbness or tingling in hands and/or feet; headache; abdominal pain; low back pain; hip pain; shoulder pain; knee pain; pain everywhere in your body.”

This study was approved by the Institutional Review Board of the University of Alabama at Birmingham (UAB).

Inclusion Criteria

The date participants completed their first pain PRO instrument was defined as their “index visit.” The study period was defined as the 1-year period following the index visit. Criteria for inclusion in this analysis were age ≥18 years, participation in CNICS for at least one year prior to the index visit to allow for assessment of prescribed opioids during this period (see prescribed opioid initiation and discontinuation, below) and to prevent inclusion of participants new to HIV care, and chronic pain. We also required participants to have two marijuana and two pain PRO measurements during the study period (including the index visit) so that changes in these variables could be assessed.

Exposure Variable

Marijuana use—Marijuana use was assessed at the PRO assessments during the study period. Among participants who reported no current use, use monthly, use 1–2 times per month, or use weekly, we defined *an increase in marijuana use* as any change to a category of more frequent use during the study period. Participants who reported daily use were not able to increase their use and therefore were not included in this analysis. Among participants who reported use 1–2 times in the past 3 months, monthly, weekly, or daily, we defined *a decrease in marijuana use* as any change to a category of less frequent use during the study period. Participants who reported no current use were not able to decrease their use and therefore were not included in this analysis. For analysis of marijuana use at the index visit, levels were combined to improve interpretations such that three groups were considered; daily/weekly use, monthly/1–2 times in past 3 months, and no current use.

Outcome Variables

The PEG score was calculated as the mean of the 3 items in the questionnaire. We defined long-term opioid therapy (LTOT) as opioid therapy for 90 consecutive days[25] based on medical record data. *Prescribed opioid discontinuation* was defined as being prescribed LTOT at any point during the year prior to the index visit, and not being prescribed LTOT during the follow-up period. *Prescribed opioid initiation* was defined as not being prescribed LTOT for one year prior to the index visit and having LTOT initiated during the study period.

Covariates

We assessed tobacco use with the CNICS smoking questionnaire[26]. Categories were any current use, past use (defined as having smoked >20 cigarettes in one’s lifetime but not currently), and never (defined as having smoked <20 cigarettes in one’s lifetime). Unhealthy alcohol use was assessed with the Alcohol Use Disorders Identification Test (AUDIT-C) and was defined as scores ≥4 if male and ≥3 if female[22,27,28]. Illicit substance use (excluding

marijuana) was assessed with the ASSIST (31) and defined as current use in the past 3 months of methamphetamine/crystal, cocaine/crack, and opioids (non-medical use)[22].

Symptoms of depression were assessed with the Patient Health Questionnaire (PHQ) – 9. Scores ≥ 10 were classified as depressive symptoms. Anxiety was assessed with the PHQ anxiety module. Anxiety and panic were classified as anxiety symptoms[29].

Statistical Analyses

While it may be of interest to examine longitudinal relationships using all potential visits, only 12% of patients (50) have more than two visits during the follow-up period and it is not clear how having less than the maximum number of observations would be considered statistically significant as this is a clinical cohort without a formal protocol.

Change in pain severity outcome: For the relationship between marijuana use and change in pain severity, we considered whether an individual's marijuana use increased or decreased during the study period. Pain severity change was calculated by subtracting the baseline PEG from the last recorded PEG; thus, negative (positive) values indicate a decrease (increase) in pain severity. To examine the impact of pain severity on changes in marijuana use, we constructed general linear models with change in pain severity as the outcome variable and change in marijuana use as independent variables. Residual diagnostics were performed to determine if linear model assumptions were satisfied.

Opioid initiation and discontinuation outcomes: For the relationship between marijuana use and opioid initiation and discontinuation, we only considered marijuana use at baseline. This allowed us to explore the assertion that marijuana use (regardless of whether it is changing or staying the same) facilitates tapering of opioids. We constructed multivariable binary logistic regression models with opioid initiation and discontinuation as the outcome variables and marijuana use at the index visit as an ordinal variable (daily/weekly use, monthly/1–2 times in past 3 months, and no current use). Due to small sample size and data separation, each logistic regression was performed using Firth's penalized maximum likelihood estimation to reduce bias in the parameter estimates[30].

