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Marijuana use and its associations with pain, opioid dose, and HIV viral suppression among persons living with HIV on chronic opioid therapy

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Abstract

Background: Medical marijuana is legal in 29 US states and the District of Columbia: both HIV and chronic pain are “approved conditions” for receipt. Chronic pain is common among people living with HIV (PLWH). We anticipate PLWH will question their providers about medical marijuana for chronic pain. We examined marijuana use and its associations with pain, opioid dose and HIV viral suppression among PLWH receiving chronic opioid therapy (COT).

Methods: PLWH prescribed COT were recruited into the Targeting Effective Analgesia in Clinics for HIV cohort. The main exposure variable was any past 12-month marijuana use. The

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primary outcomes were 1) opioid misuse (≥9 on the Current Opioid Misuse Measure) and 2) opioid dose (morphine equivalent daily dose). HIV viral load (VL) suppression (<200 copies/uL) and pain severity and interference using the Brief Pain Inventory were exploratory outcomes.

Results: Participants (n=166) were male (65%), Black (72%), and had an undetectable VL (89%). We found no significant association between current marijuana use and opioid misuse, opioid dose, or pain. Current marijuana use was associated with 3.03 times the odds of having a detectable VL (95% OR: 1.11 – 8.31, p=0.03) while controlling for depressive symptoms and other substance use.

Discussion: We did not detect an association between marijuana use and opioid misuse behaviors, opioid dose, or pain. In an exploratory analysis, current marijuana use was associated with 3x greater odds of having a detectable VL. This study provides insights into potential consequences of marijuana use among PLWH with chronic pain.

Keywords

HIV; marijuana; opioids; chronic pain

Introduction

Medical marijuana is now legal in 29 US states and the District of Columbia. In most of these locations, HIV and chronic pain are both “approved conditions” for medical marijuana receipt.[1] Chronic pain is very common among people living with HIV (PLWH), with prevalence estimates ranging from 25–85% depending on the cohort.[2–4] Therefore, we anticipate that many PLWH will ask their providers questions about medical marijuana use for chronic pain.

Little evidence informs the clinical role for medical marijuana in the care of PLWH and chronic pain. Only one study has investigated medical marijuana for chronic pain in PLWH in the current treatment era.[5] Although pain improved, treatment and follow-up was limited to 2 weeks and the study included only individuals with neuropathy despite the high burden of musculoskeletal pain in this population.[3,6] A recent systematic review indicates that evidence as to the efficacy of medical marijuana for chronic pain in the general population is likewise limited.[7]

Another important consideration is the interplay between medical marijuana and existing chronic pain treatments. Opioids are commonly prescribed for chronic pain, particularly in PLWH.[8] However, few studies have described the concurrent use of chronic opioid therapy (COT) and marijuana.[9] Some studies have suggested that marijuana potentiates the effects of opioids.[10,11] Literature about changes in opioid dose subsequent to marijuana use is limited without established causality.[11] However, a recent epidemiologic study suggested that opioid overdose deaths are lower in states that have legalized marijuana,[12] but conclusions about individual patient-level changes accounting for this could not be made.[13] Others have noted the potential dangers of combining COT with marijuana, which like COT, can cause psychomotor retardation.[9]

Despite the paucity of evidence on benefit or harm of marijuana for PLWH, states are increasingly legislating policies to increase access to recreational and medical marijuana. It is important to understand how PLWH on COT currently utilize marijuana and its reported impact in order to determine appropriate clinical approaches.

Therefore, our study has two key aims. In an existing cohort of PLWH on COT for chronic pain, we sought to 1) describe marijuana use and 2) compare opioid misuse and opioid dose between individuals who report marijuana use versus those who do not. We also conducted posthoc analyses of the relationship between marijuana use and the outcomes pain and HIV viral load suppression.

