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The Medical Marijuana and Opioids (MEMO) Study: Protocol of a longitudinal cohort study to examine if medical cannabis reduces opioid use among adults with chronic pain

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ABSTRACT

Introduction

In the US, opioid analgesic use and overdoses have increased dramatically. One rapidly expanding strategy to manage chronic pain in the context of this epidemic is medical cannabis. Cannabis has analgesic effects, but it also has potential adverse effects. Further, its impact on opioid analgesic use is not well studied. Managing pain in people living with HIV is particularly challenging, given the high prevalence of opioid analgesic and cannabis use. This study's overarching goal is to understand how medical cannabis use affects opioid analgesic use, with attention to Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content, HIV outcomes, and adverse events.

Methods and Analyses

We are conducting a cohort study of 250 adults with and without HIV infection with (a) severe or chronic pain, (b) current opioid analgesic use, and (c) who are newly certified for medical cannabis in New York. Over 18 months, we collect data via in-person visits every three months and web-based questionnaires every two weeks. Data sources include: questionnaires; medical, pharmacy, and Prescription Monitoring Program records; urine and blood samples; and physical function tests. Using marginal structural models and comparisons within participants' two-week time periods (unit of analysis), we will examine how medical cannabis use (primary exposure) affects 1) opioid analgesic use (primary outcome), 2) HIV outcomes (HIV viral load, CD4 count, antiretroviral adherence, HIV risk behaviors), and 3) adverse events (cannabis use disorder, illicit drug use, diversion, overdose/deaths, accidents/injuries, acute care utilization).

Ethics and Dissemination

This study is approved by the Montefiore Medical Center/Albert Einstein College of Medicine institutional review board and is registered on ClinicalTrials.gov (NCT03268551). Findings will be disseminated through conferences, peer-reviewed publications, and meetings with medical cannabis stakeholders.

Study registration number: NCT03268551

Strengths and Limitations of the Study:

- This study examines how long-term medical cannabis use affects opioid analgesic use, including products with different Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content.
- The study also examines how long-term medical cannabis use affects HIV outcomes and adverse events.
- Measurement of cannabis and opioid use will be precise given 39 self-reported measures every two weeks, along with dispensing data from New York's Prescription Monitoring Program.
- Because medical cannabis products dispensed to participants have undergone independent laboratory evaluation, the exact content of these products is known and accurate.
- Because the study design is a longitudinal cohort study, analyses examine changes over time within participants, and biases that could affect outcomes may be unmeasured.

INTRODUCTION

Chronic pain is common among American adults and particularly among people living with HIV.[1-17] To address pain, over the past decades, opioid analgesic use has dramatically increased.[18,19] Subsequently, opioid use disorder and overdose have increased to unprecedented levels.[18, 20, 21] Among people living with HIV, this trend is magnified; as people living with HIV have disproportionately high chronic pain and opioid analgesic use, despite their elevated risk of opioid misuse and use disorder.[6, 14, 22-26] With concerns about opioid analgesic use and guidelines recommending non-opioid therapies, medical cannabis has emerged as an important treatment option.[27] As of July 2020, 33 states and Washington, DC have legalized medical cannabis, with pain as the most common indication.[28]

Cannabis contains more than 60 active cannabinoids; the two most active in cannabinoid receptor activation are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[29] The main psychotropic cannabinoid in cannabis, THC, can produce euphoria or anxiety, along with having an effect on pain and other symptoms.[29] CBD is non-psychoactive and also has analgesic, anti-inflammatory, antioxidant, anticonvulsant, and anxiolytic effects.[29] A combination of THC and CBD may be more effective in treating pain than THC alone, as CBD appears to both potentiate and block particular pharmacologic effects of THC.[30-34]

Numerous short-term randomized controlled trials have demonstrated that compared to placebo, cannabis use reduces pain.[35-49] In 2017, a landmark review found “conclusive or substantial evidence” that cannabis is effective in treating chronic pain.[50] While existing randomized controlled trials provide evidence about the effect of cannabis on pain, they were short-term, and only one included products with different THC/CBD content.[45] Importantly, they did not examine the relationship between cannabis and opioid analgesic use.

Limited evidence from cross-sectional and ecological studies suggests that cannabis use is associated with reduced opioid analgesic use. In several cross-sectional surveys, patients taking medical cannabis reported taking less opioid analgesics after using medical cannabis or substituting it for opioid analgesics.[51-56] In population-level studies through 2013, medical cannabis availability was associated with lower rates of opioid analgesic prescribing and lower rates of fatal opioid overdoses.[57,58] To fully understand the potential implications of medical cannabis legalization on the opioid epidemic, longitudinal studies that focus on patient-level opioid analgesic use are necessary.

Cannabis use is common in people living with HIV and can impact HIV outcomes through a variety of mechanisms.[59-68] Studies examining the relationship between cannabis use and HIV outcomes have had conflicting results in terms of HIV viral load, CD4 count, and antiretroviral adherence.[59,63, 69-78] However, one consistent finding is cannabis’s association with high-risk behaviors for HIV transmission.[62, 79-83] No studies have examined how products with different THC/CBD content affect HIV outcomes.

In addition to potential benefits of cannabis, there is evidence of adverse events.[84] Important potential adverse events are cannabis use disorder, illicit drug use, diversion (selling or sharing medical cannabis), overdose or death, accidents or injuries, and acute health care utilization. Cannabis use is associated with motor vehicle accidents, poor driving performance, injuries, and increased hospitalizations.[84-92] Many studies report these adverse events among individuals using *illicit* cannabis short-term; but, few examine adverse events among those using *medical* cannabis long-term. To our knowledge, no studies have prospectively examined these adverse events after initiating medical cannabis.

Medical cannabis policies differ by state, and New York’s (NY) medical cannabis program is one of the most stringent.[93] To be certified for medical cannabis, individuals must have a qualifying condition and complication. Medical cannabis products must be purchased from a state-licensed dispensary which have pharmacists on-site, companies must offer products with a variety of THC and CBD content, and all products are tested by an independent lab to confirm content. Dispensaries upload records of all medical cannabis products dispensed to the NY

Prescription Monitoring Program (PMP). Despite states' widespread legalized medical cannabis policies, at the federal level, cannabis remains classified as a Schedule 1 substance with "no currently accepted medical use and a high potential for abuse."[94] Because of this classification, federally-funded cannabis research is extremely restricted.[50, 95] From a clinical perspective, physicians cannot prescribe medical cannabis like other medications; they can only certify patients to purchase it. In NY, unless providers recommend a specific dose or type of product, patients can choose THC/CBD content, dose, amount, and route of administration.

Because chronic pain is common and difficult to manage, non-opioid pain management strategies are recommended, and legalized medical cannabis use continues to grow, the goal of our longitudinal cohort study is to improve understanding of how medical cannabis use affects opioid analgesic use over time, with particular attention to THC/CBD content, HIV outcomes, and adverse events. We hypothesize that: 1) Medical cannabis use will be associated with a reduction in opioid analgesic use; 2) The association between medical cannabis and opioid analgesic use will differ by THC/CBD content; 3) HIV outcomes (viral load, CD4 count, antiretroviral adherence, and risk behaviors) will differ by medical cannabis use and THC/CBD content; and 4) More medical cannabis use and higher THC (vs. CBD) content will be associated with more adverse events (cannabis use disorder, illicit drug use, diversion, overdose/death, accidents/injuries, hospitalizations/emergency room visits). Here, we describe the protocol of our longitudinal cohort study to test these hypotheses.

METHODS AND ANALYSES

Settings

Recruitment and study visits occur at Montefiore Medical Center (Montefiore) and four medical cannabis dispensaries. Montefiore is the largest healthcare system in the Bronx, NY with primary, specialty, surgical, and acute care at four hospitals, four emergency rooms, and over 20 clinics. We collaborate with four medical cannabis dispensaries in the New York City (NYC) area, which are operated by Vireo Health and Columbia Care and provide services to over 30,000 patients.

Study Participants

Inclusion criteria are: 1) ≥18 years old, 2) fluency in English or Spanish, 3) new certification for medical cannabis within 90 days, 4) no medical cannabis use in the 6 months prior to certification, 5) medical cannabis qualifying complication of "chronic or severe pain", and 6) use of prescribed or illicit opioid analgesics within 30 days.

Exclusion criteria are: 1) inability to provide informed consent, 2) inability to complete study visits over 18 months, 3) qualifying conditions for medical cannabis in NY that are likely to cause unique pain syndromes (cancer, epilepsy, multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, Parkinson's disease, inflammatory bowel disease, Huntington's disease), 4) terminal illness, and 5) current or prior psychotic disorder. Inclusion criteria #3-5, and exclusion criterion #3 are from medical or Prescription Monitoring Program data.

