BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043400
Article Type:	Protocol
Date Submitted by the Author:	03-Aug-2020
Complete List of Authors:	Cunningham, Chinazo; Montefiore Health System, Division of General Internal Medicine Starrels, Joanna; Montefiore Health System, Division of General Internal Medicine Zhang, Chenshu; Montefiore Health System, Division of General Internal Medicine Bachhuber, Marcus; Louisiana State University Health Sciences Center Sohler, Nancy ; City University of New York, School of Medicine Levin, Franes; Columbia University Department of Psychiatry, Minami, Haruka; Fordham University Slawek, Deepika; Montefiore Health System, Division of General Internal Medicine Arnsten, Julia; Montefiore Health System, Division of General Internal Medicine
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, Substance misuse < PSYCHIATRY, PAIN MANAGEMENT

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

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

Chinazo O. Cunningham[1], Joanna L. Starrels[1], Chenshu Zhang[1], Marcus A. Bachhuber[2], Nancy L. Sohler[3], Frances R. Levin[4], Haruka Minami[5], Deepika E. Slawek[1], Julia H. Arnsten [1]

[1]Department of Medicine, Montefiore Health System & Albert Einstein College of Medicine, Bronx, NY, USA
[2]Department of Medicine, Louisiana State University Health Sciences Center – New Orleans, New Orleans, LA, USA
[3]Department of Community Health and Social Medicine, City University of New York School of Medicine, City College of New York, New York, NY, USA
[4]Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, and the New York State Psychiatric Institute, New York, NY, USA
[5]Department of Psychology, Fordham University, Bronx, NY, USA

Corresponding author:
Chinazo O. Cunningham, MD, MS
111 E. 210th Street
Bronx, NY 10467
USA
Phone: 718-920-5971
Email: chinazo.cunningham@einsteinmed.org

Key words: cannabis, marijuana, opioids, chronic pain, HIV

Word count: 3570

For peer review only

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.

For peer review only

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

For peer review only

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

For peer review only

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

For peer review only

(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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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.

For peer review only

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.

Funding: This study is supported by the National Institute on Drug Abuse of the National Institute of Health (R01DA044171). CC and JS are also supported by the National Institute on Drug Abuse (K24DA036955, K24DA046309). CC and JA are also supported by the National Institute of Allergy and Infectious Diseases of the National Institute of Health (P30AI124414).

Disclaimer: The content is solely the responsibility of the authors and does not represent the official views of the National Institute of Health. The funding agency has no role in design or conduct of the study, or the decision to publish study results.

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.

For peer review only

References

1. Johannes CB, Le TK, Zhou X, et al. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *The journal of pain : official journal of the American Pain Society* 2010;11(11):1230-9. doi: 10.1016/j.jpain.2010.07.002 [published Online First: 2010/08/28]
2. Breitbart W, Dibiase L. Current perspectives on pain in AIDS. *Oncology (WillistonPark)* 2002;16(7):964-8, 72.
3. Hewitt DJ, McDonald M, Portenoy RK, et al. Pain syndromes and etiologies in ambulatory AIDS patients. *Pain* 1997;70(2-3):117-23.
4. Perry BA, Westfall AO, Molony E, et al. Characteristics of an ambulatory palliative care clinic for HIV-infected patients. *J Palliat Med* 2013;16(8):934-37.
5. Koeppe J, Lyda K, Armon C. Association Between Opioid Use and Health Care Utilization as Measured by Emergency Room Visits and Hospitalizations Among Persons Living With HIV. *Clin J Pain* 2013;29(11):957-61.
6. Tsao JC, Dobalian A, Naliboff BD. Panic disorder and pain in a national sample of persons living with HIV. *Pain* 2004;109(1-2):172-80.
7. Larue F, Fontaine A, Colleau SM. Underestimation and undertreatment of pain in HIV disease: multicentre study. *BMJ* 1997;314(7073):23-28.
8. Frich LM, Borgbjerg FM. Pain and pain treatment in AIDS patients: a longitudinal study. *J Pain Symptom Manage* 2000;19(5):339-47.
9. Tsao JC, Stein JA, Dobalian A. Pain, problem drug use history, and aberrant analgesic use behaviors in persons living with HIV. *Pain* 2007;133(1-3):128-37.
10. Dobalian A, Tsao JC, Duncan RP. Pain and the use of outpatient services among persons with HIV: results from a nationally representative survey. *Med Care* 2004;42(2):129-38.
11. Tsao JC, Plankey MW, Young MA. Pain, psychological symptoms and prescription drug misuse in HIV: A literature review. *J Pain Manag* 2012;5(2):111-18.
12. Breitbart W, McDonald MV, Rosenfeld B, et al. Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. *Pain* 1996;68(2-3):315-21.
13. Kimball LR, McCormick WC. The pharmacologic management of pain and discomfort in persons with AIDS near the end of life: use of opioid analgesia in the hospice setting. *J Pain Symptom Manage* 1996;11(2):88-94.
14. Edelman EJ, Gordon K, Becker WC, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. *J Gen Intern Med* 2013;28(1):82-90.
15. Simmonds MJ, Novy D, Sandoval R. The differential influence of pain and fatigue on physical performance and health status in ambulatory patients with human immunodeficiency virus. *Clin J Pain* 2005;21(3):200-06.
16. Singer EJ, Zorilla C, Fahy-Chandon B, et al. Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study. *Pain* 1993;54(1):15-19.
17. Merlin JS, Westfall AO, Raper JL, et al. Pain, mood, and substance abuse in HIV: implications for clinic visit utilization, antiretroviral therapy adherence, and virologic failure. *J Acquir Immune Defic Syndr* 2012;61(2):164-70.
18. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb Mortal Wkly Rep* 2011;60(43):1487-92. doi: mm6043a4 [pii]
19. Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. *Open medicine : a peer-reviewed, independent, open-access journal* 2012;6(2):e41-7. [published Online First: 2012/01/01]
20. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain physician* 2014;17(2):E119-28. [published Online First: 2014/03/25]

For peer review only

21. Modarai F, Mack K, Hicks P, et al. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug Alcohol Depend* 2013;132(1-2):81-86. doi: S0376-8716(13)00018-5 [pii];10.1016/j.drugalcdep.2013.01.006 [doi]
22. Silverberg MJ, Ray GT, Saunders K, et al. Prescription long-term opioid use in HIV-infected patients. *Clin J Pain* 2012;28(1):39-46.
23. Tsao JC, Dobalian A, Moreau C, et al. Stability of anxiety and depression in a national sample of adults with human immunodeficiency virus. *J Nerv Ment Dis* 2004;192(2):111-18.
24. Koeppe J, Armon C, Lyda K, et al. Ongoing pain despite aggressive opioid pain management among persons with HIV. *Clin J Pain* 2010;26(3):190-98.
25. Vitiello B, Burnam MA, Bing EG, et al. Use of psychotropic medications among HIV-infected patients in the United States. *Am J Psychiatry* 2003;160(3):547-54.
26. Jeevanjee S, Penko J, Guzman D, et al. Opioid Analgesic Misuse is Associated with Incomplete Antiretroviral Adherence in a Cohort of HIV-Infected Indigent Adults in San Francisco. *AIDS Behav* 2013
27. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* 2016;65(1):1-49. doi: 10.15585/mmwr.rr6501e1 [published Online First: 2016/03/18]
28. ProCon.org. 28 Legal Medical Marijuana States and DC 06/28/2016 [Available from: http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881 accessed 1/15/2017].
29. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacol Rev* 2010;62(4):588-631. doi: 10.1124/pr.110.003004 [published Online First: 2010/11/17]
30. Hayakawa K, Mishima K, Hazekawa M, et al. Cannabidiol potentiates pharmacological effects of Delta(9)-tetrahydrocannabinol via CB(1) receptor-dependent mechanism. *Brain research* 2008;1188:157-64. doi: 10.1016/j.brainres.2007.09.090 [published Online First: 2007/11/21]
31. Varvel SA, Wiley JL, Yang R, et al. Interactions between THC and cannabidiol in mouse models of cannabinoid activity. *Psychopharmacology (Berl)* 2006;186(2):226-34. doi: 10.1007/s00213-006-0356-9 [published Online First: 2006/03/31]
32. Karniol IG, Shirakawa I, Kasinski N, et al. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol* 1974;28(1):172-7. [published Online First: 1974/09/01]
33. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010;39(2):167-79. doi: 10.1016/j.jpainsymman.2009.06.008 [published Online First: 2009/11/10]
34. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006;66(2):234-46. doi: 10.1016/j.mehy.2005.08.026 [published Online First: 2005/10/08]
35. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* 2015;313(24):2456-73. doi: 10.1001/jama.2015.6358 [published Online First: 2015/06/24]
36. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology* 2009;34(3):672-80. doi: 10.1038/npp.2008.120 [published Online First: 2008/08/09]

For peer review only

37. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007;133(1-3):210-20. doi: 10.1016/j.pain.2007.08.028 [published Online First: 2007/11/13]
38. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* 2007;68(7):515-21. doi: 10.1212/01.wnl.0000253187.66183.9c [published Online First: 2007/02/14]
39. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008;9(6):506-21. doi: 10.1016/j.jpain.2007.12.010 [published Online First: 2008/04/12]
40. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008;9(2):164-73. doi: 10.1016/j.jpain.2007.09.002 [published Online First: 2007/11/03]
41. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008;9(3):254-64. doi: 10.1016/j.jpain.2007.10.018 [published Online First: 2007/12/20]
42. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. *J Neurol* 2006;253(10):1337-41. doi: 10.1007/s00415-006-0218-8 [published Online First: 2006/09/22]
43. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford, England)* 2006;45(1):50-2. doi: 10.1093/rheumatology/kei183 [published Online First: 2005/11/12]
44. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA* 2015;313(24):2474-83. doi: 10.1001/jama.2015.6199 [published Online First: 2015/06/24]
45. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004;112(3):299-306. doi: 10.1016/j.pain.2004.09.013 [published Online First: 2004/11/25]
46. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. *J Pain* 2015;16(12):1221-32. doi: 10.1016/j.jpain.2015.07.009 [published Online First: 2015/09/13]
47. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003;290(13):1757-62. doi: 10.1001/jama.290.13.1757 [published Online First: 2003/10/02]
48. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-6739-4 [published Online First: 2012/11/28]
49. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65(6):812-9. doi: 10.1212/01.wnl.0000176753.45410.8b [published Online First: 2005/09/28]
50. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.