We considered covariates at baseline that are potentially associated with these exposures and outcomes: age, race, gender, other substance use (tobacco, alcohol, and illicit substances other than marijuana) and mood symptoms (depressive and anxiety symptoms)[29]. Viral load and CD4+ T-cell count were collected for descriptive purposes. Virologic failure was defined as plasma HIV RNA >1000 copies/mL at any time during the study period, without a repeated test within 30 days that found ≤1000 copies/mL[31]. Analyses were adjusted for CNICS site. All analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

Results

Most participants (N=433) were from UAB (n=267) and UCSD (n=107), consistent with prior studies from this cohort[12]. Demographic and clinical variables are summarized in Table 1. Just over half of participants were aged >50 years. Most participants were male and nearly half identified as non-Hispanic Black. The median CD4+ T-cell count at the index

visit was 582 cells/mm3, and only 16% of participants had a detectable viral load. Clinically significant symptoms of depression and anxiety were common, occurring in more than one-third of the sample. Marijuana use varied by site, with the highest current and past marijuana use reported by participants recruited from Washington (37% and 25% respectively; data not shown). Overall, most (72%) participants reported no marijuana use in the past 3 months; 8% reported daily, 5% weekly, 3% monthly, and 13% 1–2 times in the past 3 months. Of participants who reported less than daily use, 11% reported increased use during follow-up. Of participants reporting having used any marijuana, 10% reported decreased use during follow-up.

Median pain severity at baseline was 6.3/10 (IQR 4.7, 8.0), and median change in pain severity during the follow-up was 0 (IQR −1,1). The most common chronic pain locations were low back and hands/feet. During the year prior to the index visit, 47% of participants were prescribed LTOT; 8% were initiated during the study period, and 10% were discontinued during the study period.

Table 2 summarizes the analyses of the relationship between change in marijuana use and chronic pain severity during the study period. Among PLWH with chronic pain, neither increases nor decreases in marijuana use were associated with changes in pain severity.

As described in Table 3, marijuana use at the index visit was not associated with either lower odds of opioid initiation or higher odds of opioid discontinuation. Notably, marijuana use at the index visit was associated with increased opioid initiation in the unadjusted analysis (OR 2.7, 95% CI 1.1–6.9 for daily/weekly vs never; OR 1.1, 95% CI 0.4–3.3 for 1–2 times/monthly vs never) which did not achieve statistical significance in either the unadjusted or adjusted analyses, (p=0.09 and p=0.25, respectively).

Discussion

In this study, we investigated potential benefits of marijuana use in PLWH. We did not find evidence that, among patients with chronic pain, marijuana use was associated with improvements in pain or reductions in opioid prescribing. This study adds to the evidence base from which HIV providers can draw when discussing marijuana use with their patients.

Over the past several years, there has been a proliferation of research on the association between marijuana and health outcomes in the general population and in PLWH. Some studies have produced concerning findings, while other studies are more equivocal. For example, with regard to PLWH, studies suggest that marijuana use may be associated with suboptimal HIV primary care visit adherence[32] and cognitive impairment[33], but not with antiretroviral adherence, virologic suppression, or mortality[34–36]. Non–HIV-related harms of marijuana use include impaired driving, hyperemesis syndrome, cognitive impairment, psychosis, and other mood symptoms[14]. Our findings suggest that these harms are not counterbalanced by benefits in terms of pain or reductions in opioid prescribing.

We note that there are other conditions, such as multiple sclerosis and post-traumatic stress disorder, that are listed as an indication for medical marijuana in many states but have a similarly limited evidence base. Some states have legalized recreational and medical

marijuana as a result of voter petitions or legislative mandates and not as a result of scientific inquiry. Similarly, indications for medical marijuana use published by states may not have depended on evidence, but rather community and political input. Our data suggest that at least in PLWH, this is putting "the cart before the horse"[37]. Additional observational studies in populations with other chronic conditions will be essential to establishing which groups, if any, are most likely to benefit from medical marijuana.