Methods

Participants and recruitment

PLWH prescribed COT were recruited into the Targeting Effective Analgesia in Clinics for HIV (TEACH) cohort from July 2015 through December 2016 from two safety-net, hospital-based HIV clinics in Boston and Atlanta, as previously described.[14–16] In brief, potential participants were initially identified by a query of medical records through the following inclusion criteria: 1) ≥18 years of age; 2) diagnosis of HIV infection by ICD-9 codes or lab tests; 3) having received ≥3 opioid prescriptions ≥21 days apart within a 6-month period in the prior year; and 4) having attended ≥1 visit to the medical center's enrollment sites within the prior 18 months. Research staff checked the HIV clinic schedule daily using the EMR and approached potentially eligible patients for screening after informing their clinical team. The research assistant (RA) then formally screened the patient and assessed other eligibility criteria, which included: 1) provision of contact information of 2 individuals to assist with follow-up; 2) possession of a home or mobile telephone; and 3) English speaking; 4) plans to move from the area within 12 months; and 5) inability to consent or understand interviews. Written informed consent was obtained from all participants. Participants underwent 60–90 minute assessments administered by an RA at baseline and were compensated with $35. This study was reviewed and approved by the Institutional Review Boards at Boston University Medical Campus and Emory University School of Medicine, and the Grady [Health System] Research Oversight Committee.

Measures

All exposures and outcomes were measured during the baseline study visit unless noted. Here, we will describe the measures used, and when relevant, the recall period for the measure. The main exposure variable of interest was any past 12-month use of marijuana (yes vs. no), encompassing "weed" and "hash", assessed with the following questions: 1) "Have you ever used marijuana [weed]/[hash] ?"; and 2) "How often have you used marijuana [weed]/[hash] in the past 12 months" with answer responses including "never", "only a few times", "1–3 x/month", "1–5 x/week", and "daily". Substance use disorders, including marijuana use disorders, were assessed through self-report using a validated instrument that asks about DSM-5 criteria (Texas Christian University Drug Screen 5).[17,18]

The two primary outcomes were 1) a score of 9 or greater on the Current Opioid Misuse Measure (COMM), which is predictive of aberrant behaviors,[19] and 2) the morphine equivalent daily dose (MEDD), calculated as the average dose within the 30 day period prior to baseline interview calculated using each opioid prescribed and its expected duration from the dosage, doses per prescription and instructions.

In addition, in posthoc analyses we analyzed exploratory outcomes including HIV viral load (VL) suppression (<200 copies/mm^3) and the Brief Pain Inventory pain severity and interference (functional impairment) scores.[20,21] VL suppression was determined using the viral load lab test closest to baseline between the period 12 months prior and one month after baseline.

Analysis

Descriptive statistics were obtained to characterize the study sample and are presented both overall and stratified by any past 12 month marijuana use. This is considered to be a cross-sectional study as all exposure and outcome measurements were taken at or around the baseline study visit. Spearman correlation coefficients were assessed for independent variables and covariates and no pair of variables included in the regression models had a correlation > 0.40. Multivariable logistic regression models were used to evaluate the association between past 12 month marijuana use and binary outcomes (e.g., the primary outcome, COMM Score ≥ 9) controlling for a priori specified covariates that may be confounders of the relationships of interest: age, race, gender, VL (suppressed vs. unsuppressed), study site (Boston vs. Atlanta), and depression (CESD score ≥ 16).[22,23] We conducted sensitivity analyses with additional covariates that could be associated with both exposure and outcomes: pain severity, tobacco use, and other substance use. For the binary outcome (COMM score), given the limited number of events, these additional covariates were included one at a time into the main adjusted model. For the continuous outcome (MEDD), all were included simultaneously into the main adjusted model. Due to the skewed distribution of the secondary outcome Morphine Equivalent Daily Dose (MEDD), a median regression model[24,25] was used to evaluate the association between past 12 month marijuana use and this dependent variable. Multivariable linear regression models were used to analyze the exploratory outcomes pain severity and pain interference, adjusting for all covariates. Due to limited number of events for the exploratory outcome VL suppression (n = 18), only two covariates were included. The covariates chosen based on the perceived importance of their relationship to both exposure and outcome were depressive symptoms (CES-D ≥ 16) and past year substance use (excluding MJ). Two-tailed tests and a significance level of 0.05 were used for each analysis. All analyses were conducted using SAS 9.4.[26]

Results

Of 166 participants, most were male (65%) and Black (72%). Median age was 55 years (SD 8) (Table 1). At baseline, the median MEDD was 15mg (IQR 4–36), and pain severity and interference was a mean of 6/10 (SD 2). The vast majority of participants (89%) had an undetectable viral load.