For peer review only

51. Grella CE, Rodriguez L, Kim T. Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in los angeles. *J Psychoactive Drugs* 2014;46(4):267-75. doi: 10.1080/02791072.2014.944960 [doi]
52. Reiman A. Cannabis as a substitute for alcohol and other drugs. *Harm Reduct J* 2009;6:35. doi: 1477-7517-6-35 [pii];10.1186/1477-7517-6-35 [doi]
53. Nunberg H, Kilmer B, Pacula RL, et al. An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California. *J Drug Policy Anal* 2011;4(1) doi: 10.2202/1941-2851.1017 [doi]
54. Zaller N, Topletz A, Frater S, et al. Profiles of medicinal cannabis patients attending compassion centers in rhode island. *J Psychoactive Drugs* 2015;47(1):18-23. doi: 10.1080/02791072.2014.999901 [doi]
55. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain* 2016;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002 [published Online First: 2016/03/24]
56. Sohler NL, Khalid L, Starrels JO, et al. Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain. *Subst Use Misuse.* 2018 Aug 24;53(10):1602-1607. doi: 10.1080/10826084.2017.1416408. Epub 2018 Jan
57. Bachhuber MA, Saloner B, Cunningham CO, et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med* 2014;174(10):1668-73.
58. Bachhuber MA, Saloner B, Cunningham CO, et al. Could Delaware's medical marijuana law reduce harms from opioid analgesics? *Del Med J* 2014;86(11):341-43.
59. D'Souza G, Matson PA, Grady CD, et al. Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Study (WIHS) cohort, 1994-2010. *J Acquir Immune Defic Syndr* 2012;61(5):618-26. doi: 10.1097/QAI.0b013e318273ab3a [published Online First: 2012/09/27]
60. Bruce D, Harper GW, Fernandez MI. Heavy marijuana use among gay and bisexual male emerging adults living with HIV/AIDS. *J HIV AIDS Soc Serv* 2013;12(1):26-48. doi: 10.1080/15381501.2012.735171 [published Online First: 2013/06/28]
61. Prentiss D, Power R, Balmas G, et al. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr* 2004;35(1):38-45. [published Online First: 2004/01/07]
62. Mimiaga MJ, Reisner SL, Grasso C, et al. Substance use among HIV-infected patients engaged in primary care in the United States: findings from the Centers for AIDS Research Network of Integrated Clinical Systems cohort. *Am J Public Health* 2013;103(8):1457-67. doi: 10.2105/ajph.2012.301162 [published Online First: 2013/06/15]
63. Furler MD, Einarson TR, Millson M, et al. Medicinal and recreational marijuana use by patients infected with HIV. *AIDS Patient Care STDs* 2004;18(4):215-28. doi: 10.1089/108729104323038892 [published Online First: 2004/05/15]
64. Okafor CN, Cook RL, Chen X, et al. Trajectories of Marijuana Use among HIV-seropositive and HIV-seronegative MSM in the Multicenter AIDS Cohort Study (MACS), 1984-2013. *AIDS Behav* 2016 doi: 10.1007/s10461-016-1445-3 [published Online First: 2016/06/05]
65. Ompad DC, Giobazolia TT, Barton SC, et al. Drug use among HIV+ adults aged 50 and older: findings from the GOLD II study. *AIDS Care* 2016;28(11):1373-7. doi: 10.1080/09540121.2016.1178704 [published Online First: 2016/05/05]
66. Friedman H, Klein TW, Newton C, et al. Marijuana, receptors and immunomodulation. *Adv Exp Med Biol* 1995;373:103-13. [published Online First: 1995/01/01]

67. Nahas GG, Suciu-Foca N, Armand JP, et al. Inhibition of cellular mediated immunity in marihuana smokers. *Science* 1974;183(4123):419-20. [published Online First: 1974/02/01]
68. Hollister LE. Marijuana and immunity. *J Psychoactive Drugs* 1992;24(2):159-64. doi: 10.1080/02791072.1992.10471635 [published Online First: 1992/04/01]
69. Milloy MJ, Marshall B, Kerr T, et al. High-intensity cannabis use associated with lower plasma human immunodeficiency virus-1 RNA viral load among recently infected people who use injection drugs. *Drug Alcohol Rev* 2015;34(2):135-40. doi: 10.1111/dar.12223 [published Online First: 2014/11/13]
70. Ghosn J, Leruez-Ville M, Blanche J, et al. HIV-1 DNA levels in peripheral blood mononuclear cells and cannabis use are associated with intermittent HIV shedding in semen of men who have sex with men on successful antiretroviral regimens. *Clin Infect Dis* 2014;58(12):1763-70. doi: 10.1093/cid/ciu187 [published Online First: 2014/03/22]
71. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Annals Int Med* 2003;139(4):258-66. [published Online First: 2003/09/11]
72. Bredt BM, Higuera-Alhino D, Shade SB, et al. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J Clin Pharmacol* 2002;42(11 Suppl):82s-89s. [published Online First: 2002/11/05]
73. Harris GE, Dupuis L, Mugford GJ, et al. Patterns and correlates of cannabis use among individuals with HIV/AIDS in Maritime Canada. *Can J Infect Dis Med Microbiol* 2014;25(1):e1-7. [published Online First: 2014/03/19]
74. Slawson G, Milloy MJ, Balneaves L, et al. High-intensity cannabis use and adherence to antiretroviral therapy among people who use illicit drugs in a Canadian setting. *AIDS Behav* 2015;19(1):120-7. doi: 10.1007/s10461-014-0847-3 [published Online First: 2014/07/12]
75. de Jong BC, Prentiss D, McFarland W, et al. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *J Acquir Immune Defic Syndr* 2005;38(1):43-6. [published Online First: 2004/12/21]
76. Bonn-Miller MO, Oser ML, Bucossi MM, et al. Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. *J Behav Med* 2014;37(1):1-10. doi: 10.1007/s10865-012-9458-5 [published Online First: 2012/10/12]
77. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med* 2003;114(7):573-80.
78. Wilson KJ, Doxanakis A, Fairley CK. Predictors for non-adherence to antiretroviral therapy. *Sex Health* 2004;1(4):251-7. [published Online First: 2005/12/13]
79. Morgan E, Skaathun B, Michaels S, et al. Marijuana Use as a Sex-Drug is Associated with HIV Risk Among Black MSM and Their Network. *AIDS Behav* 2016;20(3):600-7. doi: 10.1007/s10461-015-1195-7 [published Online First: 2015/09/25]
80. Kelly JA, St Lawrence JS, Tarima SS, et al. Correlates of Sexual HIV Risk Among African American Men Who Have Sex With Men. *Amer J Public Health* 2016;106(1):96-102. doi: 10.2105/ajph.2015.302945 [published Online First: 2015/11/13]
81. Scivoletto S, Tsuji RK, Abdo C, et al. Use of psychoactive substances and sexual risk behavior in adolescents. *Subst Use Misuse* 2002;37(3):381-98. [published Online First: 2002/03/27]
82. Bellis MA, Hughes K, Calafat A, et al. Sexual uses of alcohol and drugs and the associated health risks: a cross sectional study of young people in nine European cities. *BMC Public Health* 2008;8:155. doi: 10.1186/1471-2458-8-155 [published Online First: 2008/05/13]

For peer review only

83. Brodbeck J, Matter M, Moggi F. Association between cannabis use and sexual risk behavior among young heterosexual adults. *AIDS Behav* 2006;10(5):599-605. doi: 10.1007/s10461-006-9103-9 [published Online First: 2006/05/13]
84. Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. *NEJM* 2014;370(23):2219-27. doi: 10.1056/NEJMra1402309 [published Online First: 2014/06/05]
85. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem* 2013;59(3):478-92. doi: 10.1373/clinchem.2012.194381 [published Online First: 2012/12/12]
86. Asbridge M, Poulin C, Donato A. Motor vehicle collision risk and driving under the influence of cannabis: evidence from adolescents in Atlantic Canada. *Accid Anal Prev* 2005;37(6):1025-34. doi: 10.1016/j.aap.2005.05.006 [published Online First: 2005/07/05]
87. Li MC, Brady JE, DiMaggio CJ, et al. Marijuana use and motor vehicle crashes. *Epidemiol Rev* 2012;34:65-72. doi: 10.1093/epirev/mxr017 [published Online First: 2011/10/07]
88. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ* 2012;344:e536. doi: 10.1136/bmj.e536 [published Online First: 2012/02/11]
89. Barrio G, Jimenez-Mejias E, Pulido J, et al. Association between cannabis use and non-traffic injuries. *Accid Anal Prev* 2012;47:172-6. doi: 10.1016/j.aap.2012.01.002 [published Online First: 2012/03/13]
90. Patel R, Wilson R, Jackson R, et al. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. *BMJ Open* 2016;6(3):e009888. doi: 10.1136/bmjopen-2015-009888 [published Online First: 2016/03/05]
91. Moore CL, Gidding HF, Jin F, et al. Patterns of Drug Use and Drug-related Hospital Admissions in HIV-Positive and -Negative Gay and Bisexual Men. *AIDS Behav* 2016;20(10):2372-86. doi: 10.1007/s10461-016-1303-3 [published Online First: 2016/02/04]
92. Jouanjus E, Pourcel L, Saivin S, et al. Use of multiple sources and capture-recapture method to estimate the frequency of hospitalizations related to drug abuse. *Pharmacoepidemiol Drug Saf* 2012;21(7):733-41. doi: 10.1002/pds.3280 [published Online First: 2012/05/03]
93. New York State Department of Health. New York State Medical Marijuana Program, 2016. [Available from https://www.health.ny.gov/regulations/medical_marijuana/ accessed on 7/30/20].
94. United States Drug Enforcement Administration. Drug Schedules [Available from: https://www.dea.gov/druginfo/ds.shtml accessed 1/20/17].
95. Nutt DJ, King LA, Nichols DE. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat Rev Neurosci* 2013;14(8):577-85. doi: 10.1038/nrn3530 [published Online First: 2013/06/13]
96. Wolf SL, Catlin PA, Gage K, et al. Establishing the reliability and validity of measurements of walking time using the Emory Functional Ambulation Profile. *Phys Ther* 1999;79(12):1122-33. [published Online First: 2000/01/12]
97. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Aging* 1997;26(1):15-9. [published Online First: 1997/01/01]
98. Bohannon RW, Andrews AW, Thomas MW. Walking speed: reference values and correlates for older adults. *J Orthop Sports Phys Ther* 1996;24(2):86-90. doi: 10.2519/jospt.1996.24.2.86 [published Online First: 1996/08/01]