Our study has limitations. First, it was conducted in a clinical cohort of PLWH who are in clinical care – that is, they attend clinic visits, and are mostly virologically suppressed. Our findings may not be generalizable to other populations of PLWH who are not as engaged in care. While our analysis was longitudinal, it was drawn from only one year of follow-up data. A longer longitudinal study would address this issue and allow for more robust investigations of causal inference. Also, due to lack of reliable opioid dose data, we were only able to investigate initiation and discontinuation of opioid prescribing, rather than an increase or decrease, which may be an outcome more sensitive to change over a one-year period. Despite CNICS being one of the largest prospective cohort studies of PLWH, our sample size of PLWH with chronic pain, with or without changes in marijuana use, was small. It is not possible to definitively determine whether we were underpowered to detect associations between marijuana use and pain/opioid outcomes, or whether these associations do not exist. Also, people with the heaviest marijuana use and people who did not use marijuana were excluded from some analyses, and sensitivity analyses could not be performed due to their small numbers. CNICS asks about "non-medical" use of marijuana, and participants' interpretation of this question may vary. Individuals may use illicit marijuana to treat pain and other symptoms, and/or may not have access to medical marijuana in their state. CNICS does not specifically query medical marijuana use. Another limitation is the inability to assess "intent"—that is, if medical providers and patients intended to use marijuana with a specific goal of reducing opioid dependency. Future clinical trials likely will focus on this as an intervention. Finally, we acknowledge that marijuana use is diverse in terms of route of administration (eg, inhalation and ingestion) and dose (eg, concentration of biologically active compounds). Therefore, we were only able to consider marijuana use status and frequency.

In conclusion, we did not find evidence that marijuana use in PLWH is associated with improved pain outcomes, or changes in opioid prescribing. This suggests that caution is warranted when counseling PLWH about potential benefits of recreational or medical marijuana. Further studies, including prospective trials of medical marijuana and large observational studies, are needed to understand what impact, if any, marijuana use can have on pain in PLWH.

Conflicts of Interest and Sources of Funding:

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Table 1.

Patients Living with HIV and At Least Moderate Chronic Pain: Sample Characteristics

	Total (N, % unless otherwise stated)
Site	
University of Alabama at Birmingham	267 (61.7)
University of California, San Diego	107 (24.7)
University of North Carolina	5 (1.2)
University of Washington	46 (10.6)
Fenway Health, Boston	8 (1.9)
Age ≥50 years	237 (54.7)
Female	123 (28.4)
Race	
Non-Hispanic Black	194 (44.8)
Non-Hispanic White	199 (46.0)
Other	40 (9.2)
Hispanic ethnicity	30 (6.9)
Median CD4+ T-cell count cells/mm3 (IQR)	582 (377, 815)
Virologic failure	68 (15.7)
Depressive symptoms	161 (37.2)
Anxiety symptoms	166 (38.3)
Smoking: Current	181 (41.8)
Past	120 (27.7)
Never	132 (30.5)
Unhealthy alcohol use	64 (14.8)
Illicit substance use other than marijuana (past 3 months	59 (13.6)
Marijuana (Past 3 Months)	
Daily	35 (8.1)
Weekly	20 (4.6)
Monthly	11 (2.5)
1–2 times	54 (12.5)
No use	313 (72.3)
Change in marijuana use	
Increase	48 (11.1)
No increase	350 (80.8)
Decrease	43 (9.9)
No decrease	77 (17.8)
PEG (median, IQR)	
Baseline	6.3 (4.7, 8)
Change in PEG	0 (−1, 1)
Pain site (past 3 months)	270 (62.9)

	Total (N, % unless otherwise stated)
Hands and/or feet	181 (42.2)
Headache	122 (28.4)
Abdominal	314 (73.2)
Lower back	175 (40.8)
Hip	178 (41.5)
Shoulder	209 (48.7)
Knee	85 (19.8)
Everywhere	
Long Term Opioid Therapy	
Year prior to index	203 (46.9)
Initiation during study period	33 (7.6)
Discontinuation during study period	42 (9.7)

All PROs are reported at baseline unless otherwise stated.

Abbreviations: PRO, Patient Reported Outcome.

Table 2.