Whereas 85% of participants (141/166) reported ever having used marijuana, 43% (61/141) reported marijuana use in the past 12 months. Of participants who used marijuana in the past 12 months, 33% (20/61) reported using only a few times, 21% (13/61) reported using 1–3 times per month, 31% (19/61) reported using 1–5 times per week, and 15% (9/61) reported daily use. Eight percent of the cohort (13/166) met criteria for a marijuana use disorder.[17,27] Forty three percent (71/166) reported opioid misuse in the COMM. Sixty-six percent (40/61) people who currently used marijuana (i.e., used within the past 12 months) used it for pain.

Primary outcomes (Table 2):

We found no significant association between any past year marijuana use and current opioid misuse in either unadjusted (OR 1.02, 95%CI: 0.54. 1.93, p=0.95) or adjusted models (AOR 0.71, 95%CI: 0.32, 1.58, p=0.40). In median regression analyses, there was no significant association between any past year marijuana use and MEDD in unadjusted (Difference in Medians −4.00, 95%CI: −12.07, 4.08, p=0.33) or adjusted models (Adjusted Difference in Medians 2.10, 95%CI: −5.25, 9.45, p=0.57). Conclusions were consistent in sensitivity analyses with additional covariates (data not shown).

Secondary outcomes (Table 3):

We found no significant relationship between past 12-month marijuana use and pain severity (AOR: 0.24, 95% CI: −0.39, 0.87, p=0.46) or interference (AOR: 0.41, 95% CI: −0.35, 1.17, p=0.29). In a post-hoc analysis controlling only for depressive symptoms and substance use disorder (other than marijuana), past 12-month marijuana use was associated with 3.03 times the odds of having a detectable HIV viral load (95% OR: 1.11 – 8.31, p=0.03).

Discussion

In this study, we describe marijuana use and its potential relationship with the outcomes pain, opioid use and HIV viral load suppression among PLWH who are on COT for chronic pain. Most participants reported using marijuana during their lifetime, and a substantial portion reported current regular use. A quarter of participants who used marijuana reported using it for pain. Regardless of the intent, it is noteworthy that a significant minority (8%) met criteria for a marijuana use disorder. We were unable to detect an association between marijuana use and opioid misuse behaviors, dose or pain severity.

This study adds to the small but growing body of literature on marijuana and opioid prescribing in PLWH. Findings from our study indicate that marijuana use is not associated with improvements in opioid misuse or reduction in opioid dose. This is consistent with a recently published cross-sectional study in a different HIV cohort, in which the study population was not limited to individuals with chronic pain on COT.[28] This contrasts with a third cross-sectional study of baseline clinical trial data from PLWH and chronic pain, in which marijuana use was associated with lower odds of prescribed opioids. It is not surprising that no definitive answer has emerged, given the diversity of settings studied and the cross-sectional nature of the work.[29]

In a post-hoc exploratory analysis, current marijuana use (i.e., marijuana use within the past 12 months) was associated with 3 times greater odds of having a detectable viral load. This

was a minimally adjusted analysis due to a small number of events. Therefore, the findings should be interpreted with caution. However, they are intriguing and merit further investigation. Marijuana is often viewed by the general public as a relatively harmless substance.[30] Given the limited medical evidence about marijuana use, some have commented that clinicians are likely to bring their layperson views to bear when talking with patients about marijuana.[30] Given recent legislation making marijuana available recreationally and medically in several states, clinicians are commonly faced with the question of whether to actively recommend marijuana to their patients. This may be especially true for clinicians caring for PLWH, where marijuana use is ubiquitous, and during earlier stages of the epidemic, was used for intractable pain, nausea, and anorexia in dying AIDS patients. Now that PLWH are living longer, there is tremendous hope that marijuana still has an important role to play, and will result in improvements in common and difficult-to-manage problems in PLWH, including improving pain, function, and reducing the need for opioid prescribing. In our experience, we often hear HIV clinicians caring for patients with chronic pain on COT acknowledge that use is already ubiquitous, so even if the benefit is minimal, what is the harm? This study raises important concerns about the potential negative association between marijuana and HIV outcomes among PLWH with chronic pain on COT. This is in contrast to a prior study in the Multicenter AIDS Cohort Study in all-comers with HIV (not restricted to individuals with chronic pain on COT) that did not find any association between marijuana use and HIV outcomes.[31] It is possible that PLWH who have chronic pain and are on COT already face significant health and quality of life challenges, and adding marijuana to this impacted their adherence to ART or retention in care. This is a hypothesis that should be explored in future studies.