For peer review only

99. Bohannon RW, Williams Andrews A. Normal walking speed: a descriptive meta-analysis. *Physiotherapy* 2011;97(3):182-9. doi: 10.1016/j.physio.2010.12.004 [published Online First: 2011/08/09]
100. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70(2):113-9. doi: 10.1080/02701367.1999.10608028 [published Online First: 1999/06/25]
101. Gill SD, de Morton NA, Mc Burney H. An investigation of the validity of six measures of physical function in people awaiting joint replacement surgery of the hip or knee. *Clin Rehabil* 2012;26(10):945-51. doi: 10.1177/0269215511434993 [published Online First: 2012/02/11]
102. Perret C, Poiraudeau S, Fermanian J, et al. Validity, reliability, and responsiveness of the fingertip-to-floor test. *Arch Phys Med Rehabil* 2001;82(11):1566-70. doi: 10.1053/apmr.2001.26064 [published Online First: 2001/11/02]
103. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. *Arthritis Care Res* 2011;63 Suppl 11:S350-70. doi: 10.1002/acr.20538 [published Online First: 2012/05/25]
104. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care* 2000;12(3):255-66.
105. Berg KM, Wilson IB, Li X, et al. Comparison of antiretroviral adherence questions. *AIDS Behav* 2012;16(2):461-68.
106. Darke S, Hall W, Heather N, et al. The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS* 1991;5(2):181-85.
107. Knight KR, Shade SB, Purcell DW, et al. Sexual transmission risk behavior reported among behaviorally bisexual HIV-positive injection drug-using men. *J Acquir Immune Defic Syndr* 2007;46 Suppl 2:S80-7. doi: 10.1097/QAI.0b013e3181576828
108. Purcell DW, Parsons JT, Halkitis PN, et al. Substance use and sexual transmission risk behavior of HIV-positive men who have sex with men. *J Subst Abuse* 2001;13(1-2):185-200.
109. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The J Clin Psychiatry* 1998;59 Suppl 20:22-33;quiz 34-57. [published Online First: 1999/01/09]
110. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat* 1992;9(3):199-213.
111. Winhusen TM, Lewis DF, Riggs PD, et al. Subjective effects, misuse, and adverse effects of osmotic-release methylphenidate treatment in adolescent substance abusers with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2011;21(5):455-63. doi: 10.1089/cap.2011.0014 [published Online First: 2011/11/02]
112. Prevention NCfHSCfDCa. National Health Interview Survey, CAPI Manual for NHIS Field representatives. .
113. Poulin C, MacNeil P, Mitic W. The validity of a province-wide student drug use survey: lessons in design. *Can J Public Health* 1993;84(4):259-64. [published Online First: 1993/07/01]
114. Keller S, Bann CM, Dodd SL, et al. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 2004;20(5):309-18.

For peer review only

115. Sullivan MJLB, S.R.; Pivik, J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7(4):524-32.
116. Stroud MW, McKnight PE, Jensen MP. Assessment of self-reported physical activity in patients with chronic pain: development of an abbreviated Roland-Morris disability scale. *J Pain* 2004;5(5):257-63.
117. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* 1993;88(6):791-804.
118. Commerce USDo. Census Bureau (2016). National Cancer Institute and Food and Drug Administration co-sponsored Tobacco Use Supplement to the Current Population Survey. 2014-15. https://cancercontrol.cancer.gov/brp/tcrb/tus-cps/.
119. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Int Med* 2001;16(9):606-13. [published Online First: 2001/09/15]
120. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Int Med* 2006;166(10):1092-7. doi: 10.1001/archinte.166.10.1092 [published Online First: 2006/05/24]
121. Lang AJ, Stein MB. An abbreviated PTSD checklist for use as a screening instrument in primary care. *Behav Res Ther* 2005;43(5):585-94. doi: 10.1016/j.brat.2004.04.005 [published Online First: 2005/05/04]
122. Lang AJ, Laffaye C, Satz LE, et al. Sensitivity and specificity of the PTSD checklist in detecting PTSD in female veterans in primary care. *J Trauma Stress* 2003;16(3):257-64. doi: 10.1023/a:1023796007788 [published Online First: 2003/06/21]
123. Ustun B, Adler LA, Rudin C, et al. The World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5. *JAMA Psychiatry* 2017;74(5):520-26. doi: 10.1001/jamapsychiatry.2017.0298 [published Online First: 2017/04/07]
124. Morin CM, Belleville G, Bélanger L, et al. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34(5):601-8. doi: 10.1093/sleep/34.5.601 [published Online First: 2011/05/03]
125. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208. [published Online First: 1990/11/05]
126. Hernan MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med* 2002;21(12):1689-709. doi: 10.1002/sim.1144
127. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-60.
128. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168(6):656-64. doi: 10.1093/aje/kwn164
129. Brumback BA, Hernan MA, Haneuse SJ, et al. Sensitivity analyses for unmeasured confounding assuming a marginal structural model for repeated measures. *Stat Med* 2004;23(5):749-67. doi: 10.1002/sim.1657
130. Banack HR, Kaufman JS. Estimating the Time-Varying Joint Effects of Obesity and Smoking on All-Cause Mortality Using Marginal Structural Models. *Am J Epidemiol* 2016;183(2):122-9. doi: 10.1093/aje/kwv168 [published Online First: 2015/12/15]
131. Howe CJ, Cole SR, Mehta SH, et al. Estimating the effects of multiple time-varying exposures using joint marginal structural models: alcohol consumption, injection drug use, and HIV acquisition. *Epidemiology* 2012;23(4):574-82. doi: 10.1097/EDE.0b013e31824d1ccb
132. Bachhuber MA, Arnsten JH, Starrels JL, et al. Willingness to Participate in Longitudinal Research Among People with Chronic Pain Who Take Medical Cannabis: A Cross-Sectional Survey. Cannabis Cannabinoid Res. 2018 Mar 1;3(1):45-53.

For peer review only

133. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12(12):1500-24. doi: 10.1016/j.ijsu.2014.07.014 [published Online First: 2014/07/22]

For peer review only

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043400.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Oct-2020
Complete List of Authors:	Cunningham, Chinazo; Montefiore Health System, Division of General Internal Medicine Starrels, Joanna; Montefiore Health System, Division of General Internal Medicine Zhang, Chenshu; Montefiore Health System, Division of General Internal Medicine Bachhuber, Marcus; Louisiana State University Health Sciences Center Sohler, Nancy ; City University of New York, School of Medicine Levin, Frances; Columbia University Irving Medical Center, Department of Psychiatry Minami, Haruka; Fordham University Slawek, Deepika; Montefiore Health System, Division of General Internal Medicine Arnsten, Julia; Montefiore Health System, Division of General Internal Medicine
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Complementary medicine, General practice / Family practice, HIV/AIDS
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, PAIN MANAGEMENT, COMPLEMENTARY MEDICINE, STATISTICS & RESEARCH METHODS

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

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

Chinazo O. Cunningham[1], Joanna L. Starrels[1], Chenshu Zhang[1], Marcus A. Bachhuber[2], Nancy L. Sohler[3], Frances R. Levin[4], Haruka Minami[5], Deepika E. Slawek[1], Julia H. Arnsten [1]

[1]Department of Medicine, Montefiore Health System & Albert Einstein College of Medicine, Bronx, NY, USA
[2]Department of Medicine, Louisiana State University Health Sciences Center – New Orleans, New Orleans, LA, USA
[3]Department of Community Health and Social Medicine, City University of New York School of Medicine, City College of New York, New York, NY, USA
[4]Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, and the New York State Psychiatric Institute, New York, NY, USA
[5]Department of Psychology, Fordham University, Bronx, NY, USA

Corresponding author:
Chinazo O. Cunningham, MD, MS
111 E. 210th Street
Bronx, NY 10467
USA
Phone: 718-920-5971
Email: chinazo.cunningham@einsteinmed.org

Key words: cannabis, marijuana, opioids, chronic pain, HIV

Word count: 3675

For peer review only

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.

For peer review only

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

For peer review only

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

For peer review only

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

For peer review only

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

For peer review only

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

For peer review only

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.

Funding: This study is supported by the National Institute on Drug Abuse of the National Institute of Health (R01DA044171). CC and JS are also supported by the National Institute on Drug Abuse (K24DA036955, K24DA046309). CC and JA are also supported by the National Institute of Allergy and Infectious Diseases of the National Institute of Health (P30AI124414).

Disclaimer: The content is solely the responsibility of the authors and does not represent the official views of the National Institute of Health. The funding agency has no role in design or conduct of the study, or the decision to publish study results.

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.

For peer review only

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

For peer review only

References

1. Johannes CB, Le TK, Zhou X, et al. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *The journal of pain : official journal of the American Pain Society* 2010;11(11):1230-9. doi: 10.1016/j.jpain.2010.07.002 [published Online First: 2010/08/28]
2. Breitbart W, Dibiase L. Current perspectives on pain in AIDS. *Oncology (WillistonPark)* 2002;16(7):964-8, 72.
3. Hewitt DJ, McDonald M, Portenoy RK, et al. Pain syndromes and etiologies in ambulatory AIDS patients. *Pain* 1997;70(2-3):117-23.
4. Perry BA, Westfall AO, Molony E, et al. Characteristics of an ambulatory palliative care clinic for HIV-infected patients. *J Palliat Med* 2013;16(8):934-37.
5. Koeppe J, Lyda K, Armon C. Association Between Opioid Use and Health Care Utilization as Measured by Emergency Room Visits and Hospitalizations Among Persons Living With HIV. *Clin J Pain* 2013;29(11):957-61.
6. Tsao JC, Dobalian A, Naliboff BD. Panic disorder and pain in a national sample of persons living with HIV. *Pain* 2004;109(1-2):172-80.
7. Larue F, Fontaine A, Colleau SM. Underestimation and undertreatment of pain in HIV disease: multicentre study. *BMJ* 1997;314(7073):23-28.
8. Frich LM, Borgbjerg FM. Pain and pain treatment in AIDS patients: a longitudinal study. *J Pain Symptom Manage* 2000;19(5):339-47.
9. Tsao JC, Stein JA, Dobalian A. Pain, problem drug use history, and aberrant analgesic use behaviors in persons living with HIV. *Pain* 2007;133(1-3):128-37.
10. Dobalian A, Tsao JC, Duncan RP. Pain and the use of outpatient services among persons with HIV: results from a nationally representative survey. *Med Care* 2004;42(2):129-38.
11. Tsao JC, Plankey MW, Young MA. Pain, psychological symptoms and prescription drug misuse in HIV: A literature review. *J Pain Manag* 2012;5(2):111-18.
12. Breitbart W, McDonald MV, Rosenfeld B, et al. Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. *Pain* 1996;68(2-3):315-21.
13. Kimball LR, McCormick WC. The pharmacologic management of pain and discomfort in persons with AIDS near the end of life: use of opioid analgesia in the hospice setting. *J Pain Symptom Manage* 1996;11(2):88-94.
14. Edelman EJ, Gordon K, Becker WC, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. *J Gen Intern Med* 2013;28(1):82-90.
15. Simmonds MJ, Novy D, Sandoval R. The differential influence of pain and fatigue on physical performance and health status in ambulatory patients with human immunodeficiency virus. *Clin J Pain* 2005;21(3):200-06.
16. Singer EJ, Zorilla C, Fahy-Chandon B, et al. Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study. *Pain* 1993;54(1):15-19.
17. Merlin JS, Westfall AO, Raper JL, et al. Pain, mood, and substance abuse in HIV: implications for clinic visit utilization, antiretroviral therapy adherence, and virologic failure. *J Acquir Immune Defic Syndr* 2012;61(2):164-70.
18. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb Mortal Wkly Rep* 2011;60(43):1487-92. doi: mm6043a4 [pii]
19. Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. *Open medicine : a peer-reviewed, independent, open-access journal* 2012;6(2):e41-7. [published Online First: 2012/01/01]
20. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain physician* 2014;17(2):E119-28. [published Online First: 2014/03/25]