Recruitment

Our target enrollment is based on HIV status (target: 62 adults with HIV infection, and 188 adults without HIV infection). On September 14, 2018, we began recruiting participants via: 1) providers at Montefiore and medical cannabis dispensaries informing patients about the study during certification or initial appointments, 2) letters mailed to potential participants who were identified in medical records with new medical cannabis certification, 3) flyers posted in facilities and websites.

Research visits

Participants have seven in-person research visits at 0, 3, 6, 9, 12, 15, 18 months. At the enrollment visit, study staff describe the study and obtain written informed consent. Tracking forms and agreements to release medical, pharmacy, and PMP records are completed. Participants receive a refillable debit card for compensation. At all in-person visits, we administer questionnaires, extract PMP records, and collect urine and blood samples (depending on HIV status). We obtain medical and pharmacy records at 0, 6, 12, and 18 months. Participants receive $40 for in-person research visits (60-90 minutes) and up to $5.50 for transportation costs, which is equivalent to round-trip fare on NYC public transit.

In addition to in-person visits, participants complete 39 brief (2-5 minutes) web-based questionnaires every two weeks. At the baseline visit, participants are trained to access and complete web-based questionnaires on cellphones. If participants have discomfort with or poor access to the internet, they can complete the questionnaires via voice phone calls with study staff. After completing each web-based questionnaire, $5 is deposited into participants' debit card. If all web-based questionnaires are completed between each in-person visit, a $10 bonus is provided.

Data sources and collection

Questionnaires

At all in-person research visits that occur every three months, study staff administer questionnaires using Audio Computer-Assisted Self-Interview (ACASI) technology. The ACASI system displays questions on a computer while playing an audio recording of the question. Participants enter responses onto the computer.

For web-based questionnaires that occur every two weeks, participants receive personalized links to a web-based questionnaire from TelASK Technologies, Inc (Nepean, ON, Canada). Participants choose how (text or email) and when (day of the week and time) to receive automated links. Web-based questionnaires focus on pain, medical and illicit cannabis use, and prescribed and illicit opioid analgesic use during the previous 2 weeks.

Medical record data

We extract medical record data from medical facilities that participants visited 6 months prior to enrollment through 18 months after enrollment. Data include medical cannabis certification forms, lab values, prescriptions, and notes regarding pain treatment.

Pharmacy and Prescription Monitoring Program records

We extract medications dispensed 6 months prior to enrollment through 18 months after enrollment. From pharmacy records, we extract medication data for all HIV medications and all pain medications. From PMP records, we extract medication data for all controlled substances, including medical cannabis and opioid analgesics.

Urine toxicology tests

At all in-person visits, we collect unobserved urine specimens. Urine is tested for cannabinoids, opiates, oxycodone, methadone, buprenorphine, benzodiazepines, and cocaine using an enzyme immunoassay test (RapidTox8 from American Bio Medica Corporation, Kinderhook, NY, USA).

HIV tests and labs

Among participants with HIV infection, we collect blood every 6 months to measure HIV viral load (Abbott RealTime HIV-1 Assay from Abbott Laboratories, Abbott Park, IL, USA) and CD4 counts (AQUIOS CL flow cytometer from Beckman Coulter Life Sciences, Indianapolis, IN, USA), which are processed at Montefiore's central lab. In addition, at the baseline visit, we offer

all participants rapid HIV tests (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test from OraSure Technologies, Inc., Bethlehem, PA, USA).

Physical function tests

At all in-person visits, participants perform three standardized exercises—Ten Meter Walk Test,[96-99] Chair Stand Test,[100, 101] and Fingertip to Floor Test.[102] With the Ten Meter Walk Test, we record the amount of time it takes participants to walk ten meters two times, with the assistance of any device (e.g., walking cane) that the participant normally uses. With the Chair Stand Test, over a 30-second period, we record the number of times that participants are able to stand from a seated position. For the Fingertip to Floor Test, after participants bend over from a standing position towards the floor, we measure the distance between participants' fingertips and floor. All are reliable, valid, and responsive measures of physical function in patients with chronic pain conditions including low back pain, arthritis, and neuropathy and are simple to administer in a clinical setting.[103]

Key variables

Main exposure variable

Our main exposure variable is medical cannabis use and is measured by combining PMP and questionnaire data. PMP data include: date, product (which specifies THC/CBD content), dose, formulation, route, directions, amount dispensed, and dispensary. Web-based questionnaires inquire about both *medical* and *illicit* cannabis use for every 2-week period. For *medical* cannabis use, participants are asked: number of days used, medical cannabis product (which specifies THC/CBD content and formulation), route, and amount used on a typical day. For *illicit* cannabis use, participants are asked: number of days used, dollar amount of cannabis purchased, route, type of cannabis, and amount used on a typical day.

For each of the 39 2-week periods, our primary measure of exposure to medical cannabis is number of days of *medical* cannabis use. Alternate measures are number of days of *medical and illicit* cannabis use, cumulative dose of THC, and cumulative dose of CBD.

Primary outcome variable

Opioid analgesic use is the primary outcome and is measured by combining prescribed and illicit opioid analgesic use from the PMP and web-based questionnaires. Our primary measure of opioid analgesic use is cumulative dose of all opioid analgesics over each of the 39 2-week periods (in morphine milligram equivalents [MME]). Alternative measures are number of days of all opioid analgesic use, mean daily dose (in MME) of all opioid analgesics, and number of days of only prescribed (not illicit) opioid analgesics (all continuous measures).

Secondary outcome variables

HIV outcomes are examined in the subgroup of participants with HIV infection. Viral load is the main HIV outcome, and the primary measure is log10 copies/ml. CD4 count is analyzed as cells/mm3. Viral load and CD4 count are measured from study blood samples every 6 months. Antiretroviral adherence is analyzed using the proportion of days in which antiretroviral medications are filled (pharmacy records) and self-reported adherence.[104, 105] HIV risk behaviors are measured using the HIV Risk-taking Behavior Scale.[106-108]

Several adverse events are secondary outcomes. Cannabis use disorder is assessed using the Mini-International Neuropsychiatric Interview.109 Illicit drug use is measured using the Addiction Severity Index[110] and urine toxicology tests. Diversion of medical cannabis is measured using a modified version of the Massachusetts General Hospital Medication Questionnaire.[111] Nonfatal overdose is measured using items on the Addiction Severity Index; death is ascertained from the National Death Index. Accidents/injuries are measured using questions from national surveys in the US and Canada.[112, 113] Acute health care utilization

(hospitalizations and emergency room visits) are self-reported using the National Institute on Drug Abuse data harmonization instrument.

Other key variables

Other key variables that are potential confounders include sociodemographic characteristics, pain severity and interference,[114] pain catrastrophizing,[115] pain-related function and disability,[116] pain treatment, alcohol use,[117] tobacco use,[118] symptoms of depression,[119] anxiety,[120] post-traumatic stress disorder,[121, 122] attention deficit hyperactivity disorder,[123] insomnia,[124] physical functional tests, and quality of life.[125]

Data Analyses

Participants' 39 assessments for each 2-week time period is the unit of analysis. We will determine the association between medical cannabis use (exposure) and opioid analgesic use (outcome) using marginal structural models. Marginal structural models are necessary because they can account for time-varying confounding (i.e., variables that are both predictors of the subsequent outcome and subsequent exposure).[126, 127] Consistent with the steps of marginal structural models, we will first calculate inverse probability-of-exposure weights for each participant's 2-week time period. Calculation of these weights is based on the predicted probability of the exposure in each of the 39 2-week time periods, given time-invariant and time-varying confounders. After calculation of weights, we will create the main marginal structural model--a linear generalized estimating equations model for repeated measures on a natural logarithm scale, incorporating weights, accounting for clustering within participants, and estimating robust standard errors.[126]

In our main analysis, we will examine whether medical cannabis use is associated with reductions in opioid analgesic use. We will also conduct sensitivity analyses to determine robustness of our findings to different specifications of the weighting model.[128] We will also conduct simulation analyses to determine the robustness of our findings to potential unmeasured confounders.[129] Finally, we will repeat our model-building processes using alternative measures of medical cannabis and opioid analgesic use as described above.

In one set of secondary analyses, we will determine the association between THC and CBD and opioid analgesic use, using similar marginal structural models as described above. However, in one model, the exposure will be cumulative dose of THC in each 2-week period, and in the other model the exposure will be cumulative dose of CBD in each 2-week period. To determine the effects of cumulative THC and CBD dose together, we will use a joint marginal structural model.[130, 131] We will multiply the estimated stabilized weights for THC by the estimated stabilized weights for CBD to produce a joint weight. To analyze this, we will visually plot combinations of cumulative THC and CBD doses and the expected change in cumulative opioid analgesic dose, accounting for the interaction between THC and CBD.