This study has limitations. It is a cross-sectional study, so we are not able to comment on causality. MEDD was based on electronic medical record data, which one would expect to reflect clinically important changes. However, pharmacy refill data would more accurately reflect what was actually dispensed. Opioid misuse was measured by self-report, which may not reflect actual behavior. Most importantly, most marijuana use in the sample was reportedly recreational, and not for pain. Many providers are seeking information on how to advise patients on medical marijuana. While we may be able to generalize from recreational to medical marijuana, we did not study medical marijuana, but rather illicit marijuana use. Accordingly, while we have self-report of the frequency of use, we do not have information on marijuana attributes relevant to medical marijuana, such as the ratio of active components (e.g., ratio of tetrahydracannabinol to cannabidiol), the route of consumption (e.g., smoked vs. edible), or quantity consumed. Some participants (25%) did report using marijuana for pain. However, this is not true medical use, and the distinction between true “recreational” use and use for pain may be difficult to disentangle and such distinctions may not matter when it comes to marijuana-related harms. Our sample was recruited from safety net clinics comprised of predominantly Black men. Our sample was also comprised of patients prescribed COT without regard to illicit opioid use. This should be taken into consideration when generalizing our findings to other populations. Other limitations include potential lack of power given it is a secondary data analysis, and a limited number of detectable viral load events.

In sum, in this cross-sectional, observational study we did not detect associations between marijuana use and opioid misuse, dose, or pain. We did identify a potential association between marijuana use and lack of HIV viral suppression that should be further explored in larger studies. Our pain and opioid findings add to the body of literature on marijuana and opioids, and suggests a potential adverse relationship between marijuana use and HIV-related outcomes. Prospective studies, including marijuana intervention studies, to understand the impact of marijuana, whether medical or recreational, on pain, opioid use, and HIV outcomes are needed. In the meantime, this study, along with the other observational studies cited, may provide insights into the potential risks and benefits of marijuana to PLWH with chronic pain.

Conflicts of Interest and Sources of Funding:

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Table 1.

Descriptive characteristics of people living with HIV taking chronic opioid therapy and stratified by marijuana use in the past year and overall (n=166)

