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MEDICAL CANNABIS USE AMONG CHRONIC PAIN PATIENTS AND ASSOCIATIONS WITH PRESCRIPTION OPIOID USE: A RETROSPECTIVE STUDY

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ABSTRACT

Medical cannabis is increasingly used as a treatment for chronic pain, and there is initial evidence that medical cannabis may lead to a subsequent decrease in prescription opioid use. The objective of the current study was to conduct a retrospective, naturalistic examination of medical cannabis use (i.e., dose, frequency, type) and subsequent changes in prescription opioid use among a sample of treatment-seeking chronic (non-cancer-related) pain patients (N =277). Data from the electronic medical record (EMR) was paired with information from the State Prescription Drug Monitoring Program and collected at time of initial certification and at six months post-certification. Results indicated that 91% of patients used their certification to buy medical cannabis at least once within the first six months. Heterogeneity in purchase patterns was observed (range of total doses purchased = 5 to 417, mean = 64.5, SD = 67). High THC:low CBD and vaporization-based products were the most common formulations purchased. A total of 37% of all patients who purchased medical cannabis at least once evinced a clinically significant reduction (i.e., ≥ 30% MME) in prescription opioid use by six months post-certification.

Keywords: medical cannabis, marijuana, chronic pain, prescription opioids

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TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendices

Medical Cannabis Use among Chronic Pain Patients and Associations with Prescription Opioid Use: A Retrospective Study

Chronic (non-cancer related) pain is a debilitating, critical national health problem that affects up to twenty percent of adults in the United States (Dahlhamer et al., 2018), with more than 25 million experiencing pain every day (Nahin, 2015). As a result, chronic pain accounts for nearly $600 billion annually in health care expenses and lost productivity (Gaskin & Richard, 2012). Opioid-based pain medicines are a common treatment for chronic pain (Guy et al., 2017) and 2.9 million U.S. adults initiate long-term (> 3 months) opioid therapy each year (Boudreau et al., 2009). Rates of opioid prescriptions have fallen in recent years (CDC, 2019). However, chronic pain patients often receive high doses of prescription opioids for long periods of time (Boudreau et al., 2009; Von Korff et al., 2008), placing them at greater risk for opioid overdose and related problems (Bohnert et al., 2011; Edlund et al., 2014). For example, accidental opioid overdose is more common among individuals who are prescribed opioids for chronic pain (vs. illicit opioid use; Johnson et al., 2013). In response to these findings and the current opioid misuse epidemic, investigators have called for research into alternative pain management interventions (Mackey, 2016; Qaseem, Wilt, McLean, Forciea, & Clinical Guidelines Committee of the American College of, 2017).

Cannabis-based medicines (CBMs) including medical cannabis are one promising approach to the management of chronic pain (Aviram & Samuelly-Leichtag, 2017; Gruber et al., 2017) and may serve as an adjunct to prescription opioids (National Academies of Sciences, 2017). The cannabis plant and has been used as an analgesic for at least 2,000 years (Pain, 2015), and a comprehensive review by the National Academy of Sciences concluded that there is "*substantial evidence*" supporting cannabis as an effective treatment for chronic pain (National

Academies of Sciences, 2017). Cannabis appears to reduce pain by activating the endocannabinoid receptors and downregulating pain signaling in the central and peripheral nervous system (Woodhams, Sagar, Burston, & Chapman, 2015). Reductions in pain may also be a function of anti-inflammatory and mood-enhancing properties of specific cannabinoids (Woodhams et al., 2015).

The term *medical cannabis* has been used to reference prescription preparations of the cannabis plant for therapeutic purposes. Chronic pain is the most common self-reported reason that patients use medical cannabis (Kosiba et al., 2019), and severe or chronic pain is the most frequently condition cited for seeking a medical cannabis certification (Light, 2014; Troutt & DiDonato, 2015). Medical cannabis patients also report that the drug is highly efficacious for managing chronic pain. For example, approximately 83% of those who endorsed chronic pain indicated that their prescription resulted in "*a lot or almost complete relief*" of pain, among a sample of 367 medical cannabis dispensary visitors with chronic pain (Troutt & DiDonato, 2015). A second study reported that 67% of 217 medical cannabis users in California described medical cannabis as beneficial for managing chronic pain (Bonn-Miller et al., 2014).