In the second set of secondary analyses, we will examine the effect of medical cannabis use, THC content, and CBD content use on HIV outcomes (viral load, CD4 count, antiretroviral adherence, risk behaviors). Because time-dependent confounding is not a problem for HIV outcomes, we will use standard mixed effects regression models with generalized estimating equations, with a working first-order autoregressive covariance matrix and robust estimates of variance. Because HIV viral load will be measured every 6 months, a 6-month time period is the unit of analysis.

In the third set of secondary analyses, we will examine the effect of medical cannabis use, THC content, and CBD content on adverse events (cannabis use disorder, illicit drug use, diversion of medical cannabis, overdose/death, accidents/injuries, and hospitalizations and emergency room visits). Depending on whether the adverse event is dichotomous (e.g., cannabis use disorder) or continuous (e.g., number of hospitalizations), we will use similar

marginal structural models as described above using separate logistic or linear marginal structural models for each adverse event.

Sample size

We estimated the sample size needed to detect a 0.5% change in cumulative opioid analgesic dose with one additional day of medical cannabis. We chose this value because 14 days of medical cannabis use would then be associated with a 7% change in cumulative opioid analgesic dose over 2 weeks. This degree of dosage reduction is within the range of what is considered clinically meaningful.[27] To estimate our sample size, we used linear mixed effects models with simulations repeated 1000 times. Accounting for 20% attrition, 250 is the target sample size, as a sample size of 200 can detect associations between medical cannabis use and the outcome greater than 90% of the time. We selected a sample size with a higher power than typically chosen to ensure sufficient sample for the marginal structural model which includes several variables representing time-dependent confounding.

For HIV outcomes, we calculated power based on log10 viral load (main HIV outcome). With viral load measured every 6 months and a sample of 50 HIV+ participants, we would have greater than 99% power to detect a change of 0.5 log10 viral load. With 20% attrition, we will enroll 62 HIV+ participants. For adverse events, we calculated power based on illicit drug use as the main outcome measure (continuous measure from the Addiction Severity Index alcohol/drug subscale). A sample size of 200 participants would have greater than 99% power to detect a 5% change in the continuous subscale measure.

Timeline and monitoring

We began enrolling participants on September 14, 2018. We anticipate that enrollment will be completed by December 31, 2021, and study visits will conclude on June 30, 2023. The principal investigator oversees data and safety monitoring, including review of protocol deviations and submission of annual reports to the affiliated institutional review board and funder (National Institute of Health). Because the study observational and therefore minimal risk, we did not establish a formal data and safety monitoring board, nor will we conduct interim analyses with stopping rules.

Limitations

As a longitudinal cohort study, this study has limitations. Because of federal cannabis policies in the US, cannabis is extremely restricted in federal research. Therefore, it is not feasible to use a randomized controlled trial design and administer cannabis to 250 participants over 18 months. By using advanced analytical methods that exploit variation in medical cannabis products and patterns of use, we will estimate the impact of medical cannabis use on opioid analgesic use. While our study design and analytic approach will improve our understanding of how medical cannabis use affects opioid analgesic use, we will be unable to account for all potential biases, and we are limited to conducted analyses within, instead of between, participants.

Patient and public involvement

The design of this study was informed by clinical experiences of several of the authors, along with our prior study examining potential interest in participating in a medical cannabis research study among adults receiving medical cannabis.[132] The research questions and design were reviewed by physician-investigators at Montefiore Medical Center/Albert Einstein College of Medicine who have expertise in substance use and infectious diseases, along with chief medical officers of two medical cannabis companies. In addition, the research questions and design were reviewed by a study section at the National Institute of Health.

Ethics and dissemination

This study was approved by the Montefiore Medical Center/Albert Einstein College of Medicine institutional review board (IRB protocol number: 2017-7857). Oral informed consent is obtained prior to conducting screening questionnaires, and written informed consent is obtained at the time of enrollment into the study. Several steps are taken to protect participant confidentiality, including using a data management system that separates “name-based” and “Study ID-based” documents, obtaining a Certificate of Confidentiality from the National Institute of Health, and using a two-step verification process to access the study database.

We will disseminate study findings through presentations at scientific conferences, publications in peer-reviewed journals, and presentations to medical cannabis stakeholders. Study findings will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[133]

Authors’ contributions: CC is the Principal Investigator of this study and led its conception and design. JS, CZ, MB, NS, FL, HM, JA made substantial contributions to the conception and design of the study. CC drafted the manuscript, and all authors revised it for critically important content (CC, JS, CA, MB, NS, FL, HM, DS, JA). All authors (CC, JS, CA, MB, NS, FL, HM, DS, JA) provided final approval of the manuscript.

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Competing interests: None declared.

Participant consent: All participants provide oral informed consent prior to participating in the study screening interview, and written informed consent prior to study enrollment.

Ethics approval: The Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board.

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The Medical Marijuana and Opioids (MEMO) Study: Protocol of a longitudinal cohort study to examine if medical cannabis reduces opioid use among adults with chronic pain

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ABSTRACT

Introduction

In the United States, opioid analgesic use and overdoses have increased dramatically. One rapidly expanding strategy to manage chronic pain in the context of this epidemic is medical cannabis. Cannabis has analgesic effects, but it also has potential adverse effects. Further, its impact on opioid analgesic use is not well studied. Managing pain in people living with HIV is particularly challenging, given the high prevalence of opioid analgesic and cannabis use. This study's overarching goal is to understand how medical cannabis use affects opioid analgesic use, with attention to Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content, HIV outcomes, and adverse events.

Methods and Analyses

We are conducting a cohort study of 250 adults with and without HIV infection with (a) severe or chronic pain, (b) current opioid use, and (c) who are newly certified for medical cannabis in New York. Over 18 months, we collect data via in-person visits every three months and web-based questionnaires every two weeks. Data sources include: questionnaires; medical, pharmacy, and Prescription Monitoring Program records; urine and blood samples; and physical function tests. Using marginal structural models and comparisons within participants' two-week time periods (unit of analysis), we will examine how medical cannabis use (primary exposure) affects 1) opioid analgesic use (primary outcome), 2) HIV outcomes (HIV viral load, CD4 count, antiretroviral adherence, HIV risk behaviors), and 3) adverse events (cannabis use disorder, illicit drug use, diversion, overdose/deaths, accidents/injuries, acute care utilization).

Ethics and Dissemination

This study is approved by the Montefiore Medical Center/Albert Einstein College of Medicine institutional review board and is registered on ClinicalTrials.gov (NCT03268551). Findings will be disseminated through conferences, peer-reviewed publications, and meetings with medical cannabis stakeholders.

Study registration number: NCT03268551

Strengths and Limitations of the Study:

- This study examines how long-term medical cannabis use affects opioid analgesic use, including products with different Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content.
- The study also examines how long-term medical cannabis use affects HIV outcomes and adverse events.
- Measurement of cannabis and opioid use will be precise given 39 self-reported measures every two weeks, along with dispensing data from New York's Prescription Monitoring Program.
- Because medical cannabis products dispensed to participants have undergone independent laboratory evaluation, the exact content of these products is known and accurate.
- Because the study design is a longitudinal cohort study, analyses examine changes over time within participants, and biases that could affect outcomes may be unmeasured.

INTRODUCTION

Chronic pain is common among American adults and particularly among people living with HIV.[1-17] To address pain, over the past decades, opioid analgesic use has dramatically increased.[18,19] Subsequently, opioid use disorder and overdose have increased to unprecedented levels.[18, 20, 21] Among people living with HIV, this trend is magnified; as people living with HIV have disproportionately high chronic pain and opioid analgesic use, despite their elevated risk of opioid misuse and use disorder.[6, 14, 22-26] With concerns about opioid analgesic use and guidelines recommending non-opioid therapies, medical cannabis has emerged as an important treatment option.[27] As of July 2020, 33 states and Washington, DC have legalized medical cannabis, with pain as the most common indication.[28]

Cannabis contains more than 60 active cannabinoids; the two most active in cannabinoid receptor activation are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[29] The main psychotropic cannabinoid in cannabis, THC, can produce euphoria or anxiety, along with having an effect on pain and other symptoms.[29] CBD is non-psychoactive and also has analgesic, anti-inflammatory, antioxidant, anticonvulsant, and anxiolytic effects.[29] A combination of THC and CBD may be more effective in treating pain than THC alone, as CBD appears to both potentiate and block particular pharmacologic effects of THC.[30-34]

Numerous short-term randomized controlled trials have demonstrated that compared to placebo, cannabis use reduces pain.[35-49] In 2017, a landmark review found “conclusive or substantial evidence” that cannabis is effective in treating chronic pain.[50] While existing randomized controlled trials provide evidence about the effect of cannabis on pain, they were short-term, and only one included products with different THC/CBD content.[45] Importantly, they did not examine the relationship between cannabis and opioid analgesic use.