	Overall (n=166)	Past year use (n=61)	No use in the past year (n=105)
Demographic Characteristics			
Study site			
Boston	54 (32.5%)	14 (23.0%)	40 (38.1%)
Atlanta	112 (67.5%)	47 (77.0%)	65 (61.9%)
Age (Mean, standard deviation)	53.92 (7.75)	51.85 (8.02)	55.11 (7.36)
Gender			
Male	108 (65.1%)	42 (68.9%)	66 (62.9%)
Female	57 (34.3%)	19 (31.1%)	38 (36.2%)
Transgender (male to female)	1 (0.6%)	0 (0.0%)	1 (1.0%)
Race			
White	31 (18.7%)	11 (18.0%)	20 (19.0%)
African American/Black	120 (72.3%)	46 (75.4%)	74 (70.5%)
Other	15 (9.0%)	4 (6.6%)	11 (10.5%)
Hispanic ethnicity	15 (9.1%)	5 (8.2%)	10 (9.6%)
Employment			
Working (full-time/part-time)	33 (19.8%)	13 (21.3%)	20 (19.0%)
Disabled	119 (71.7%)	44 (72.1%)	75 (71.4%)
Other	14 (8.4%)	4 (6.6%)	10 (9.5%)
High school graduate	111 (66.9%)	44 (72.1%)	67 (63.8%)
In the past 12 months, how many times did you run out of money for basic necessities?			
Daily	1 (0.6%)	1 (1.6%)	0 (0.0%)
Weekly	13 (7.8%)	4 (6.6%)	9 (8.6%)
Monthly	34 (20.5%)	13 (21.3%)	21 (20.0%)
Occasionally	55 (33.1%)	21 (34.4%)	34 (32.4%)
Never	63 (38.0%)	22 (36.1%)	41 (39.0%)
HIV Characteristics			
HIV Transmission Route			
MSM/IDU	9 (5.4%)	3 (4.9%)	6 (5.7%)
MSM only	42 (25.3%)	19 (31.1%)	23 (21.9%)
IDU only	20 (12.0%)	7 (11.5%)	13 (12.4%)
Presumed heterosexual + blood/blood products	13 (7.8%)	7 (11.5%)	6 (5.7%)
Presumed heterosexual only	82 (49.4%)	25 (41.0%)	57 (54.3%)
HIV viral load <200	147 (89.1%)	50 (82.0%)	97 (93.3%)
CD4 Count (Mean, standard deviation)	530.87 (322.79)	480.95 (327.98)	560.14 (317.64)
Pain Characteristics			
MEDD at baseline (Mean, standard deviation)	35.32 (53.55)	30.45 (54.38)	38.16 (53.12)
Median (25^{th}, 75^{th})	14.83 (4.00, 36.46)	12.00 (2.67, 30.00)	16.00 (5.00, 40.00)

	Overall (n=166)	Past year use (n=61)	No use in the past year (n=105)
COMM Score			
≥ 9	71 (42.8%)	26 (42.6%)	45 (42.9%)
< 9	94 (56.6%)	34 (55.7%)	60 (57.1%)
Don't know/refused	1 (0.6%)	1 (1.6%)	0 (0.0%)
Pain severity * (Mean, standard deviation)	6.47 (1.95)	6.62 (1.70)	6.39 (2.08)
Pain interference * (Mean, standard deviation)	6.04 (2.41)	6.26 (2.32)	5.92 (2.47)
Site of worst pain			
Back	53 (31.9%)	19 (31.1%)	34 (32.4%)
Feet	21 (12.7%)	9 (14.8%)	12 (11.4%)
Other	92 (55.4%)	33 (54.1%)	59 (56.2%)
Mental Health Characteristics			
Depression (CES-D ≥ 16)	68 (41.0%)	26 (42.6%)	42 (40.0%)
Anxiety score ** (Mean, standard deviation)	31.52 (8.84)	32.00 (9.71)	31.25 (8.32)
Co-prescribed benzodiazepine	22 (13.3%)	8 (13.1%)	14 (13.3%)
Substance Use Characteristics - Marijuana			
Ever used marijuana (weed or hash)	141 (84.9%)	61 (100.0%)	80 (76.2%)
Marijuana use in past 12 months			
Never	105 (63.3%)	0 (0.0%)	105 (100.0%)
Only a few times	20 (12.0%)	20 (32.8%)	0 (0.0%)
1 to 3 times a month	13 (7.8%)	13 (21.3%)	0 (0.0%)
1 to 5 times a week	19 (11.4%)	19 (31.1%)	0 (0.0%)
Daily	9 (5.4%)	9 (14.8%)	0 (0.0%)
Days of marijuana use in past 30 days (Mean, standard deviation)	3.43 (8.35)	9.33 (11.65)	0.00 (0.00)
Daily marijuana user	9 (5.4%)	9 (14.8%)	0 (0.0%)
Past year marijuana use disorder	13 (7.8%)	13 (21.3%)	0 (0.0%)
Use marijuana to help chronic pain	41 (24.7%)	40 (65.6%)	1 (1.0%)
Has medical marijuana card for marijuana (among those who use marijuana for chronic pain)	2 (4.9%)	2 (5.0%)	0 (0.0%)
Substance Use Characteristics – All Substances			
Past year alcohol use disorder	28 (16.9%)	11 (18.0%)	17 (16.2%)
Past year drug use disorder	32 (19.3%)	20 (32.8%)	12 (11.4%)
Past year substance use disorder (alcohol or drug)	44 (26.5%)	22 (36.1%)	22 (21.0%)
Past year substance use disorder, excluding marijuana	36 (21.7%)	14 (23.0%)	22 (21.0%)

* Brief Pain Inventory, possible scores range from 0 (no pain, does not interfere) to 10 (pain as bad as you can imagine, completely interferes)

** State Trait Anxiety Inventory - 20 questions scored 1 to 4 and summed, questions reverse scored where applicable, range is 20–80, higher scores means higher anxiety

Table 2.