Critical questions remain regarding the use of medical cannabis among chronic pain patients. First, research has only begun to characterize the frequency and type of medical cannabis used by chronic pain patients and little data is available among persons seeking *initial* certification (Boehnke, Scott, Litinas, Sisley, Clauw, et al., 2019; O'Connell, Sandgren, Frantzen, Bower, & Erickson, 2019). Indeed, up to 36% of certified patients may not purchase medical cannabis at all, thus negating possible therapeutic benefits (O'Connell et al., 2019; Zolotov, Baruch, Reuveni, & Magnezi, 2016). Furthermore, self-report of medical cannabis use has rarely been verified with purchase data (i.e., via prescription drug monitoring programs), and possible

predictors of use have not been examined. Addressing these questions is an essential step in understanding medical cannabis use and facilitating effective use among patients with chronic pain (Fischer et al., 2017a; Kahan, Srivastava, Spithoff, & Bromley, 2014).

A second critical question is whether or not chronic pain patients reduce their use of prescription opioids after purchasing medical cannabis, thereby mitigating exposure to associated risks and side effects. Animal studies indicate that cannabis may exert an opioid-sparing effect via cannabinoid receptor activation (Chen et al., 2019; Cooper et al., 2018), and cross-sectional, self-report surveys indicate that up to 53% of medical cannabis users have substituted the drug for prescription opioids (Boehnke, Litinas, & Clauw, 2016; Boehnke, Scott, Litinas, Sisley, Williams, et al., 2019; Ishida et al., 2019; Lucas & Walsh, 2017). However, only two longitudinal studies have used medical record data to examine changes in prescription opioid use among chronic pain patients certified for medical cannabis (i.e., O'Connell et al., 2019; Vigil, Stith, Adams, & Reeve, 2017).

Vigil et al. (2017) conducted a single-center, retrospective study among opioid-maintained chronic pain patients enrolled in a medical cannabis program in New Mexico (N = 29; 46% female, M_{age} = 54). Results indicated that medical cannabis re-certification (vs. no certification) was associated with greater odds of stopping opioid medications (OR = 17.3), and of reducing daily dosage of prescription opioids (OR = 5.1). However, this study was limited to patients seeking re-certification for medical cannabis, thus presenting a potential selection bias. O'Connell et al (2019) conducted a single-center, retrospective study of opioid-maintained patients (N = 77; 58% female, M_{age} = 54) certified to use medical cannabis for intractable pain in Michigan. Patients evinced a statistically-significant reduction in the median prescription opioid dose (-39 MME) while maintaining analgesic response, given that no change in pain intensity

ratings was observed over the six month study. This study was imited such that patients were included only if they filled their medical cannabis certification (64%). Research is needed that can increase generalizability by conducting analyses in other states and among patients receiving their *initial* certification (O'Connell et al., 2019; Vigil et al., 2017). Furthermore, the relatively small sample size of both studies precluded the ability to test frequency/dosage of medical cannabis purchases in relation to changes in prescription opioid use, and examine variables potentially related to medication usage such as age and sex. This is important as males may experience greater cannabis-induced analgesia than females (Cooper & Haney, 2016), and older age has been associated with more consistent adherence to prescribed medications (Hertz, Unger, & Lustik, 2005; Rolnick, Pawloski, Hedblom, Asche, & Bruzek, 2013).

The first objective of the current study was to characterize medical cannabis use in terms of dosage, type, and purchase frequency over the first six months following certification among a sample of treatment-seeking chronic pain patients. We hypothesized that at least 75% of patients would purchase medical cannabis at least once (i.e., primary adherence; Raebel, Schmittdiel, Karter, Konieczny, & Steiner, 2013). The second objective was to test for changes in prescription opioid use as a function of purchasing medical cannabis. We predicted that at least 50% of those who purchased medical cannabis would either discontinue or reduce their use of prescription opioids, and that the magnitude of reduction would be positively associated with medical cannabis purchases. The third objective was to test the hypothesis that greater age and male (vs. female) sex, would be positively associated with medical cannabis purchase frequency, as well as reductions in prescription opioid use among patients who purchased medical cannabis at least once. Finally, exploratory analyses were conducted to test the interaction of age and sex in terms of medical cannabis purchase frequency, given initial data supporting such an interaction in

terms of analgesic response (Britch, Goodman, Wiley, Pondelick, & Craft, 2020; Craft, Britch, Buzitis, & Clowers, 2019).