For peer review only

21. Modarai F, Mack K, Hicks P, et al. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug Alcohol Depend* 2013;132(1-2):81-86. doi: S0376-8716(13)00018-5 [pii];10.1016/j.drugalcdep.2013.01.006 [doi]
22. Silverberg MJ, Ray GT, Saunders K, et al. Prescription long-term opioid use in HIV-infected patients. *Clin J Pain* 2012;28(1):39-46.
23. Tsao JC, Dobalian A, Moreau C, et al. Stability of anxiety and depression in a national sample of adults with human immunodeficiency virus. *J Nerv Ment Dis* 2004;192(2):111-18.
24. Koeppe J, Armon C, Lyda K, et al. Ongoing pain despite aggressive opioid pain management among persons with HIV. *Clin J Pain* 2010;26(3):190-98.
25. Vitiello B, Burnam MA, Bing EG, et al. Use of psychotropic medications among HIV-infected patients in the United States. *Am J Psychiatry* 2003;160(3):547-54.
26. Jeevanjee S, Penko J, Guzman D, et al. Opioid Analgesic Misuse is Associated with Incomplete Antiretroviral Adherence in a Cohort of HIV-Infected Indigent Adults in San Francisco. *AIDS Behav* 2013
27. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* 2016;65(1):1-49. doi: 10.15585/mmwr.rr6501e1 [published Online First: 2016/03/18]
28. ProCon.org. 28 Legal Medical Marijuana States and DC 06/28/2016 [Available from: http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881 accessed 1/15/2017].
29. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacol Rev* 2010;62(4):588-631. doi: 10.1124/pr.110.003004 [published Online First: 2010/11/17]
30. Hayakawa K, Mishima K, Hazekawa M, et al. Cannabidiol potentiates pharmacological effects of Delta(9)-tetrahydrocannabinol via CB(1) receptor-dependent mechanism. *Brain research* 2008;1188:157-64. doi: 10.1016/j.brainres.2007.09.090 [published Online First: 2007/11/21]
31. Varvel SA, Wiley JL, Yang R, et al. Interactions between THC and cannabidiol in mouse models of cannabinoid activity. *Psychopharmacology (Berl)* 2006;186(2):226-34. doi: 10.1007/s00213-006-0356-9 [published Online First: 2006/03/31]
32. Karniol IG, Shirakawa I, Kasinski N, et al. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol* 1974;28(1):172-7. [published Online First: 1974/09/01]
33. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010;39(2):167-79. doi: 10.1016/j.jpainsymman.2009.06.008 [published Online First: 2009/11/10]
34. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006;66(2):234-46. doi: 10.1016/j.mehy.2005.08.026 [published Online First: 2005/10/08]
35. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* 2015;313(24):2456-73. doi: 10.1001/jama.2015.6358 [published Online First: 2015/06/24]
36. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology* 2009;34(3):672-80. doi: 10.1038/npp.2008.120 [published Online First: 2008/08/09]

For peer review only

37. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007;133(1-3):210-20. doi: 10.1016/j.pain.2007.08.028 [published Online First: 2007/11/13]
38. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* 2007;68(7):515-21. doi: 10.1212/01.wnl.0000253187.66183.9c [published Online First: 2007/02/14]
39. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008;9(6):506-21. doi: 10.1016/j.jpain.2007.12.010 [published Online First: 2008/04/12]
40. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008;9(2):164-73. doi: 10.1016/j.jpain.2007.09.002 [published Online First: 2007/11/03]
41. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008;9(3):254-64. doi: 10.1016/j.jpain.2007.10.018 [published Online First: 2007/12/20]
42. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. *J Neurol* 2006;253(10):1337-41. doi: 10.1007/s00415-006-0218-8 [published Online First: 2006/09/22]
43. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford, England)* 2006;45(1):50-2. doi: 10.1093/rheumatology/kei183 [published Online First: 2005/11/12]
44. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA* 2015;313(24):2474-83. doi: 10.1001/jama.2015.6199 [published Online First: 2015/06/24]
45. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004;112(3):299-306. doi: 10.1016/j.pain.2004.09.013 [published Online First: 2004/11/25]
46. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. *J Pain* 2015;16(12):1221-32. doi: 10.1016/j.jpain.2015.07.009 [published Online First: 2015/09/13]
47. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003;290(13):1757-62. doi: 10.1001/jama.290.13.1757 [published Online First: 2003/10/02]
48. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-6739-4 [published Online First: 2012/11/28]
49. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65(6):812-9. doi: 10.1212/01.wnl.0000176753.45410.8b [published Online First: 2005/09/28]
50. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.

For peer review only

51. Grella CE, Rodriguez L, Kim T. Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in los angeles. *J Psychoactive Drugs* 2014;46(4):267-75. doi: 10.1080/02791072.2014.944960 [doi]
52. Reiman A. Cannabis as a substitute for alcohol and other drugs. *Harm Reduct J* 2009;6:35. doi: 1477-7517-6-35 [pii];10.1186/1477-7517-6-35 [doi]
53. Nunberg H, Kilmer B, Pacula RL, et al. An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California. *J Drug Policy Anal* 2011;4(1) doi: 10.2202/1941-2851.1017 [doi]
54. Zaller N, Topletz A, Frater S, et al. Profiles of medicinal cannabis patients attending compassion centers in rhode island. *J Psychoactive Drugs* 2015;47(1):18-23. doi: 10.1080/02791072.2014.999901 [doi]
55. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain* 2016;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002 [published Online First: 2016/03/24]
56. Sohler NL, Khalid L, Starrels JO, et al. Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain. *Subst Use Misuse.* 2018 Aug 24;53(10):1602-1607. doi: 10.1080/10826084.2017.1416408. Epub 2018 Jan
57. Bachhuber MA, Saloner B, Cunningham CO, et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med* 2014;174(10):1668-73.
58. Bachhuber MA, Saloner B, Cunningham CO, et al. Could Delaware's medical marijuana law reduce harms from opioid analgesics? *Del Med J* 2014;86(11):341-43.
59. D'Souza G, Matson PA, Grady CD, et al. Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Study (WIHS) cohort, 1994-2010. *J Acquir Immune Defic Syndr* 2012;61(5):618-26. doi: 10.1097/QAI.0b013e318273ab3a [published Online First: 2012/09/27]
60. Bruce D, Harper GW, Fernandez MI. Heavy marijuana use among gay and bisexual male emerging adults living with HIV/AIDS. *J HIV AIDS Soc Serv* 2013;12(1):26-48. doi: 10.1080/15381501.2012.735171 [published Online First: 2013/06/28]
61. Prentiss D, Power R, Balmas G, et al. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr* 2004;35(1):38-45. [published Online First: 2004/01/07]
62. Mimiaga MJ, Reisner SL, Grasso C, et al. Substance use among HIV-infected patients engaged in primary care in the United States: findings from the Centers for AIDS Research Network of Integrated Clinical Systems cohort. *Am J Public Health* 2013;103(8):1457-67. doi: 10.2105/ajph.2012.301162 [published Online First: 2013/06/15]
63. Furler MD, Einarson TR, Millson M, et al. Medicinal and recreational marijuana use by patients infected with HIV. *AIDS Patient Care STDs* 2004;18(4):215-28. doi: 10.1089/108729104323038892 [published Online First: 2004/05/15]
64. Okafor CN, Cook RL, Chen X, et al. Trajectories of Marijuana Use among HIV-seropositive and HIV-seronegative MSM in the Multicenter AIDS Cohort Study (MACS), 1984-2013. *AIDS Behav* 2016 doi: 10.1007/s10461-016-1445-3 [published Online First: 2016/06/05]
65. Ompad DC, Giobazolia TT, Barton SC, et al. Drug use among HIV+ adults aged 50 and older: findings from the GOLD II study. *AIDS Care* 2016;28(11):1373-7. doi: 10.1080/09540121.2016.1178704 [published Online First: 2016/05/05]
66. Friedman H, Klein TW, Newton C, et al. Marijuana, receptors and immunomodulation. *Adv Exp Med Biol* 1995;373:103-13. [published Online First: 1995/01/01]