Relationship between Change in Marijuana Use and Change in Pain Severity

Change in Pain Severity in subset who used marijuana at all at baseline (N=85)	Unadjusted Mean Difference (CI)	P-value	Adjusted Mean Difference (CI)	**P-value**
Decreased marijuana use vs. same or increased use	-0.37(−1.25,0.51)	0.4054	-0.5(−1.45,0.46)	0.3008
Cigarette Use:				0.5195
current vs never	0.16(−0.42,0.73)	0.5955	0.41(−0.84,1.66)	
past vs never	0.48(−0.16,1.13)	0.1414	0.84(−0.63,2.32)	
Unhealthy alcohol use (yes vs. no)	-0.68(−1.41,0.05)	0.0697	-0.17(−1.34,1)	0.7698
Illicit drug use past 3 months	-0.14(−0.85,0.57)	0.6964	-0.97(−1.95,0.02)	0.0543
Age ≥ 50			1.06(0.16,1.96)	0.0210
Female			-0.21(−1.35,0.93)	0.7104
Race				0.0538
Non-Hispanic Black vs. White			1.24(0.21,2.27)	
Other vs. White			-0.2(−1.88,1.47)	
Anxiety symptoms			0.16(−0.98,1.29)	0.7845
Depressive symptoms			0.75(−0.36,1.86)	0.1835
Change in Pain Severity in subset who used less than daily marijuana at baseline (N=281)	**Unadjusted Mean Difference (CI)**	**P-value**	**Adjusted Mean Difference (CI)**	**P-value**
Increased marijuana use vs. same or decreased use	0.25(−0.56,1.05)	0.5475	0.42(−0.41,1.25)	0.3242
Cigarette Use:				0.2611
current vs never	0.16(−0.42,0.73)	0.5955	0.08(−0.55,0.71)	
past vs never	0.48(−0.16,1.13)	0.1414	0.53(−0.16,1.21)	
Unhealthy alcohol use (yes vs. no)	-0.68(−1.41,0.05)	0.0697	-0.71(−1.53,0.1)	0.0851
Illicit drug use past 3 months	-0.14(−0.85,0.57)	0.6964	-0.1(−0.89,0.68)	0.7953
Age ≥ 50			0.25(−0.29,0.79)	0.3596
Female			0.16(−0.43,0.75)	0.5935
Race				0.2228
Non-Hispanic Black vs. White			0.06(−0.55,0.66)	
Other vs. White			-0.78(−1.71,0.14)	
Anxiety symptoms			-0.16(−0.76,0.44)	0.5945
Depressive symptoms			0.16(−0.43,0.75)	0.5914

Table 3.

Relationship between Marijuana Use at the Index Visit and Prescribed Opioid Initiation and Discontinuation

Initiation (N=230)	**Unadjusted OR (CI)**	**P-value**	**Adjusted OR (CI)**	**P-value**
Marijuana use		0.0933		0.2458
Daily/Weekly vs never	2.74 (1.09, 6.86)		2.29 (0.86, 6.16)	
1–2 times/Monthly vs never	1.07 (0.35, 3.27)		1.11 (0.36, 3.49)	
Cigarette Use:		0.5775		0.9356
current vs never	1.61 (0.66, 3.97)		1.19 (0.45, 3.12)	
past vs never	1.27 (0.44, 3.66)		1.15 (0.38, 3.48)	
Unhealthy alcohol use (yes vs. no)	1.09 0.41, 2.88)	0.8576	1.06 (0.39, 2.89)	0.9090
Illicit substance use past 3 months	1.14 (0.41, 3.23)	0.7993	0.93 (0.31, 2.81)	0.9009
Age ≥ 50 years			0.78 (0.36, 1.71)	0.538
Female			0.67 (0.25, 1.82)	0.4331
Race				0.4714
Non-Hispanic Black vs. White			0.81 (0.34, 1.94)	
Other vs. White			0.40 (0.09, 1.82)	
Anxiety symptoms			3.36 (1.38, 8.18)	0.0075
Depressive symptoms			0.53 (0.22, 1.32)	0.1718
Discontinuation (N=203)	**Unadjusted OR (CI)**	**P-value**	**Adjusted OR (CI)**	**P-value**
Marijuana use		0.2196		
Daily/Weekly vs never	1.93 (0.64, 5.88)		1.67 (0.52, 5.37)	
1–2 times/Monthly vs never	2.05 (0.79, 5.27)		2.08 (0.72, 6.03)	
Cigarette Use:		0.5290		0.5602
current vs never	1.64 (0.68, 3.95)		1.62 (0.63, 4.15)	
past vs never	1.28 (0.49, 3.37)		1.59 (0.58, 4.36)	
Unhealthy alcohol use (yes vs. no)	3.34 (1.31, 8.55)	0.0137	2.71 (1.01, 7.27)	0.0476
Drug use past 3 months	2.78 (0.96, 8.01)	0.0584	1.57 (0.48, 5.12)	0.4579
Age ≥ 50			1.24 (0.58, 2.66)	0.5867
Female			1.64 (0.74, 3.64)	0.2232
Race				0.2077
Non-Hispanic Black vs. White			1.55 (0.65, 3.73)	
Other vs. White			3.39 (0.79, 14.6)	
Anxiety symptoms			1.50 (0.62, 3.62)	0.3700
Depressive symptoms			0.94 (0.39, 2.24)	0.8803