Relationships between past 12-month marijuana use and Current Opioid Misuse Measure (COMM) scores and morphine equivalent daily dose (MEDD), using logistic and median regression models, unadjusted and adjusted

COMM Score ≥ 9	**Unadjusted OR (95% CI)**	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Marijuana use in past 12 months	1.02 (0.54, 1.93)	0.95	0.71 (0.32, 1.58)	0.40
African American/Black			2.03 (0.84, 4.89)	0.12
Male			0.61 (0.28, 1.34)	0.22
CES-D ≥ 16			10.63 (4.82, 23.43)	**<.001**
HIV viral load < 200			0.40 (0.11, 1.40)	0.15
Study site (Atlanta vs. Boston)			1.25 (0.54, 2.90)	0.60
Age (per 10-year increase)			0.62 (0.38, 1.02)	0.06
MEDD	**Unadjusted Difference in Medians (CI)**	**p-value**	**Adjusted Difference in Medians (CI)**	**p-value**
Marijuana use in past 12 months	−4.00 (−12.07, 4.07)	0.33	2.10 (−5.25, 9.45)	0.57
African American/Black			−12.41 (−25.65, 0.82)	0.07
Male			6.97 (−0.45, 14.39)	0.07
CES-D ≥ 16			−0.12 (−7.42, 7.17)	0.97
HIV viral load < 200			6.14 (−4.00, 16.28)	0.23
Study site (Atlanta vs. Boston)			−7.83 (−18.10, 2.44)	0.13
Age (per 10-year increase)			2.83 (−1.47, 7.13)	0.20

Table 3.

Relationships between past 12-month marijuana use and pain severity, pain interference and viral load suppression using linear and logistic regression models, unadjusted and adjusted (exploratory)

Pain severity	**Unadjusted Difference in Means (CI)**	**p-value**	**Adjusted Difference in Means (CI)**	**p-value**
Marijuana use in past 12 months	0.22 (−0.40, 0.85)	0.48	0.24 (−0.39, 0.87)	0.46
African American/Black			0.35 (−0.34, 1.03)	0.32
Male			−0.48 (−1.12, 0.15)	0.13
CES-D ≥ 16			0.47 (−0.13, 1.07)	0.13
HIV viral load < 200			−0.13 (−1.11, 0.84)	0.79
Grady study site			0.54 (−0.12, 1.20)	0.11
Age (10-year difference)			0.27 (−0.13, 0.67)	0.18
Pain interference	**Unadjusted Difference in Means (CI)**	**p-value**	**Adjusted Difference in Means (CI)**	**p-value**
Marijuana use in past 12 months	0.34 (−0.43, 1.11)	0.3807	0.41 (−0.35, 1.17)	0.29
African American/Black			0.21 (−0.61, 1.03)	0.62
Male			−0.37 (−1.13, 0.39)	0.34
CES-D ≥ 16			1.63 (0.91, 2.35)	**<.001**
HIV viral load < 200			0.24 (−0.92, 1.41)	0.68
Grady study site			0.11 (−0.67, 0.90)	0.78
Age (10 year difference)			0.18 (−0.30, 0.65)	0.47
HIV viral load < 200	**Unadjusted OR (CI)**	**p-value**	**Adjusted OR (CI)**	**p-value**
Marijuana use in past 12 months	3.05 (1.11, 8.35)	0.0301	3.03 (1.11, 8.31)	**0.03**
CES-D ≥ 16			1.08 (0.39, 2.99)	0.89
Past year substance use disorder, excluding marijuana			1.39 (0.44, 4.38)	0.57