67. Nahas GG, Suciu-Foca N, Armand JP, et al. Inhibition of cellular mediated immunity in marihuana smokers. *Science* 1974;183(4123):419-20. [published Online First: 1974/02/01]
68. Hollister LE. Marijuana and immunity. *J Psychoactive Drugs* 1992;24(2):159-64. doi: 10.1080/02791072.1992.10471635 [published Online First: 1992/04/01]
69. Milloy MJ, Marshall B, Kerr T, et al. High-intensity cannabis use associated with lower plasma human immunodeficiency virus-1 RNA viral load among recently infected people who use injection drugs. *Drug Alcohol Rev* 2015;34(2):135-40. doi: 10.1111/dar.12223 [published Online First: 2014/11/13]
70. Ghosn J, Leruez-Ville M, Blanche J, et al. HIV-1 DNA levels in peripheral blood mononuclear cells and cannabis use are associated with intermittent HIV shedding in semen of men who have sex with men on successful antiretroviral regimens. *Clin Infect Dis* 2014;58(12):1763-70. doi: 10.1093/cid/ciu187 [published Online First: 2014/03/22]
71. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Annals Int Med* 2003;139(4):258-66. [published Online First: 2003/09/11]
72. Bredt BM, Higuera-Alhino D, Shade SB, et al. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J Clin Pharmacol* 2002;42(11 Suppl):82s-89s. [published Online First: 2002/11/05]
73. Harris GE, Dupuis L, Mugford GJ, et al. Patterns and correlates of cannabis use among individuals with HIV/AIDS in Maritime Canada. *Can J Infect Dis Med Microbiol* 2014;25(1):e1-7. [published Online First: 2014/03/19]
74. Slawson G, Milloy MJ, Balneaves L, et al. High-intensity cannabis use and adherence to antiretroviral therapy among people who use illicit drugs in a Canadian setting. *AIDS Behav* 2015;19(1):120-7. doi: 10.1007/s10461-014-0847-3 [published Online First: 2014/07/12]
75. de Jong BC, Prentiss D, McFarland W, et al. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *J Acquir Immune Defic Syndr* 2005;38(1):43-6. [published Online First: 2004/12/21]
76. Bonn-Miller MO, Oser ML, Bucossi MM, et al. Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. *J Behav Med* 2014;37(1):1-10. doi: 10.1007/s10865-012-9458-5 [published Online First: 2012/10/12]
77. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med* 2003;114(7):573-80.
78. Wilson KJ, Doxanakis A, Fairley CK. Predictors for non-adherence to antiretroviral therapy. *Sex Health* 2004;1(4):251-7. [published Online First: 2005/12/13]
79. Morgan E, Skaathun B, Michaels S, et al. Marijuana Use as a Sex-Drug is Associated with HIV Risk Among Black MSM and Their Network. *AIDS Behav* 2016;20(3):600-7. doi: 10.1007/s10461-015-1195-7 [published Online First: 2015/09/25]
80. Kelly JA, St Lawrence JS, Tarima SS, et al. Correlates of Sexual HIV Risk Among African American Men Who Have Sex With Men. *Amer J Public Health* 2016;106(1):96-102. doi: 10.2105/ajph.2015.302945 [published Online First: 2015/11/13]
81. Scivoletto S, Tsuji RK, Abdo C, et al. Use of psychoactive substances and sexual risk behavior in adolescents. *Subst Use Misuse* 2002;37(3):381-98. [published Online First: 2002/03/27]
82. Bellis MA, Hughes K, Calafat A, et al. Sexual uses of alcohol and drugs and the associated health risks: a cross sectional study of young people in nine European cities. *BMC Public Health* 2008;8:155. doi: 10.1186/1471-2458-8-155 [published Online First: 2008/05/13]

83. Brodbeck J, Matter M, Moggi F. Association between cannabis use and sexual risk behavior among young heterosexual adults. *AIDS Behav* 2006;10(5):599-605. doi: 10.1007/s10461-006-9103-9 [published Online First: 2006/05/13]
84. Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. *NEJM* 2014;370(23):2219-27. doi: 10.1056/NEJMra1402309 [published Online First: 2014/06/05]
85. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem* 2013;59(3):478-92. doi: 10.1373/clinchem.2012.194381 [published Online First: 2012/12/12]
86. Asbridge M, Poulin C, Donato A. Motor vehicle collision risk and driving under the influence of cannabis: evidence from adolescents in Atlantic Canada. *Accid Anal Prev* 2005;37(6):1025-34. doi: 10.1016/j.aap.2005.05.006 [published Online First: 2005/07/05]
87. Li MC, Brady JE, DiMaggio CJ, et al. Marijuana use and motor vehicle crashes. *Epidemiol Rev* 2012;34:65-72. doi: 10.1093/epirev/mxr017 [published Online First: 2011/10/07]
88. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ* 2012;344:e536. doi: 10.1136/bmj.e536 [published Online First: 2012/02/11]
89. Barrio G, Jimenez-Mejias E, Pulido J, et al. Association between cannabis use and non-traffic injuries. *Accid Anal Prev* 2012;47:172-6. doi: 10.1016/j.aap.2012.01.002 [published Online First: 2012/03/13]
90. Patel R, Wilson R, Jackson R, et al. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. *BMJ Open* 2016;6(3):e009888. doi: 10.1136/bmjopen-2015-009888 [published Online First: 2016/03/05]
91. Moore CL, Gidding HF, Jin F, et al. Patterns of Drug Use and Drug-related Hospital Admissions in HIV-Positive and -Negative Gay and Bisexual Men. *AIDS Behav* 2016;20(10):2372-86. doi: 10.1007/s10461-016-1303-3 [published Online First: 2016/02/04]
92. Jouanjus E, Pourcel L, Saivin S, et al. Use of multiple sources and capture-recapture method to estimate the frequency of hospitalizations related to drug abuse. *Pharmacoepidemiol Drug Saf* 2012;21(7):733-41. doi: 10.1002/pds.3280 [published Online First: 2012/05/03]
93. New York State Department of Health. New York State Medical Marijuana Program, 2016. [Available from https://www.health.ny.gov/regulations/medical_marijuana/ accessed on 7/30/20].
94. United States Drug Enforcement Administration. Drug Schedules [Available from: https://www.dea.gov/druginfo/ds.shtml accessed 1/20/17].
95. Nutt DJ, King LA, Nichols DE. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat Rev Neurosci* 2013;14(8):577-85. doi: 10.1038/nrn3530 [published Online First: 2013/06/13]
96. Wolf SL, Catlin PA, Gage K, et al. Establishing the reliability and validity of measurements of walking time using the Emory Functional Ambulation Profile. *Phys Ther* 1999;79(12):1122-33. [published Online First: 2000/01/12]
97. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Aging* 1997;26(1):15-9. [published Online First: 1997/01/01]
98. Bohannon RW, Andrews AW, Thomas MW. Walking speed: reference values and correlates for older adults. *J Orthop Sports Phys Ther* 1996;24(2):86-90. doi: 10.2519/jospt.1996.24.2.86 [published Online First: 1996/08/01]

For peer review only

99. Bohannon RW, Williams Andrews A. Normal walking speed: a descriptive meta-analysis. *Physiotherapy* 2011;97(3):182-9. doi: 10.1016/j.physio.2010.12.004 [published Online First: 2011/08/09]
100. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70(2):113-9. doi: 10.1080/02701367.1999.10608028 [published Online First: 1999/06/25]
101. Gill SD, de Morton NA, Mc Burney H. An investigation of the validity of six measures of physical function in people awaiting joint replacement surgery of the hip or knee. *Clin Rehabil* 2012;26(10):945-51. doi: 10.1177/0269215511434993 [published Online First: 2012/02/11]
102. Perret C, Poiraudeau S, Fermanian J, et al. Validity, reliability, and responsiveness of the fingertip-to-floor test. *Arch Phys Med Rehabil* 2001;82(11):1566-70. doi: 10.1053/apmr.2001.26064 [published Online First: 2001/11/02]
103. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. *Arthritis Care Res* 2011;63 Suppl 11:S350-70. doi: 10.1002/acr.20538 [published Online First: 2012/05/25]
104. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care* 2000;12(3):255-66.
105. Berg KM, Wilson IB, Li X, et al. Comparison of antiretroviral adherence questions. *AIDS Behav* 2012;16(2):461-68.
106. Darke S, Hall W, Heather N, et al. The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS* 1991;5(2):181-85.
107. Knight KR, Shade SB, Purcell DW, et al. Sexual transmission risk behavior reported among behaviorally bisexual HIV-positive injection drug-using men. *J Acquir Immune Defic Syndr* 2007;46 Suppl 2:S80-7. doi: 10.1097/QAI.0b013e3181576828
108. Purcell DW, Parsons JT, Halkitis PN, et al. Substance use and sexual transmission risk behavior of HIV-positive men who have sex with men. *J Subst Abuse* 2001;13(1-2):185-200.
109. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The J Clin Psychiatry* 1998;59 Suppl 20:22-33;quiz 34-57. [published Online First: 1999/01/09]
110. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat* 1992;9(3):199-213.
111. Winhusen TM, Lewis DF, Riggs PD, et al. Subjective effects, misuse, and adverse effects of osmotic-release methylphenidate treatment in adolescent substance abusers with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2011;21(5):455-63. doi: 10.1089/cap.2011.0014 [published Online First: 2011/11/02]
112. Prevention NCfHSCfDCa. National Health Interview Survey, CAPI Manual for NHIS Field representatives. .
113. Poulin C, MacNeil P, Mitic W. The validity of a province-wide student drug use survey: lessons in design. *Can J Public Health* 1993;84(4):259-64. [published Online First: 1993/07/01]
114. Keller S, Bann CM, Dodd SL, et al. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 2004;20(5):309-18.

For peer review only

115. Sullivan MJLB, S.R.; Pivik, J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7(4):524-32.
116. Stroud MW, McKnight PE, Jensen MP. Assessment of self-reported physical activity in patients with chronic pain: development of an abbreviated Roland-Morris disability scale. *J Pain* 2004;5(5):257-63.
117. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* 1993;88(6):791-804.
118. Commerce USDo. Census Bureau (2016). National Cancer Institute and Food and Drug Administration co-sponsored Tobacco Use Supplement to the Current Population Survey. 2014-15. https://cancercontrol.cancer.gov/brp/tcrb/tus-cps/.
119. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Int Med* 2001;16(9):606-13. [published Online First: 2001/09/15]
120. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Int Med* 2006;166(10):1092-7. doi: 10.1001/archinte.166.10.1092 [published Online First: 2006/05/24]
121. Lang AJ, Stein MB. An abbreviated PTSD checklist for use as a screening instrument in primary care. *Behav Res Ther* 2005;43(5):585-94. doi: 10.1016/j.brat.2004.04.005 [published Online First: 2005/05/04]
122. Lang AJ, Laffaye C, Satz LE, et al. Sensitivity and specificity of the PTSD checklist in detecting PTSD in female veterans in primary care. *J Trauma Stress* 2003;16(3):257-64. doi: 10.1023/a:1023796007788 [published Online First: 2003/06/21]
123. Ustun B, Adler LA, Rudin C, et al. The World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5. *JAMA Psychiatry* 2017;74(5):520-26. doi: 10.1001/jamapsychiatry.2017.0298 [published Online First: 2017/04/07]
124. Morin CM, Belleville G, Bélanger L, et al. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34(5):601-8. doi: 10.1093/sleep/34.5.601 [published Online First: 2011/05/03]
125. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208. [published Online First: 1990/11/05]
126. Hernan MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med* 2002;21(12):1689-709. doi: 10.1002/sim.1144
127. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-60.
128. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168(6):656-64. doi: 10.1093/aje/kwn164
129. Brumback BA, Hernan MA, Haneuse SJ, et al. Sensitivity analyses for unmeasured confounding assuming a marginal structural model for repeated measures. *Stat Med* 2004;23(5):749-67. doi: 10.1002/sim.1657
130. Banack HR, Kaufman JS. Estimating the Time-Varying Joint Effects of Obesity and Smoking on All-Cause Mortality Using Marginal Structural Models. *Am J Epidemiol* 2016;183(2):122-9. doi: 10.1093/aje/kwv168 [published Online First: 2015/12/15]
131. Howe CJ, Cole SR, Mehta SH, et al. Estimating the effects of multiple time-varying exposures using joint marginal structural models: alcohol consumption, injection drug use, and HIV acquisition. *Epidemiology* 2012;23(4):574-82. doi: 10.1097/EDE.0b013e31824d1ccb
132. Centers for Disease Control and Prevention. Opioid Overdose. U.S. Prescribing Rate Maps. Accessed on 10/17/20 at https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