Method

Participants and Procedures

Participants were patients seeking treatment at a tertiary outpatient pain clinic who presented for an initial medical cannabis certification. All procedures were approved by the Institutional Review Board of Syracuse University. An office visit with a licensed physician was required to confirm a diagnosis of chronic (non-cancer) pain prior to certification. Patients were then registered to use medical cannabis through the State. Finally, patients were instructed to schedule a separate appointment with one of the local dispensaries to purchase medical cannabis. Cannabis flower products are not permitted in New York State, otherwise patients have full discretion to self-manage the type, frequency, potency of medical cannabis they use. Patients are permitted to use medical cannabis in conjunction with other medical treatments including opioid pain medications. Patients are not provided instructions for altering opioid medications or other prescription medications while using medical cannabis. A follow-up period of six months was chosen based on theories of medication behavior change (Rottman, Marcum, Thorpe, & Gellad, 2017), existing data among medical cannabis users (Zolotov et al., 2016), and is consistent with previous retrospective studies (O'Connell et al., 2019).

Inclusion and Exclusion Criteria

Inclusion criteria. The sample was limited by internal clinic guidelines which specify that patients seeking medical cannabis certification must be a current patient of the practice and seeking certification for chronic pain only, and not receiving medication assisted treatment (MAT) for opioid use disorder (OUD). The sample was also limited to patients prescribed an

opioid-based pain medication to treat chronic pain. Current federal law also prohibits patients from receiving workers compensation to pay out of pocket for healthcare expenses, including medical cannabis. Further, insurance companies do not currently consider medical cannabis to be a valid medical intervention. Thus, the current study is limited to patients who were not receiving workers compensation and able to pay out of pocket for the cost of the medical cannabis certification visit ($150.00 USD).

Exclusion criteria. Patients were excluded if they left the clinic practice (i.e., moved), died, or were discharged for any reason during the study period (i.e., non-payment for services, lapse in insurance, disagreement with provider).

Measures

Demographic and visit data. Demographic data and dates of clinical visits were extracted from the Electronic Medical Record (EMR) for all patients who received an initial medical cannabis certification over one calendar year between 1/1/2018 and 12/31/2018.

Medical Cannabis Data. Patient use of their medical cannabis certification was extracted from electronic medical records using New York State Prescription Drug Monitoring Program (PDMP) data indicating whether medical cannabis was purchased. Purchase(s) of medical cannabis during the six-month observation period (i.e., primary adherence) was dummy coded, where “0” represented that no medical cannabis was purchased, and “1” represented that medical cannabis was purchased at least once. Doses of medical cannabis were based on the recommended daily dose (RDD) for each product as determined by the licensed pharmacist at the dispensary. Purchase frequency was determined by summing each day that a purchase was made (only one visit is allowed per day). Active product at follow-up was operationalized as having purchased product with RDD carried through at least the six-month post-certification date.

Product formulations and administration methods were based on those required my NY State (e.g., THC:CBD ratios).

Opioid Prescription Data. Prescription opioid data was extracted from the electronic medical record which is based on New York State PDMP data. Medication data was extracted at the time of medical cannabis certification, and at six months following certification (Bellnier, Brown, & Ortega, 2018; Simmonds, Finley, Vale, Pugh, & Turner, 2015). Two metrics were used to evaluate change in opioid consumption over time to be consistent with previous research (Vigil et al., 2017). First, dummy coding was accomplished by creating a dichotomous variable where "1" is defined as having filled any opioid prescription at the time of the six-month follow-up, and "0" indicates that no prescription was filled. Second, a mean daily dose of prescription opioid medication in morphine milligram equivalents (MME) was calculated at time of certification and at six months post-certification. Consistent with previous research (Vigil et al., 2017), dosages of opioid prescription(s) filled at both time points were aggregated after converting to morphine milligram equivalents based on CDC guidelines (Dowell, Haegerich, & Chou, 2016), and using the GLOBALRPh calculator.

Pain Intensity. The Numerical Rating Scale (NRS; McCaffery & Beebe, 1989) was used to index pain intensity. Patients are asked to rate current pain intensity from 0 (no pain) to 10 (pain as bad as you can imagine). The NRS has been used extensively to index pain in both research and clinical settings and has demonstrated excellent construct and discriminant validity (Hjermstad et al., 2011; Williamson & Hoggart, 2005). The current study used data from the medical cannabis certification visit and the office visit closest to the six-month follow-up.