Limited evidence from cross-sectional and ecological studies suggests that cannabis use is associated with reduced opioid analgesic use. In several cross-sectional surveys, patients taking medical cannabis reported taking less opioid analgesics after using medical cannabis or substituting it for opioid analgesics.[51-56] In population-level studies through 2013, medical cannabis availability was associated with lower rates of opioid analgesic prescribing and lower rates of fatal opioid overdoses.[57,58] To fully understand the potential implications of medical cannabis legalization on the opioid epidemic, longitudinal studies that focus on patient-level opioid analgesic use are necessary.

Cannabis use is common in people living with HIV and can impact HIV outcomes through a variety of mechanisms.[59-68] Studies examining the relationship between cannabis use and HIV outcomes have had conflicting results in terms of HIV viral load, CD4 count, and antiretroviral adherence.[59,63, 69-78] However, one consistent finding is cannabis’s association with high-risk behaviors for HIV transmission.[62, 79-83] No studies have examined how products with different THC/CBD content affect HIV outcomes.

In addition to potential benefits of cannabis, there is evidence of adverse events.[84] Important potential adverse events are cannabis use disorder, illicit drug use, diversion (selling or sharing medical cannabis), overdose or death, accidents or injuries, and acute health care utilization. Cannabis use is associated with motor vehicle accidents, poor driving performance, injuries, and increased hospitalizations.[84-92] Many studies report these adverse events among individuals using *illicit* cannabis short-term; but, few examine adverse events among those using *medical* cannabis long-term. To our knowledge, no studies have prospectively examined these adverse events after initiating medical cannabis.

Medical cannabis policies differ by state, and New York’s (NY) medical cannabis program is one of the most stringent.[93] To be certified for medical cannabis, individuals must have at least one qualifying condition (cancer, HIV infection or AIDS, amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis, spinal cord injury with spasticity, epilepsy, inflammatory bowel disease, neuropathy, Huntington's disease, post-traumatic stress disorder, chronic pain, pain that degrades health and functional capability as an alternative to opioid use, or substance

use disorder) and at least one complication (severe or chronic pain resulting in substantial limitation of function, cachexia or wasting syndrome, severe nausea, seizures, severe or persistent muscle spasms, post-traumatic stress disorder, or opioid use disorder). Medical cannabis products must be purchased from a state-licensed dispensary which have pharmacists on-site, companies must offer products with a variety of THC and CBD content, and all products are tested by an independent lab to confirm content. Dispensaries upload records of all medical cannabis products dispensed to the NY Prescription Monitoring Program (PMP). Despite states' widespread legalized medical cannabis policies, at the federal level, cannabis remains classified as a Schedule 1 substance with "no currently accepted medical use and a high potential for abuse."[94] Because of this classification, federally-funded cannabis research is extremely restricted.[50, 95] From a clinical perspective, physicians cannot prescribe medical cannabis like other medications; they can only certify patients to purchase it. In NY, unless providers recommend a specific dose or type of product, patients can choose THC/CBD content, dose, amount, and route of administration.

Because chronic pain is common and difficult to manage, non-opioid pain management strategies are recommended, and legalized medical cannabis use continues to grow, the goal of our longitudinal cohort study is to improve understanding of how medical cannabis use affects opioid analgesic use over time, with particular attention to THC/CBD content, HIV outcomes, and adverse events. We hypothesize that: 1) Medical cannabis use will be associated with a reduction in opioid analgesic use; 2) The association between medical cannabis and opioid analgesic use will differ by THC/CBD content; 3) HIV outcomes (viral load, CD4 count, antiretroviral adherence, and risk behaviors) will differ by medical cannabis use and THC/CBD content; and 4) More medical cannabis use and higher THC (vs. CBD) content will be associated with more adverse events (cannabis use disorder, illicit drug use, diversion, overdose/death, accidents/injuries, hospitalizations/emergency room visits). Here, we describe the protocol of our longitudinal cohort study to test these hypotheses.

METHODS AND ANALYSES

Settings

Recruitment and study visits occur at Montefiore Medical Center (Montefiore) and four medical cannabis dispensaries. Montefiore is the largest healthcare system in the Bronx, NY with primary, specialty, surgical, and acute care at four hospitals, four emergency rooms, and over 20 clinics. We collaborate with four medical cannabis dispensaries in the New York City (NYC) area, which are operated by Vireo Health and Columbia Care and provide services to over 30,000 patients.

Study Participants

Inclusion criteria are: 1) ≥18 years old, 2) fluency in English or Spanish, 3) new certification for medical cannabis within 90 days, 4) no medical cannabis use in the 6 months prior to certification, 5) medical cannabis qualifying condition of "chronic pain", or "pain that degrades health and functional capability as an alternative to opioid use" or qualifying complication of "severe or chronic pain resulting in substantial limitation of function," and 6) use of prescribed or illicit opioids within 30 days.

Exclusion criteria are: 1) inability to provide informed consent, 2) inability to complete study visits over 18 months, 3) qualifying conditions for medical cannabis in NY that are likely to cause unique pain syndromes (cancer, epilepsy, multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, Parkinson's disease, inflammatory bowel disease, Huntington's disease), 4) terminal illness, and 5) current or prior psychotic disorder. Inclusion criteria #3-5, and exclusion criterion #3 are from medical or Prescription Monitoring Program data.

Recruitment

Our target enrollment is based on HIV status (target: 62 adults with HIV infection, and 188 adults without HIV infection). On September 14, 2018, we began recruiting participants via: 1) providers at Montefiore and medical cannabis dispensaries informing patients about the study during certification or initial appointments, 2) letters mailed to potential participants who were identified in medical records with new medical cannabis certification, 3) flyers posted in facilities and websites.

Research visits

Participants have seven in-person research visits at 0, 3, 6, 9, 12, 15, 18 months. At the enrollment visit, study staff describe the study and obtain written informed consent. Tracking forms and agreements to release medical, pharmacy, and PMP records are completed. Participants receive a refillable debit card for compensation. At all in-person visits, we administer questionnaires, extract PMP records, and collect urine and blood samples (depending on HIV status). We obtain medical and pharmacy records at 0, 6, 12, and 18 months. Participants receive $40 for in-person research visits (60-90 minutes) and up to $5.50 for transportation costs, which is equivalent to round-trip fare on NYC public transit.

In addition to in-person visits, participants complete 39 brief (2-5 minutes) web-based questionnaires every two weeks. At the baseline visit, participants are trained to access and complete web-based questionnaires on cellphones. If participants have discomfort with or poor access to the internet, they can complete the questionnaires via voice phone calls with study staff. After completing each web-based questionnaire, $5 is deposited into participants' debit card. If all web-based questionnaires are completed between each in-person visit, a $10 bonus is provided.

Data sources and collection

Questionnaires

At all in-person research visits that occur every three months, study staff administer questionnaires using Audio Computer-Assisted Self-Interview (ACASI) technology. The ACASI system displays questions on a computer while playing an audio recording of the question. Participants enter responses onto the computer.

For web-based questionnaires that occur every two weeks, participants receive personalized links to a web-based questionnaire from TelASK Technologies, Inc (Nepean, ON, Canada). Participants choose how (text or email) and when (day of the week and time) to receive automated links. Web-based questionnaires focus on pain, medical and illicit cannabis use, and prescribed and illicit opioid analgesic use during the previous 2 weeks.

Medical record data

We extract medical record data from medical facilities that participants visited 6 months prior to enrollment through 18 months after enrollment. Data include medical cannabis certification forms, lab values, prescriptions, and notes regarding pain treatment.

Pharmacy and Prescription Monitoring Program records

We extract medications dispensed 6 months prior to enrollment through 18 months after enrollment. From pharmacy records, we extract medication data for all HIV medications and all pain medications. From PMP records, we extract medication data for all controlled substances, including medical cannabis and opioid analgesics.

Urine toxicology tests

At all in-person visits, we collect unobserved urine specimens. Urine is tested for cannabinoids, opiates, oxycodone, methadone, buprenorphine, benzodiazepines, and cocaine

using an enzyme immunoassay test (RapidTox8 from American Bio Medica Corporation, Kinderhook, NY, USA).

HIV tests and labs

Among participants with HIV infection, we collect blood every 6 months to measure HIV viral load (Abbott RealTime HIV-1 Assay from Abbott Laboratories, Abbott Park, IL, USA) and CD4 counts (AQUIOS CL flow cytometer from Beckman Coulter Life Sciences, Indianapolis, IN, USA), which are processed at Montefiore's central lab. In addition, at the baseline visit, we offer all participants rapid HIV tests (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test from OraSure Technologies, Inc., Bethlehem, PA, USA).