For peer review only

133. Bachhuber MA, Arnsten JH, Starrels JL, et al. Willingness to Participate in Longitudinal Research Among People with Chronic Pain Who Take Medical Cannabis: A Cross-Sectional Survey. Cannabis Cannabinoid Res. 2018 Mar 1;3(1):45-53.
134. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12(12):1500-24. doi: 10.1016/j.ijsu.2014.07.014 [published Online First: 2014/07/22]

For peer review only

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-043400.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Nov-2020
Complete List of Authors:	Cunningham, Chinazo; Montefiore Health System, Division of General Internal Medicine Starrels, Joanna; Montefiore Health System, Division of General Internal Medicine Zhang, Chenshu; Montefiore Health System, Division of General Internal Medicine Bachhuber, Marcus; Louisiana State University Health Sciences Center Sohler, Nancy ; City University of New York, School of Medicine Levin, Frances; Columbia University Irving Medical Center, Department of Psychiatry Minami, Haruka; Fordham University Slawek, Deepika; Montefiore Health System, Division of General Internal Medicine Arnsten, Julia; Montefiore Health System, Division of General Internal Medicine
Primary Subject Heading:	Research methods
Secondary Subject Heading:	Complementary medicine, General practice / Family practice, HIV/AIDS
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, PAIN MANAGEMENT, COMPLEMENTARY MEDICINE, STATISTICS & RESEARCH METHODS

SCHOLARONE™
Manuscripts

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

For peer review only

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

Chinazo O. Cunningham[1], Joanna L. Starrels[1], Chenshu Zhang[1], Marcus A. Bachhuber[2], Nancy L. Sohler[3], Frances R. Levin[4], Haruka Minami[5], Deepika E. Slawek[1], Julia H. Arnsten [1]

[1]Department of Medicine, Montefiore Health System & Albert Einstein College of Medicine, Bronx, NY, USA
[2]Department of Medicine, Louisiana State University Health Sciences Center – New Orleans, New Orleans, LA, USA
[3]Department of Community Health and Social Medicine, City University of New York School of Medicine, City College of New York, New York, NY, USA
[4]Department of Psychiatry, Vagelos College of Physicians and Surgeons, Columbia University, and the New York State Psychiatric Institute, New York, NY, USA
[5]Department of Psychology, Fordham University, Bronx, NY, USA

Corresponding author:
Chinazo O. Cunningham, MD, MS
111 E. 210th Street
Bronx, NY 10467
USA
Phone: 718-920-5971
Email: chinazo.cunningham@einsteinmed.org

Key words: cannabis, marijuana, opioids, chronic pain, HIV

Word count: 3676

For peer review only

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.

For peer review only

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

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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

For peer review only

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

For peer review only

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

For peer review only

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

For peer review only

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

For peer review only

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.

Funding: This study is supported by the National Institute on Drug Abuse of the National Institute of Health (R01DA044171). CC and JS are also supported by the National Institute on Drug Abuse (K24DA036955, K24DA046309). CC and JA are also supported by the National Institute of Allergy and Infectious Diseases of the National Institute of Health (P30AI124414).

Disclaimer: The content is solely the responsibility of the authors and does not represent the official views of the National Institute of Health. The funding agency has no role in design or conduct of the study, or the decision to publish study results.

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.

For peer review only

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

For peer review only

References

1. Johannes CB, Le TK, Zhou X, et al. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *The journal of pain : official journal of the American Pain Society* 2010;11(11):1230-9. doi: 10.1016/j.jpain.2010.07.002 [published Online First: 2010/08/28]
2. Breitbart W, Dibiase L. Current perspectives on pain in AIDS. *Oncology (WillistonPark)* 2002;16(7):964-8, 72.
3. Hewitt DJ, McDonald M, Portenoy RK, et al. Pain syndromes and etiologies in ambulatory AIDS patients. *Pain* 1997;70(2-3):117-23.
4. Perry BA, Westfall AO, Molony E, et al. Characteristics of an ambulatory palliative care clinic for HIV-infected patients. *J Palliat Med* 2013;16(8):934-37.
5. Koeppe J, Lyda K, Armon C. Association Between Opioid Use and Health Care Utilization as Measured by Emergency Room Visits and Hospitalizations Among Persons Living With HIV. *Clin J Pain* 2013;29(11):957-61.
6. Tsao JC, Dobalian A, Naliboff BD. Panic disorder and pain in a national sample of persons living with HIV. *Pain* 2004;109(1-2):172-80.
7. Larue F, Fontaine A, Colleau SM. Underestimation and undertreatment of pain in HIV disease: multicentre study. *BMJ* 1997;314(7073):23-28.
8. Frich LM, Borgbjerg FM. Pain and pain treatment in AIDS patients: a longitudinal study. *J Pain Symptom Manage* 2000;19(5):339-47.
9. Tsao JC, Stein JA, Dobalian A. Pain, problem drug use history, and aberrant analgesic use behaviors in persons living with HIV. *Pain* 2007;133(1-3):128-37.
10. Dobalian A, Tsao JC, Duncan RP. Pain and the use of outpatient services among persons with HIV: results from a nationally representative survey. *Med Care* 2004;42(2):129-38.
11. Tsao JC, Plankey MW, Young MA. Pain, psychological symptoms and prescription drug misuse in HIV: A literature review. *J Pain Manag* 2012;5(2):111-18.
12. Breitbart W, McDonald MV, Rosenfeld B, et al. Pain in ambulatory AIDS patients. I: Pain characteristics and medical correlates. *Pain* 1996;68(2-3):315-21.
13. Kimball LR, McCormick WC. The pharmacologic management of pain and discomfort in persons with AIDS near the end of life: use of opioid analgesia in the hospice setting. *J Pain Symptom Manage* 1996;11(2):88-94.
14. Edelman EJ, Gordon K, Becker WC, et al. Receipt of opioid analgesics by HIV-infected and uninfected patients. *J Gen Intern Med* 2013;28(1):82-90.
15. Simmonds MJ, Novy D, Sandoval R. The differential influence of pain and fatigue on physical performance and health status in ambulatory patients with human immunodeficiency virus. *Clin J Pain* 2005;21(3):200-06.
16. Singer EJ, Zorilla C, Fahy-Chandon B, et al. Painful symptoms reported by ambulatory HIV-infected men in a longitudinal study. *Pain* 1993;54(1):15-19.
17. Merlin JS, Westfall AO, Raper JL, et al. Pain, mood, and substance abuse in HIV: implications for clinic visit utilization, antiretroviral therapy adherence, and virologic failure. *J Acquir Immune Defic Syndr* 2012;61(2):164-70.
18. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. *MMWR Morb Mortal Wkly Rep* 2011;60(43):1487-92. doi: mm6043a4 [pii]
19. Kenan K, Mack K, Paulozzi L. Trends in prescriptions for oxycodone and other commonly used opioids in the United States, 2000-2010. *Open medicine : a peer-reviewed, independent, open-access journal* 2012;6(2):e41-7. [published Online First: 2012/01/01]
20. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain physician* 2014;17(2):E119-28. [published Online First: 2014/03/25]

For peer review only

21. Modarai F, Mack K, Hicks P, et al. Relationship of opioid prescription sales and overdoses, North Carolina. *Drug Alcohol Depend* 2013;132(1-2):81-86. doi: S0376-8716(13)00018-5 [pii];10.1016/j.drugalcdep.2013.01.006 [doi]
22. Silverberg MJ, Ray GT, Saunders K, et al. Prescription long-term opioid use in HIV-infected patients. *Clin J Pain* 2012;28(1):39-46.
23. Tsao JC, Dobalian A, Moreau C, et al. Stability of anxiety and depression in a national sample of adults with human immunodeficiency virus. *J Nerv Ment Dis* 2004;192(2):111-18.
24. Koeppe J, Armon C, Lyda K, et al. Ongoing pain despite aggressive opioid pain management among persons with HIV. *Clin J Pain* 2010;26(3):190-98.
25. Vitiello B, Burnam MA, Bing EG, et al. Use of psychotropic medications among HIV-infected patients in the United States. *Am J Psychiatry* 2003;160(3):547-54.
26. Jeevanjee S, Penko J, Guzman D, et al. Opioid Analgesic Misuse is Associated with Incomplete Antiretroviral Adherence in a Cohort of HIV-Infected Indigent Adults in San Francisco. *AIDS Behav* 2013
27. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain - United States, 2016. *MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control* 2016;65(1):1-49. doi: 10.15585/mmwr.rr6501e1 [published Online First: 2016/03/18]
28. ProCon.org. 28 Legal Medical Marijuana States and DC [Available from: https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/ accessed 11/28/20].
29. Pertwee RG, Howlett AC, Abood ME, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacol Rev* 2010;62(4):588-631. doi: 10.1124/pr.110.003004 [published Online First: 2010/11/17]
30. Hayakawa K, Mishima K, Hazekawa M, et al. Cannabidiol potentiates pharmacological effects of Delta(9)-tetrahydrocannabinol via CB(1) receptor-dependent mechanism. *Brain research* 2008;1188:157-64. doi: 10.1016/j.brainres.2007.09.090 [published Online First: 2007/11/21]
31. Varvel SA, Wiley JL, Yang R, et al. Interactions between THC and cannabidiol in mouse models of cannabinoid activity. *Psychopharmacology (Berl)* 2006;186(2):226-34. doi: 10.1007/s00213-006-0356-9 [published Online First: 2006/03/31]
32. Karniol IG, Shirakawa I, Kasinski N, et al. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol* 1974;28(1):172-7. [published Online First: 1974/09/01]
33. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010;39(2):167-79. doi: 10.1016/j.jpainsymman.2009.06.008 [published Online First: 2009/11/10]
34. Russo E, Guy GW. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses* 2006;66(2):234-46. doi: 10.1016/j.mehy.2005.08.026 [published Online First: 2005/10/08]
35. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. *JAMA* 2015;313(24):2456-73. doi: 10.1001/jama.2015.6358 [published Online First: 2015/06/24]
36. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology* 2009;34(3):672-80. doi: 10.1038/npp.2008.120 [published Online First: 2008/08/09]

For peer review only

37. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain* 2007;133(1-3):210-20. doi: 10.1016/j.pain.2007.08.028 [published Online First: 2007/11/13]
38. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology* 2007;68(7):515-21. doi: 10.1212/01.wnl.0000253187.66183.9c [published Online First: 2007/02/14]
39. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain* 2008;9(6):506-21. doi: 10.1016/j.jpain.2007.12.010 [published Online First: 2008/04/12]
40. Skrabek RQ, Galimova L, Ethans K, et al. Nabilone for the treatment of pain in fibromyalgia. *J Pain* 2008;9(2):164-73. doi: 10.1016/j.jpain.2007.09.002 [published Online First: 2007/11/03]
41. Narang S, Gibson D, Wasan AD, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J Pain* 2008;9(3):254-64. doi: 10.1016/j.jpain.2007.10.018 [published Online First: 2007/12/20]
42. Wissel J, Haydn T, Muller J, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. *J Neurol* 2006;253(10):1337-41. doi: 10.1007/s00415-006-0218-8 [published Online First: 2006/09/22]
43. Blake DR, Robson P, Ho M, et al. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology (Oxford, England)* 2006;45(1):50-2. doi: 10.1093/rheumatology/kei183 [published Online First: 2005/11/12]
44. Hill KP. Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review. *JAMA* 2015;313(24):2474-83. doi: 10.1001/jama.2015.6199 [published Online First: 2015/06/24]
45. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004;112(3):299-306. doi: 10.1016/j.pain.2004.09.013 [published Online First: 2004/11/25]
46. Andreae MH, Carter GM, Shaparin N, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. *J Pain* 2015;16(12):1221-32. doi: 10.1016/j.jpain.2015.07.009 [published Online First: 2015/09/13]
47. Karst M, Salim K, Burstein S, et al. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003;290(13):1757-62. doi: 10.1001/jama.290.13.1757 [published Online First: 2003/10/02]
48. Langford RM, Mares J, Novotna A, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *J Neurol* 2013;260(4):984-97. doi: 10.1007/s00415-012-6739-4 [published Online First: 2012/11/28]
49. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005;65(6):812-9. doi: 10.1212/01.wnl.0000176753.45410.8b [published Online First: 2005/09/28]
50. National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.

For peer review only

51. Grella CE, Rodriguez L, Kim T. Patterns of medical marijuana use among individuals sampled from medical marijuana dispensaries in los angeles. *J Psychoactive Drugs* 2014;46(4):267-75. doi: 10.1080/02791072.2014.944960 [doi]
52. Reiman A. Cannabis as a substitute for alcohol and other drugs. *Harm Reduct J* 2009;6:35. doi: 1477-7517-6-35 [pii];10.1186/1477-7517-6-35 [doi]
53. Nunberg H, Kilmer B, Pacula RL, et al. An Analysis of Applicants Presenting to a Medical Marijuana Specialty Practice in California. *J Drug Policy Anal* 2011;4(1) doi: 10.2202/1941-2851.1017 [doi]
54. Zaller N, Topletz A, Frater S, et al. Profiles of medicinal cannabis patients attending compassion centers in rhode island. *J Psychoactive Drugs* 2015;47(1):18-23. doi: 10.1080/02791072.2014.999901 [doi]
55. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain* 2016;17(6):739-44. doi: 10.1016/j.jpain.2016.03.002 [published Online First: 2016/03/24]
56. Sohler NL, Khalid L, Starrels JO, et al. Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain. *Subst Use Misuse.* 2018 Aug 24;53(10):1602-1607. doi: 10.1080/10826084.2017.1416408. Epub 2018 Jan
57. Bachhuber MA, Saloner B, Cunningham CO, et al. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med* 2014;174(10):1668-73.
58. Bachhuber MA, Saloner B, Cunningham CO, et al. Could Delaware's medical marijuana law reduce harms from opioid analgesics? *Del Med J* 2014;86(11):341-43.
59. D'Souza G, Matson PA, Grady CD, et al. Medicinal and recreational marijuana use among HIV-infected women in the Women's Interagency HIV Study (WIHS) cohort, 1994-2010. *J Acquir Immune Defic Syndr* 2012;61(5):618-26. doi: 10.1097/QAI.0b013e318273ab3a [published Online First: 2012/09/27]
60. Bruce D, Harper GW, Fernandez MI. Heavy marijuana use among gay and bisexual male emerging adults living with HIV/AIDS. *J HIV AIDS Soc Serv* 2013;12(1):26-48. doi: 10.1080/15381501.2012.735171 [published Online First: 2013/06/28]
61. Prentiss D, Power R, Balmas G, et al. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr* 2004;35(1):38-45. [published Online First: 2004/01/07]
62. Mimiaga MJ, Reisner SL, Grasso C, et al. Substance use among HIV-infected patients engaged in primary care in the United States: findings from the Centers for AIDS Research Network of Integrated Clinical Systems cohort. *Am J Public Health* 2013;103(8):1457-67. doi: 10.2105/ajph.2012.301162 [published Online First: 2013/06/15]
63. Furler MD, Einarson TR, Millson M, et al. Medicinal and recreational marijuana use by patients infected with HIV. *AIDS Patient Care STDs* 2004;18(4):215-28. doi: 10.1089/108729104323038892 [published Online First: 2004/05/15]
64. Okafor CN, Cook RL, Chen X, et al. Trajectories of Marijuana Use among HIV-seropositive and HIV-seronegative MSM in the Multicenter AIDS Cohort Study (MACS), 1984-2013. *AIDS Behav* 2016 doi: 10.1007/s10461-016-1445-3 [published Online First: 2016/06/05]
65. Ompad DC, Giobazolia TT, Barton SC, et al. Drug use among HIV+ adults aged 50 and older: findings from the GOLD II study. *AIDS Care* 2016;28(11):1373-7. doi: 10.1080/09540121.2016.1178704 [published Online First: 2016/05/05]
66. Friedman H, Klein TW, Newton C, et al. Marijuana, receptors and immunomodulation. *Adv Exp Med Biol* 1995;373:103-13. [published Online First: 1995/01/01]

67. Nahas GG, Suciu-Foca N, Armand JP, et al. Inhibition of cellular mediated immunity in marihuana smokers. *Science* 1974;183(4123):419-20. [published Online First: 1974/02/01]
68. Hollister LE. Marijuana and immunity. *J Psychoactive Drugs* 1992;24(2):159-64. doi: 10.1080/02791072.1992.10471635 [published Online First: 1992/04/01]
69. Milloy MJ, Marshall B, Kerr T, et al. High-intensity cannabis use associated with lower plasma human immunodeficiency virus-1 RNA viral load among recently infected people who use injection drugs. *Drug Alcohol Rev* 2015;34(2):135-40. doi: 10.1111/dar.12223 [published Online First: 2014/11/13]
70. Ghosn J, Leruez-Ville M, Blanche J, et al. HIV-1 DNA levels in peripheral blood mononuclear cells and cannabis use are associated with intermittent HIV shedding in semen of men who have sex with men on successful antiretroviral regimens. *Clin Infect Dis* 2014;58(12):1763-70. doi: 10.1093/cid/ciu187 [published Online First: 2014/03/22]
71. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Annals Int Med* 2003;139(4):258-66. [published Online First: 2003/09/11]
72. Bredt BM, Higuera-Alhino D, Shade SB, et al. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J Clin Pharmacol* 2002;42(11 Suppl):82s-89s. [published Online First: 2002/11/05]
73. Harris GE, Dupuis L, Mugford GJ, et al. Patterns and correlates of cannabis use among individuals with HIV/AIDS in Maritime Canada. *Can J Infect Dis Med Microbiol* 2014;25(1):e1-7. [published Online First: 2014/03/19]
74. Slawson G, Milloy MJ, Balneaves L, et al. High-intensity cannabis use and adherence to antiretroviral therapy among people who use illicit drugs in a Canadian setting. *AIDS Behav* 2015;19(1):120-7. doi: 10.1007/s10461-014-0847-3 [published Online First: 2014/07/12]
75. de Jong BC, Prentiss D, McFarland W, et al. Marijuana use and its association with adherence to antiretroviral therapy among HIV-infected persons with moderate to severe nausea. *J Acquir Immune Defic Syndr* 2005;38(1):43-6. [published Online First: 2004/12/21]
76. Bonn-Miller MO, Oser ML, Bucossi MM, et al. Cannabis use and HIV antiretroviral therapy adherence and HIV-related symptoms. *J Behav Med* 2014;37(1):1-10. doi: 10.1007/s10865-012-9458-5 [published Online First: 2012/10/12]
77. Tucker JS, Burnam MA, Sherbourne CD, et al. Substance use and mental health correlates of nonadherence to antiretroviral medications in a sample of patients with human immunodeficiency virus infection. *Am J Med* 2003;114(7):573-80.
78. Wilson KJ, Doxanakis A, Fairley CK. Predictors for non-adherence to antiretroviral therapy. *Sex Health* 2004;1(4):251-7. [published Online First: 2005/12/13]
79. Morgan E, Skaathun B, Michaels S, et al. Marijuana Use as a Sex-Drug is Associated with HIV Risk Among Black MSM and Their Network. *AIDS Behav* 2016;20(3):600-7. doi: 10.1007/s10461-015-1195-7 [published Online First: 2015/09/25]
80. Kelly JA, St Lawrence JS, Tarima SS, et al. Correlates of Sexual HIV Risk Among African American Men Who Have Sex With Men. *Amer J Public Health* 2016;106(1):96-102. doi: 10.2105/ajph.2015.302945 [published Online First: 2015/11/13]
81. Scivoletto S, Tsuji RK, Abdo C, et al. Use of psychoactive substances and sexual risk behavior in adolescents. *Subst Use Misuse* 2002;37(3):381-98. [published Online First: 2002/03/27]
82. Bellis MA, Hughes K, Calafat A, et al. Sexual uses of alcohol and drugs and the associated health risks: a cross sectional study of young people in nine European cities. *BMC Public Health* 2008;8:155. doi: 10.1186/1471-2458-8-155 [published Online First: 2008/05/13]