Physical function tests

At all in-person visits, participants perform three standardized exercises—Ten Meter Walk Test,[96-99] Chair Stand Test,[100, 101] and Fingertip to Floor Test.[102] With the Ten Meter Walk Test, we record the amount of time it takes participants to walk ten meters two times, with the assistance of any device (e.g., walking cane) that the participant normally uses. With the Chair Stand Test, over a 30-second period, we record the number of times that participants are able to stand from a seated position. For the Fingertip to Floor Test, after participants bend over from a standing position towards the floor, we measure the distance between participants' fingertips and floor. All are reliable, valid, and responsive measures of physical function in patients with chronic pain conditions including low back pain, arthritis, and neuropathy and are simple to administer in a clinical setting.[103]

Key variables

Main exposure variable

Our main exposure variable is medical cannabis use and is measured by combining PMP and questionnaire data. PMP data include: date, product (which specifies THC/CBD content), dose, formulation, route, directions, amount dispensed, and dispensary. Web-based questionnaires inquire about both *medical* and *illicit* cannabis use for every 2-week period. For *medical* cannabis use, participants are asked: number of days used, medical cannabis product (which specifies THC/CBD content and formulation), route, and amount used on a typical day. For *illicit* cannabis use, participants are asked: number of days used, dollar amount of cannabis purchased, route, type of cannabis, and amount used on a typical day.

For each of the 39 2-week periods, our primary measure of exposure to medical cannabis is number of days of *medical* cannabis use. Alternate measures are number of days of *medical and illicit* cannabis use, cumulative dose of THC, and cumulative dose of CBD.

Primary outcome variable

Opioid analgesic use is the primary outcome and is measured by combining prescribed and illicit opioid analgesic use from the PMP and web-based questionnaires. Our primary measure of opioid analgesic use is cumulative dose of all opioid analgesics over each of the 39 2-week periods (in morphine milligram equivalents [MME]). Alternative measures are number of days of all opioid analgesic use, mean daily dose (in MME) of all opioid analgesics, and number of days of only prescribed (not illicit) opioid analgesics (all continuous measures).

Secondary outcome variables

HIV outcomes are examined in the subgroup of participants with HIV infection. Viral load is the main HIV outcome, and the primary measure is log10 copies/ml. CD4 count is analyzed as cells/mm3. Viral load and CD4 count are measured from study blood samples every 6 months. Antiretroviral adherence is analyzed using the proportion of days in which antiretroviral

medications are filled (pharmacy records) and self-reported adherence.[104, 105] HIV risk behaviors are measured using the HIV Risk-taking Behavior Scale.[106-108]

Several adverse events are secondary outcomes. Cannabis use disorder is assessed using the Mini-International Neuropsychiatric Interview.[109] Illicit drug use is measured using the Addiction Severity Index[110] and urine toxicology tests. Diversion of medical cannabis is measured using a modified version of the Massachusetts General Hospital Medication Questionnaire.[111] Nonfatal overdose is measured using items on the Addiction Severity Index; death is ascertained from the National Death Index. Accidents/injuries are measured using questions from national surveys in the United States and Canada.[112, 113] Acute health care utilization (hospitalizations and emergency room visits) are self-reported using the National Institute on Drug Abuse data harmonization instrument.

Other key variables

Other key variables that are potential confounders include sociodemographic characteristics, pain severity and interference,[114] pain catrastrophizing,[115] pain-related function and disability,[116] pain treatment, alcohol use,[117] tobacco use,[118] other substance use,[110] symptoms of depression,[119] anxiety,[120] post-traumatic stress disorder,[121, 122] attention deficit hyperactivity disorder,[123] insomnia,[124] physical functional tests, and quality of life.[125]

Data Analyses

Participants' 39 assessments for each 2-week time period is the unit of analysis. We will determine the association between medical cannabis use (exposure) and opioid analgesic use (outcome) using marginal structural models. Marginal structural models are necessary because they can account for time-varying confounding (i.e., variables that are both predictors of the subsequent outcome and subsequent exposure).[126, 127] Consistent with the steps of marginal structural models, we will first calculate inverse probability-of-exposure weights for each participant's 2-week time period. Calculation of these weights is based on the predicted probability of the exposure in each of the 39 2-week time periods, given time-invariant and time-varying confounders. After calculation of weights, we will create the main marginal structural model--a linear generalized estimating equations model for repeated measures on a natural logarithm scale, incorporating weights, accounting for clustering within participants, and estimating robust standard errors.[126]

In our main analysis, we will examine whether medical cannabis use is associated with reductions in opioid analgesic use. We will also conduct sensitivity analyses to determine robustness of our findings to different specifications of the weighting model.[128] We will also conduct simulation analyses to determine the robustness of our findings to potential unmeasured confounders.[129] Finally, we will repeat our model-building processes using alternative measures of medical cannabis and opioid analgesic use as described above.

In one set of secondary analyses, we will determine the association between THC and CBD and opioid analgesic use, using similar marginal structural models as described above. However, in one model, the exposure will be cumulative dose of THC in each 2-week period, and in the other model the exposure will be cumulative dose of CBD in each 2-week period. To determine the effects of cumulative THC and CBD dose together, we will use a joint marginal structural model.[130, 131] We will multiply the estimated stabilized weights for THC by the estimated stabilized weights for CBD to produce a joint weight. To analyze this, we will visually plot combinations of cumulative THC and CBD doses and the expected change in cumulative opioid analgesic dose, accounting for the interaction between THC and CBD.

In the second set of secondary analyses, we will examine the effect of medical cannabis use, THC content, and CBD content use on HIV outcomes (viral load, CD4 count, antiretroviral adherence, risk behaviors). Because time-dependent confounding is not a problem for HIV

outcomes, we will use standard mixed effects regression models with generalized estimating equations, with a working first-order autoregressive covariance matrix and robust estimates of variance. Because HIV viral load will be measured every 6 months, a 6-month time period is the unit of analysis.

In the third set of secondary analyses, we will examine the effect of medical cannabis use, THC content, and CBD content on adverse events (cannabis use disorder, illicit drug use, diversion of medical cannabis, overdose/death, accidents/injuries, and hospitalizations and emergency room visits). Depending on whether the adverse event is dichotomous (e.g., cannabis use disorder) or continuous (e.g., number of hospitalizations), we will use similar marginal structural models as described above using separate logistic or linear marginal structural models for each adverse event.

Sample size

We estimated the sample size needed to detect a 0.5% change in cumulative opioid analgesic dose with one additional day of medical cannabis. We chose this value because 14 days of medical cannabis use would then be associated with a 7% change in cumulative opioid analgesic dose over 2 weeks. This degree of dosage reduction is within the range of what is considered clinically meaningful.[27] To estimate our sample size, we used linear mixed effects models with simulations repeated 1000 times. Accounting for 20% attrition, 250 is the target sample size, as a sample size of 200 can detect associations between medical cannabis use and the outcome greater than 90% of the time. We selected a sample size with a higher power than typically chosen to ensure sufficient sample for the marginal structural model which includes several variables representing time-dependent confounding.

For HIV outcomes, we calculated power based on log10 viral load (main HIV outcome). With viral load measured every 6 months and a sample of 50 HIV+ participants, we would have greater than 99% power to detect a change of 0.5 log10 viral load. With 20% attrition, we will enroll 62 HIV+ participants. For adverse events, we calculated power based on illicit drug use as the main outcome measure (continuous measure from the Addiction Severity Index alcohol/drug subscale). A sample size of 200 participants would have greater than 99% power to detect a 5% change in the continuous subscale measure.

Timeline and monitoring

We began enrolling participants on September 14, 2018. We anticipate that enrollment will be completed by December 31, 2021, and study visits will conclude on June 30, 2023. The principal investigator oversees data and safety monitoring, including review of protocol deviations and submission of annual reports to the affiliated institutional review board and funder (National Institute of Health). Because the study observational and therefore minimal risk, we did not establish a formal data and safety monitoring board, nor will we conduct interim analyses with stopping rules.