83. Brodbeck J, Matter M, Moggi F. Association between cannabis use and sexual risk behavior among young heterosexual adults. *AIDS Behav* 2006;10(5):599-605. doi: 10.1007/s10461-006-9103-9 [published Online First: 2006/05/13]
84. Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. *NEJM* 2014;370(23):2219-27. doi: 10.1056/NEJMra1402309 [published Online First: 2014/06/05]
85. Hartman RL, Huestis MA. Cannabis effects on driving skills. *Clin Chem* 2013;59(3):478-92. doi: 10.1373/clinchem.2012.194381 [published Online First: 2012/12/12]
86. Asbridge M, Poulin C, Donato A. Motor vehicle collision risk and driving under the influence of cannabis: evidence from adolescents in Atlantic Canada. *Accid Anal Prev* 2005;37(6):1025-34. doi: 10.1016/j.aap.2005.05.006 [published Online First: 2005/07/05]
87. Li MC, Brady JE, DiMaggio CJ, et al. Marijuana use and motor vehicle crashes. *Epidemiol Rev* 2012;34:65-72. doi: 10.1093/epirev/mxr017 [published Online First: 2011/10/07]
88. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: systematic review of observational studies and meta-analysis. *BMJ* 2012;344:e536. doi: 10.1136/bmj.e536 [published Online First: 2012/02/11]
89. Barrio G, Jimenez-Mejias E, Pulido J, et al. Association between cannabis use and non-traffic injuries. *Accid Anal Prev* 2012;47:172-6. doi: 10.1016/j.aap.2012.01.002 [published Online First: 2012/03/13]
90. Patel R, Wilson R, Jackson R, et al. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. *BMJ Open* 2016;6(3):e009888. doi: 10.1136/bmjopen-2015-009888 [published Online First: 2016/03/05]
91. Moore CL, Gidding HF, Jin F, et al. Patterns of Drug Use and Drug-related Hospital Admissions in HIV-Positive and -Negative Gay and Bisexual Men. *AIDS Behav* 2016;20(10):2372-86. doi: 10.1007/s10461-016-1303-3 [published Online First: 2016/02/04]
92. Jouanjus E, Pourcel L, Saivin S, et al. Use of multiple sources and capture-recapture method to estimate the frequency of hospitalizations related to drug abuse. *Pharmacoepidemiol Drug Saf* 2012;21(7):733-41. doi: 10.1002/pds.3280 [published Online First: 2012/05/03]
93. New York State Department of Health. New York State Medical Marijuana Program, 2016. [Available from https://www.health.ny.gov/regulations/medical_marijuana/ accessed on 7/30/20].
94. United States Drug Enforcement Administration. Drug Schedules [Available from: https://www.dea.gov/druginfo/ds.shtml accessed 1/20/17].
95. Nutt DJ, King LA, Nichols DE. Effects of Schedule I drug laws on neuroscience research and treatment innovation. *Nat Rev Neurosci* 2013;14(8):577-85. doi: 10.1038/nrn3530 [published Online First: 2013/06/13]
96. Wolf SL, Catlin PA, Gage K, et al. Establishing the reliability and validity of measurements of walking time using the Emory Functional Ambulation Profile. *Phys Ther* 1999;79(12):1122-33. [published Online First: 2000/01/12]
97. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Aging* 1997;26(1):15-9. [published Online First: 1997/01/01]
98. Bohannon RW, Andrews AW, Thomas MW. Walking speed: reference values and correlates for older adults. *J Orthop Sports Phys Ther* 1996;24(2):86-90. doi: 10.2519/jospt.1996.24.2.86 [published Online First: 1996/08/01]

For peer review only

99. Bohannon RW, Williams Andrews A. Normal walking speed: a descriptive meta-analysis. *Physiotherapy* 2011;97(3):182-9. doi: 10.1016/j.physio.2010.12.004 [published Online First: 2011/08/09]
100. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport* 1999;70(2):113-9. doi: 10.1080/02701367.1999.10608028 [published Online First: 1999/06/25]
101. Gill SD, de Morton NA, Mc Burney H. An investigation of the validity of six measures of physical function in people awaiting joint replacement surgery of the hip or knee. *Clin Rehabil* 2012;26(10):945-51. doi: 10.1177/0269215511434993 [published Online First: 2012/02/11]
102. Perret C, Poiraudeau S, Fermanian J, et al. Validity, reliability, and responsiveness of the fingertip-to-floor test. *Arch Phys Med Rehabil* 2001;82(11):1566-70. doi: 10.1053/apmr.2001.26064 [published Online First: 2001/11/02]
103. Bennell K, Dobson F, Hinman R. Measures of physical performance assessments: Self-Paced Walk Test (SPWT), Stair Climb Test (SCT), Six-Minute Walk Test (6MWT), Chair Stand Test (CST), Timed Up & Go (TUG), Sock Test, Lift and Carry Test (LCT), and Car Task. *Arthritis Care Res* 2011;63 Suppl 11:S350-70. doi: 10.1002/acr.20538 [published Online First: 2012/05/25]
104. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care* 2000;12(3):255-66.
105. Berg KM, Wilson IB, Li X, et al. Comparison of antiretroviral adherence questions. *AIDS Behav* 2012;16(2):461-68.
106. Darke S, Hall W, Heather N, et al. The reliability and validity of a scale to measure HIV risk-taking behaviour among intravenous drug users. *AIDS* 1991;5(2):181-85.
107. Knight KR, Shade SB, Purcell DW, et al. Sexual transmission risk behavior reported among behaviorally bisexual HIV-positive injection drug-using men. *J Acquir Immune Defic Syndr* 2007;46 Suppl 2:S80-7. doi: 10.1097/QAI.0b013e3181576828
108. Purcell DW, Parsons JT, Halkitis PN, et al. Substance use and sexual transmission risk behavior of HIV-positive men who have sex with men. *J Subst Abuse* 2001;13(1-2):185-200.
109. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The J Clin Psychiatry* 1998;59 Suppl 20:22-33;quiz 34-57. [published Online First: 1999/01/09]
110. McLellan AT, Kushner H, Metzger D, et al. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat* 1992;9(3):199-213.
111. Winhusen TM, Lewis DF, Riggs PD, et al. Subjective effects, misuse, and adverse effects of osmotic-release methylphenidate treatment in adolescent substance abusers with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2011;21(5):455-63. doi: 10.1089/cap.2011.0014 [published Online First: 2011/11/02]
112. Prevention NCfHSCfDCa. National Health Interview Survey, CAPI Manual for NHIS Field representatives. .
113. Poulin C, MacNeil P, Mitic W. The validity of a province-wide student drug use survey: lessons in design. *Can J Public Health* 1993;84(4):259-64. [published Online First: 1993/07/01]
114. Keller S, Bann CM, Dodd SL, et al. Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. *Clin J Pain* 2004;20(5):309-18.

For peer review only

115. Sullivan MJLB, S.R.; Pivik, J. The pain catastrophizing scale: development and validation. *Psychol Assess* 1995;7(4):524-32.
116. Stroud MW, McKnight PE, Jensen MP. Assessment of self-reported physical activity in patients with chronic pain: development of an abbreviated Roland-Morris disability scale. *J Pain* 2004;5(5):257-63.
117. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* 1993;88(6):791-804.
118. Commerce USDo. Census Bureau (2016). National Cancer Institute and Food and Drug Administration co-sponsored Tobacco Use Supplement to the Current Population Survey. 2014-15. https://cancercontrol.cancer.gov/brp/tcrb/tus-cps/.
119. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Int Med* 2001;16(9):606-13. [published Online First: 2001/09/15]
120. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Int Med* 2006;166(10):1092-7. doi: 10.1001/archinte.166.10.1092 [published Online First: 2006/05/24]
121. Lang AJ, Stein MB. An abbreviated PTSD checklist for use as a screening instrument in primary care. *Behav Res Ther* 2005;43(5):585-94. doi: 10.1016/j.brat.2004.04.005 [published Online First: 2005/05/04]
122. Lang AJ, Laffaye C, Satz LE, et al. Sensitivity and specificity of the PTSD checklist in detecting PTSD in female veterans in primary care. *J Trauma Stress* 2003;16(3):257-64. doi: 10.1023/a:1023796007788 [published Online First: 2003/06/21]
123. Ustun B, Adler LA, Rudin C, et al. The World Health Organization Adult Attention-Deficit/Hyperactivity Disorder Self-Report Screening Scale for DSM-5. *JAMA Psychiatry* 2017;74(5):520-26. doi: 10.1001/jamapsychiatry.2017.0298 [published Online First: 2017/04/07]
124. Morin CM, Belleville G, Bélanger L, et al. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;34(5):601-8. doi: 10.1093/sleep/34.5.601 [published Online First: 2011/05/03]
125. EuroQol--a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16(3):199-208. [published Online First: 1990/11/05]
126. Hernan MA, Brumback BA, Robins JM. Estimating the causal effect of zidovudine on CD4 count with a marginal structural model for repeated measures. *Stat Med* 2002;21(12):1689-709. doi: 10.1002/sim.1144
127. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-60.
128. Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol* 2008;168(6):656-64. doi: 10.1093/aje/kwn164
129. Brumback BA, Hernan MA, Haneuse SJ, et al. Sensitivity analyses for unmeasured confounding assuming a marginal structural model for repeated measures. *Stat Med* 2004;23(5):749-67. doi: 10.1002/sim.1657
130. Banack HR, Kaufman JS. Estimating the Time-Varying Joint Effects of Obesity and Smoking on All-Cause Mortality Using Marginal Structural Models. *Am J Epidemiol* 2016;183(2):122-9. doi: 10.1093/aje/kwv168 [published Online First: 2015/12/15]
131. Howe CJ, Cole SR, Mehta SH, et al. Estimating the effects of multiple time-varying exposures using joint marginal structural models: alcohol consumption, injection drug use, and HIV acquisition. *Epidemiology* 2012;23(4):574-82. doi: 10.1097/EDE.0b013e31824d1ccb
132. Centers for Disease Control and Prevention. Opioid Overdose. U.S. Prescribing Rate Maps. Accessed on 10/17/20 at https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

For peer review only

133. Bachhuber MA, Arnsten JH, Starrels JL, et al. Willingness to Participate in Longitudinal Research Among People with Chronic Pain Who Take Medical Cannabis: A Cross-Sectional Survey. Cannabis Cannabinoid Res. 2018 Mar 1;3(1):45-53.
134. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Int J Surg* 2014;12(12):1500-24. doi: 10.1016/j.ijsu.2014.07.014 [published Online First: 2014/07/22]

For peer review only