Limitations

As a longitudinal cohort study, this study has limitations. Because of federal cannabis policies in the United States, cannabis is extremely restricted in federal research. Therefore, it is not feasible to use a randomized controlled trial design and administer cannabis to 250 participants over 18 months. By using advanced analytical methods that exploit variation in medical cannabis products and patterns of use, we will estimate the impact of medical cannabis use on opioid analgesic use. While our study design and analytic approach will improve our understanding of how medical cannabis use affects opioid analgesic use, we will be unable to account for all potential biases, and we are limited to conducting analyses within, instead of between, participants. In addition, because adults with HIV infection may have unique pain conditions, to determine if including participants with HIV infection in the sample leads to

differences in findings, we will conduct two sets of main analyses—one including participants with HIV infection, and one excluding participants with HIV infection. While our study will examine a range of potential adverse events from medical cannabis use, it does not examine all potential adverse events, including neurocognitive changes. Finally, because opioid prescribing in the United States has decreased over the past several years,[132] it is possible that further decreases in opioid prescribing may make it difficult to interpret the relationship between medical cannabis and opioid use.

Patient and public involvement

The design of this study was informed by clinical experiences of several of the authors, along with our prior study examining potential interest in participating in a medical cannabis research study among adults receiving medical cannabis.[133] The research questions and design were reviewed by physician-investigators at Montefiore Medical Center/Albert Einstein College of Medicine who have expertise in substance use and infectious diseases, along with chief medical officers of two medical cannabis companies. In addition, the research questions and design were reviewed by a study section at the National Institute of Health.

Ethics and dissemination

This study was approved by the Montefiore Medical Center/Albert Einstein College of Medicine institutional review board (IRB protocol number: 2017-7857). Oral informed consent is obtained prior to conducting screening questionnaires, and written informed consent is obtained at the time of enrollment into the study. Several steps are taken to protect participant confidentiality, including using a data management system that separates “name-based” and “Study ID-based” documents, obtaining a Certificate of Confidentiality from the National Institute of Health, and using a two-step verification process to access the study database.

We will disseminate study findings through presentations at scientific conferences, publications in peer-reviewed journals, and presentations to medical cannabis stakeholders. Study findings will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[134]

Authors’ contributions: CC is the Principal Investigator of this study and led its conception and design. JS, CZ, MB, NS, FL, HM, JA made substantial contributions to the conception and design of the study. CC drafted the manuscript, and all authors revised it for critically important content (CC, JS, CA, MB, NS, FL, HM, DS, JA). All authors (CC, JS, CA, MB, NS, FL, HM, DS, JA) provided final approval of the manuscript.

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Competing interests: None declared.

Participant consent: All participants provide oral informed consent prior to participating in the study screening interview, and written informed consent prior to study enrollment.

Ethics approval: The Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board.

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The Medical Marijuana and Opioids (MEMO) Study: Protocol of a longitudinal cohort study to examine if medical cannabis reduces opioid use among adults with chronic pain

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The Medical Marijuana and Opioids (MEMO) Study: Protocol of a longitudinal cohort study to examine if medical cannabis reduces opioid use among adults with chronic pain

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ABSTRACT

Introduction

In the United States, opioid analgesic use and overdoses have increased dramatically. One rapidly expanding strategy to manage chronic pain in the context of this epidemic is medical cannabis. Cannabis has analgesic effects, but it also has potential adverse effects. Further, its impact on opioid analgesic use is not well studied. Managing pain in people living with HIV is particularly challenging, given the high prevalence of opioid analgesic and cannabis use. This study's overarching goal is to understand how medical cannabis use affects opioid analgesic use, with attention to Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content, HIV outcomes, and adverse events.

Methods and Analyses

We are conducting a cohort study of 250 adults with and without HIV infection with (a) severe or chronic pain, (b) current opioid use, and (c) who are newly certified for medical cannabis in New York. Over 18 months, we collect data via in-person visits every three months and web-based questionnaires every two weeks. Data sources include: questionnaires; medical, pharmacy, and Prescription Monitoring Program records; urine and blood samples; and physical function tests. Using marginal structural models and comparisons within participants' two-week time periods (unit of analysis), we will examine how medical cannabis use (primary exposure) affects 1) opioid analgesic use (primary outcome), 2) HIV outcomes (HIV viral load, CD4 count, antiretroviral adherence, HIV risk behaviors), and 3) adverse events (cannabis use disorder, illicit drug use, diversion, overdose/deaths, accidents/injuries, acute care utilization).

Ethics and Dissemination

This study is approved by the Montefiore Medical Center/Albert Einstein College of Medicine institutional review board and is registered on ClinicalTrials.gov (NCT03268551). Findings will be disseminated through conferences, peer-reviewed publications, and meetings with medical cannabis stakeholders.

Study registration number: NCT03268551

Strengths and Limitations of the Study:

- This study examines how long-term medical cannabis use affects opioid analgesic use, including products with different Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) content.
- The study also examines how long-term medical cannabis use affects HIV outcomes and adverse events.
- Measurement of cannabis and opioid use will be precise given 39 self-reported measures every two weeks, along with dispensing data from New York's Prescription Monitoring Program.
- Because medical cannabis products dispensed to participants have undergone independent laboratory evaluation, the exact content of these products is known and accurate.
- Because the study design is a longitudinal cohort study, analyses examine changes over time within participants, and biases that could affect outcomes may be unmeasured.

INTRODUCTION

Chronic pain is common among American adults and particularly among people living with HIV.[1-17] To address pain, over the past decades, opioid analgesic use has dramatically increased.[18,19] Subsequently, opioid use disorder and overdose have increased to unprecedented levels.[18, 20, 21] Among people living with HIV, this trend is magnified; as people living with HIV have disproportionately high chronic pain and opioid analgesic use, despite their elevated risk of opioid misuse and use disorder.[6, 14, 22-26] With concerns about opioid analgesic use and guidelines recommending non-opioid therapies, medical cannabis has emerged as an important treatment option.[27] As of November 2020, 35 states and Washington, DC have legalized medical cannabis, with pain as the most common indication.[28]

Cannabis contains more than 60 active cannabinoids; the two most active in cannabinoid receptor activation are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[29] The main psychotropic cannabinoid in cannabis, THC, can produce euphoria or anxiety, along with having an effect on pain and other symptoms.[29] CBD is non-psychoactive and also has analgesic, anti-inflammatory, antioxidant, anticonvulsant, and anxiolytic effects.[29] A combination of THC and CBD may be more effective in treating pain than THC alone, as CBD appears to both potentiate and block particular pharmacologic effects of THC.[30-34]

Numerous short-term randomized controlled trials have demonstrated that compared to placebo, cannabis use reduces pain.[35-49] In 2017, a landmark review found “conclusive or substantial evidence” that cannabis is effective in treating chronic pain.[50] While existing randomized controlled trials provide evidence about the effect of cannabis on pain, they were short-term, and only one included products with different THC/CBD content.[45] Importantly, they did not examine the relationship between cannabis and opioid analgesic use.

Limited evidence from cross-sectional and ecological studies suggests that cannabis use is associated with reduced opioid analgesic use. In several cross-sectional surveys, patients taking medical cannabis reported taking less opioid analgesics after using medical cannabis or substituting it for opioid analgesics.[51-56] In population-level studies through 2013, medical cannabis availability was associated with lower rates of opioid analgesic prescribing and lower rates of fatal opioid overdoses.[57,58] To fully understand the potential implications of medical cannabis legalization on the opioid epidemic, longitudinal studies that focus on patient-level opioid analgesic use are necessary.

Cannabis use is common in people living with HIV and can impact HIV outcomes through a variety of mechanisms.[59-68] Studies examining the relationship between cannabis use and HIV outcomes have had conflicting results in terms of HIV viral load, CD4 count, and antiretroviral adherence.[59,63, 69-78] However, one consistent finding is cannabis’s association with high-risk behaviors for HIV transmission.[62, 79-83] No studies have examined how products with different THC/CBD content affect HIV outcomes.

In addition to potential benefits of cannabis, there is evidence of adverse events.[84] Important potential adverse events are cannabis use disorder, illicit drug use, diversion (selling or sharing medical cannabis), overdose or death, accidents or injuries, and acute health care utilization. Cannabis use is associated with motor vehicle accidents, poor driving performance, injuries, and increased hospitalizations.[84-92] Many studies report these adverse events among individuals using *illicit* cannabis short-term; but, few examine adverse events among those using *medical* cannabis long-term. To our knowledge, no studies have prospectively examined these adverse events after initiating medical cannabis.

Medical cannabis policies differ by state, and New York’s (NY) medical cannabis program is one of the most stringent.[93] To be certified for medical cannabis, individuals must have at least one qualifying condition (cancer, HIV infection or AIDS, amyotrophic lateral sclerosis, Parkinson's disease, multiple sclerosis, spinal cord injury with spasticity, epilepsy, inflammatory bowel disease, neuropathy, Huntington's disease, post-traumatic stress disorder, chronic pain, pain that degrades health and functional capability as an alternative to opioid use, or substance

use disorder) and at least one complication (severe or chronic pain resulting in substantial limitation of function, cachexia or wasting syndrome, severe nausea, seizures, severe or persistent muscle spasms, post-traumatic stress disorder, or opioid use disorder). Medical cannabis products must be purchased from a state-licensed dispensary which have pharmacists on-site, companies must offer products with a variety of THC and CBD content, and all products are tested by an independent lab to confirm content. Dispensaries upload records of all medical cannabis products dispensed to the NY Prescription Monitoring Program (PMP). Despite states' widespread legalized medical cannabis policies, at the federal level, cannabis remains classified as a Schedule 1 substance with "no currently accepted medical use and a high potential for abuse."[94] Because of this classification, federally-funded cannabis research is extremely restricted.[50, 95] From a clinical perspective, physicians cannot prescribe medical cannabis like other medications; they can only certify patients to purchase it. In NY, unless providers recommend a specific dose or type of product, patients can choose THC/CBD content, dose, amount, and route of administration.

Because chronic pain is common and difficult to manage, non-opioid pain management strategies are recommended, and legalized medical cannabis use continues to grow, the goal of our longitudinal cohort study is to improve understanding of how medical cannabis use affects opioid analgesic use over time, with particular attention to THC/CBD content, HIV outcomes, and adverse events. We hypothesize that: 1) Medical cannabis use will be associated with a reduction in opioid analgesic use; 2) The association between medical cannabis and opioid analgesic use will differ by THC/CBD content; 3) HIV outcomes (viral load, CD4 count, antiretroviral adherence, and risk behaviors) will differ by medical cannabis use and THC/CBD content; and 4) More medical cannabis use and higher THC (vs. CBD) content will be associated with more adverse events (cannabis use disorder, illicit drug use, diversion, overdose/death, accidents/injuries, hospitalizations/emergency room visits). Here, we describe the protocol of our longitudinal cohort study to test these hypotheses.

METHODS AND ANALYSES

Settings

Recruitment and study visits occur at Montefiore Medical Center (Montefiore) and four medical cannabis dispensaries. Montefiore is the largest healthcare system in the Bronx, NY with primary, specialty, surgical, and acute care at four hospitals, four emergency rooms, and over 20 clinics. We collaborate with four medical cannabis dispensaries in the New York City (NYC) area, which are operated by Vireo Health and Columbia Care and provide services to over 30,000 patients.

Study Participants

Inclusion criteria are: 1) ≥18 years old, 2) fluency in English or Spanish, 3) new certification for medical cannabis within 90 days, 4) no medical cannabis use in the 6 months prior to certification, 5) medical cannabis qualifying condition of "chronic pain", or "pain that degrades health and functional capability as an alternative to opioid use" or qualifying complication of "severe or chronic pain resulting in substantial limitation of function," and 6) use of prescribed or illicit opioids within 30 days.

Exclusion criteria are: 1) inability to provide informed consent, 2) inability to complete study visits over 18 months, 3) qualifying conditions for medical cannabis in NY that are likely to cause unique pain syndromes (cancer, epilepsy, multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis, Parkinson's disease, inflammatory bowel disease, Huntington's disease), 4) terminal illness, and 5) current or prior psychotic disorder. Inclusion criteria #3-5, and exclusion criterion #3 are from medical or Prescription Monitoring Program data.

Recruitment

Our target enrollment is based on HIV status (target: 62 adults with HIV infection, and 188 adults without HIV infection). On September 14, 2018, we began recruiting participants via: 1) providers at Montefiore and medical cannabis dispensaries informing patients about the study during certification or initial appointments, 2) letters mailed to potential participants who were identified in medical records with new medical cannabis certification, 3) flyers posted in facilities and websites.

Research visits

Participants have seven in-person research visits at 0, 3, 6, 9, 12, 15, 18 months. At the enrollment visit, study staff describe the study and obtain written informed consent. Tracking forms and agreements to release medical, pharmacy, and PMP records are completed. Participants receive a refillable debit card for compensation. At all in-person visits, we administer questionnaires, extract PMP records, and collect urine and blood samples (depending on HIV status). We obtain medical and pharmacy records at 0, 6, 12, and 18 months. Participants receive $40 for in-person research visits (60-90 minutes) and up to $5.50 for transportation costs, which is equivalent to round-trip fare on NYC public transit.

In addition to in-person visits, participants complete 39 brief (2-5 minutes) web-based questionnaires every two weeks. At the baseline visit, participants are trained to access and complete web-based questionnaires on cellphones. If participants have discomfort with or poor access to the internet, they can complete the questionnaires via voice phone calls with study staff. After completing each web-based questionnaire, $5 is deposited into participants' debit card. If all web-based questionnaires are completed between each in-person visit, a $10 bonus is provided.

Data sources and collection

Questionnaires

At all in-person research visits that occur every three months, study staff administer questionnaires using Audio Computer-Assisted Self-Interview (ACASI) technology. The ACASI system displays questions on a computer while playing an audio recording of the question. Participants enter responses onto the computer.

For web-based questionnaires that occur every two weeks, participants receive personalized links to a web-based questionnaire from TelASK Technologies, Inc (Nepean, ON, Canada). Participants choose how (text or email) and when (day of the week and time) to receive automated links. Web-based questionnaires focus on pain, medical and illicit cannabis use, and prescribed and illicit opioid analgesic use during the previous 2 weeks.

Medical record data

We extract medical record data from medical facilities that participants visited 6 months prior to enrollment through 18 months after enrollment. Data include medical cannabis certification forms, lab values, prescriptions, and notes regarding pain treatment.

Pharmacy and Prescription Monitoring Program records

We extract medications dispensed 6 months prior to enrollment through 18 months after enrollment. From pharmacy records, we extract medication data for all HIV medications and all pain medications. From PMP records, we extract medication data for all controlled substances, including medical cannabis and opioid analgesics.

Urine toxicology tests

At all in-person visits, we collect unobserved urine specimens. Urine is tested for cannabinoids, opiates, oxycodone, methadone, buprenorphine, benzodiazepines, and cocaine

using an enzyme immunoassay test (RapidTox8 from American Bio Medica Corporation, Kinderhook, NY, USA).

HIV tests and labs

Among participants with HIV infection, we collect blood every 6 months to measure HIV viral load (Abbott RealTime HIV-1 Assay from Abbott Laboratories, Abbott Park, IL, USA) and CD4 counts (AQUIOS CL flow cytometer from Beckman Coulter Life Sciences, Indianapolis, IN, USA), which are processed at Montefiore's central lab. In addition, at the baseline visit, we offer all participants rapid HIV tests (OraQuick ADVANCE® Rapid HIV-1/2 Antibody Test from OraSure Technologies, Inc., Bethlehem, PA, USA).

Physical function tests

At all in-person visits, participants perform three standardized exercises—Ten Meter Walk Test,[96-99] Chair Stand Test,[100, 101] and Fingertip to Floor Test.[102] With the Ten Meter Walk Test, we record the amount of time it takes participants to walk ten meters two times, with the assistance of any device (e.g., walking cane) that the participant normally uses. With the Chair Stand Test, over a 30-second period, we record the number of times that participants are able to stand from a seated position. For the Fingertip to Floor Test, after participants bend over from a standing position towards the floor, we measure the distance between participants' fingertips and floor. All are reliable, valid, and responsive measures of physical function in patients with chronic pain conditions including low back pain, arthritis, and neuropathy and are simple to administer in a clinical setting.[103]

Key variables

Main exposure variable

Our main exposure variable is medical cannabis use and is measured by combining PMP and questionnaire data. PMP data include: date, product (which specifies THC/CBD content), dose, formulation, route, directions, amount dispensed, and dispensary. Web-based questionnaires inquire about both *medical* and *illicit* cannabis use for every 2-week period. For *medical* cannabis use, participants are asked: number of days used, medical cannabis product (which specifies THC/CBD content and formulation), route, and amount used on a typical day. For *illicit* cannabis use, participants are asked: number of days used, dollar amount of cannabis purchased, route, type of cannabis, and amount used on a typical day.

For each of the 39 2-week periods, our primary measure of exposure to medical cannabis is number of days of *medical* cannabis use. Alternate measures are number of days of *medical and illicit* cannabis use, cumulative dose of THC, and cumulative dose of CBD.

Primary outcome variable

Opioid analgesic use is the primary outcome and is measured by combining prescribed and illicit opioid analgesic use from the PMP and web-based questionnaires. Our primary measure of opioid analgesic use is cumulative dose of all opioid analgesics over each of the 39 2-week periods (in morphine milligram equivalents [MME]). Alternative measures are number of days of all opioid analgesic use, mean daily dose (in MME) of all opioid analgesics, and number of days of only prescribed (not illicit) opioid analgesics (all continuous measures).

Secondary outcome variables

HIV outcomes are examined in the subgroup of participants with HIV infection. Viral load is the main HIV outcome, and the primary measure is log10 copies/ml. CD4 count is analyzed as cells/mm3. Viral load and CD4 count are measured from study blood samples every 6 months. Antiretroviral adherence is analyzed using the proportion of days in which antiretroviral

medications are filled (pharmacy records) and self-reported adherence.[104, 105] HIV risk behaviors are measured using the HIV Risk-taking Behavior Scale.[106-108]

Several adverse events are secondary outcomes. Cannabis use disorder is assessed using the Mini-International Neuropsychiatric Interview.[109] Illicit drug use is measured using the Addiction Severity Index[110] and urine toxicology tests. Diversion of medical cannabis is measured using a modified version of the Massachusetts General Hospital Medication Questionnaire.[111] Nonfatal overdose is measured using items on the Addiction Severity Index; death is ascertained from the National Death Index. Accidents/injuries are measured using questions from national surveys in the United States and Canada.[112, 113] Acute health care utilization (hospitalizations and emergency room visits) are self-reported using the National Institute on Drug Abuse data harmonization instrument.

Other key variables

Other key variables that are potential confounders include sociodemographic characteristics, pain severity and interference,[114] pain catrastrophizing,[115] pain-related function and disability,[116] pain treatment, alcohol use,[117] tobacco use,[118] other substance use,[110] symptoms of depression,[119] anxiety,[120] post-traumatic stress disorder,[121, 122] attention deficit hyperactivity disorder,[123] insomnia,[124] physical functional tests, and quality of life.[125]

Data Analyses

Participants' 39 assessments for each 2-week time period is the unit of analysis. We will determine the association between medical cannabis use (exposure) and opioid analgesic use (outcome) using marginal structural models. Marginal structural models are necessary because they can account for time-varying confounding (i.e., variables that are both predictors of the subsequent outcome and subsequent exposure).[126, 127] Consistent with the steps of marginal structural models, we will first calculate inverse probability-of-exposure weights for each participant's 2-week time period. Calculation of these weights is based on the predicted probability of the exposure in each of the 39 2-week time periods, given time-invariant and time-varying confounders. After calculation of weights, we will create the main marginal structural model--a linear generalized estimating equations model for repeated measures on a natural logarithm scale, incorporating weights, accounting for clustering within participants, and estimating robust standard errors.[126]

In our main analysis, we will examine whether medical cannabis use is associated with reductions in opioid analgesic use. We will also conduct sensitivity analyses to determine robustness of our findings to different specifications of the weighting model.[128] We will also conduct simulation analyses to determine the robustness of our findings to potential unmeasured confounders.[129] Finally, we will repeat our model-building processes using alternative measures of medical cannabis and opioid analgesic use as described above.

In one set of secondary analyses, we will determine the association between THC and CBD and opioid analgesic use, using similar marginal structural models as described above. However, in one model, the exposure will be cumulative dose of THC in each 2-week period, and in the other model the exposure will be cumulative dose of CBD in each 2-week period. To determine the effects of cumulative THC and CBD dose together, we will use a joint marginal structural model.[130, 131] We will multiply the estimated stabilized weights for THC by the estimated stabilized weights for CBD to produce a joint weight. To analyze this, we will visually plot combinations of cumulative THC and CBD doses and the expected change in cumulative opioid analgesic dose, accounting for the interaction between THC and CBD.

In the second set of secondary analyses, we will examine the effect of medical cannabis use, THC content, and CBD content use on HIV outcomes (viral load, CD4 count, antiretroviral adherence, risk behaviors). Because time-dependent confounding is not a problem for HIV

outcomes, we will use standard mixed effects regression models with generalized estimating equations, with a working first-order autoregressive covariance matrix and robust estimates of variance. Because HIV viral load will be measured every 6 months, a 6-month time period is the unit of analysis.

In the third set of secondary analyses, we will examine the effect of medical cannabis use, THC content, and CBD content on adverse events (cannabis use disorder, illicit drug use, diversion of medical cannabis, overdose/death, accidents/injuries, and hospitalizations and emergency room visits). Depending on whether the adverse event is dichotomous (e.g., cannabis use disorder) or continuous (e.g., number of hospitalizations), we will use similar marginal structural models as described above using separate logistic or linear marginal structural models for each adverse event.

Sample size

We estimated the sample size needed to detect a 0.5% change in cumulative opioid analgesic dose with one additional day of medical cannabis. We chose this value because 14 days of medical cannabis use would then be associated with a 7% change in cumulative opioid analgesic dose over 2 weeks. This degree of dosage reduction is within the range of what is considered clinically meaningful.[27] To estimate our sample size, we used linear mixed effects models with simulations repeated 1000 times. Accounting for 20% attrition, 250 is the target sample size, as a sample size of 200 can detect associations between medical cannabis use and the outcome greater than 90% of the time. We selected a sample size with a higher power than typically chosen to ensure sufficient sample for the marginal structural model which includes several variables representing time-dependent confounding.

For HIV outcomes, we calculated power based on log10 viral load (main HIV outcome). With viral load measured every 6 months and a sample of 50 HIV+ participants, we would have greater than 99% power to detect a change of 0.5 log10 viral load. With 20% attrition, we will enroll 62 HIV+ participants. For adverse events, we calculated power based on illicit drug use as the main outcome measure (continuous measure from the Addiction Severity Index alcohol/drug subscale). A sample size of 200 participants would have greater than 99% power to detect a 5% change in the continuous subscale measure.

Timeline and monitoring

We began enrolling participants on September 14, 2018. We anticipate that enrollment will be completed by December 31, 2021, and study visits will conclude on June 30, 2023. The principal investigator oversees data and safety monitoring, including review of protocol deviations and submission of annual reports to the affiliated institutional review board and funder (National Institute of Health). Because the study is observational and therefore minimal risk, we did not establish a formal data and safety monitoring board, nor will we conduct interim analyses with stopping rules.

Limitations

As a longitudinal cohort study, this study has limitations. Because of federal cannabis policies in the United States, cannabis is extremely restricted in federal research. Therefore, it is not feasible to use a randomized controlled trial design and administer cannabis to 250 participants over 18 months. By using advanced analytical methods that exploit variation in medical cannabis products and patterns of use, we will estimate the impact of medical cannabis use on opioid analgesic use. While our study design and analytic approach will improve our understanding of how medical cannabis use affects opioid analgesic use, we will be unable to account for all potential biases, and we are limited to conducting analyses within, instead of between, participants. In addition, because adults with HIV infection may have unique pain conditions, to determine if including participants with HIV infection in the sample leads to

differences in findings, we will conduct two sets of main analyses—one including participants with HIV infection, and one excluding participants with HIV infection. While our study will examine a range of potential adverse events from medical cannabis use, it does not examine all potential adverse events, including neurocognitive changes. Finally, because opioid prescribing in the United States has decreased over the past several years,[132] it is possible that further decreases in opioid prescribing may make it difficult to interpret the relationship between medical cannabis and opioid use.

Patient and public involvement

The design of this study was informed by clinical experiences of several of the authors, along with our prior study examining potential interest in participating in a medical cannabis research study among adults receiving medical cannabis.[133] The research questions and design were reviewed by physician-investigators at Montefiore Medical Center/Albert Einstein College of Medicine who have expertise in substance use and infectious diseases, along with chief medical officers of two medical cannabis companies. In addition, the research questions and design were reviewed by a study section at the National Institute of Health.

Ethics and dissemination

This study was approved by the Montefiore Medical Center/Albert Einstein College of Medicine institutional review board (IRB protocol number: 2017-7857). Oral informed consent is obtained prior to conducting screening questionnaires, and written informed consent is obtained at the time of enrollment into the study. Several steps are taken to protect participant confidentiality, including using a data management system that separates “name-based” and “Study ID-based” documents, obtaining a Certificate of Confidentiality from the National Institute of Health, and using a two-step verification process to access the study database.

We will disseminate study findings through presentations at scientific conferences, publications in peer-reviewed journals, and presentations to medical cannabis stakeholders. Study findings will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[134]

Authors’ contributions: CC is the Principal Investigator of this study and led its conception and design. JS, CZ, MB, NS, FL, HM, JA made substantial contributions to the conception and design of the study. CC drafted the manuscript, and all authors revised it for critically important content (CC, JS, CA, MB, NS, FL, HM, DS, JA). All authors (CC, JS, CA, MB, NS, FL, HM, DS, JA) provided final approval of the manuscript.

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Competing interests: None declared.

Participant consent: All participants provide oral informed consent prior to participating in the study screening interview, and written informed consent prior to study enrollment.

Ethics approval: The Montefiore Medical Center/Albert Einstein College of Medicine Institutional Review Board.

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