Data Analytic Plan

All analyses were conducted using SPSS Statistics 21 (IBM Corp, 2012), and the conduct and reporting of logistic regression models is based on recommended procedures (Moss, Wellman, & Cotsonis, 2003). The distributions of all continuous variables were examined for normality. Positive skewness was observed for morphine milligram equivalents at both baseline and follow-up (skew = 2.45 and 2.59, respectively), as well as frequency of purchasing medical cannabis (skew = 1.96). Recommended corrections were applied (i.e., $\log_{10}$; Tabachnick & Fidell, 2004), which resulted in a normalized distribution for all three variables (skew = 0.16, -0.53, and -0.1, respectively). Analyses to evaluate mean difference among baseline variables and NRS pain scores between timepoints (i.e., *t*-tests) were calculated using a bootstrapped re-sampling approach set at 5,000 resamples to generate 95% CIs.

Inferential analyses were conducted with resampling using bootstrapping, an analytic approach which reduces limitations associated with statistical power and Type 1 error inherent to regression modeling. This approach is also recommended to reduce optimistic prediction errors in logistic regression (Smith, Seaman, Wood, Royston, & White, 2014). For both linear and logistic regression models, bootstrapping was set at 5,000 re-samples, and the PROCESS macro was employed for testing moderation (Preacher & Hayes, 2008). A maximum likelihood approach was used to evaluate the validity of the logistic regression models. Odds ratios, and Nagelkerke's R^2 values were used to evaluate the statistical significance and relative explanatory power of the logistic regression models. The Wald statistic was examined to estimate the contribution of each predictor. Linear regression models were based on an ordinary least-squares-based approach, and statistical significance of each model was evaluated based on regression coefficients and corresponding 95% confidence intervals. The relative contribution of

each predictor variable in explaining observed variance in each criterion variable were assessed by examining the *R*-squared statistic (R^2).

Results

Participant Characteristics and Pain Ratings

Participants included 277 patients with chronic pain (60.6% female; 90.6% White/Caucasian; 89.9% non-Hispanic/Latino; M_{age} = 56.3, *SD* = 13.2, Median = 58). Female patients were older than male patients; $t(274) = 2.9$, $p = .005$, 95% CI = 1.42:7.72 (female; M = 58.1, SD = 13.4, male; M = 53.5, SD = 12.2). Most patients (51.3%) were using Medicare as their primary insurance. The most common pain location was in the lumbar and thoracic regions (87%), and patients reported a mean of two pain locations (*M* = 1.9; range 0-5). A diagnosis of pain with neuropathic features was present for most patients (79.4%). Pain intensity ratings (NRS) at the most recent pain clinic visit (*M* = 5.9, *SD* = 2.1) indicate that the sample was experiencing moderate and clinically significant pain (Krebs, Carey, & Weinberger, 2007). Paired samples *t*-test indicated no change in NRS ratings collected closest to date of certification (M = 5.93) vs. NRS ratings closest to the six-months follow-up (M = 5.66); $t(234) = 1.81$, $p = .07$, 95% CI = -0.03:0.56. See Tables 1 and 2 for sociodemographic and pain characteristics organized by use of medical cannabis.

Characteristics of Medical Cannabis Purchases

Consistent with hypothesis, approximately 91% of the sample filled their certification for medical cannabis at least once by six months following initial certification (*n* = 253, 91.3%). Patients purchased medical cannabis using their certification a median of three separate times during the six months following initial certification (Mean = 3.8; SD = 3.4). Of those who

purchased medical cannabis at least once 45% had active product at follow-up. The most commonly purchased product in terms of method of administration was vaporization (61.3% of patients purchased at least once) and the least common method purchased was oral spray (32.8% purchased at least once). Product formulations containing low CBD and high THC content were the frequently purchased in terms of total doses (50.5%). See Table 3 for details of medical cannabis use.

Changes in Prescription Opioid Use at Six Months Post-Certification

The median aggregated dose of prescribed opioids was 44.3 MME at time of certification (mean = 47.4, range = 5:320). At six-month follow-up, the median aggregated dose of prescribed opioids was 20 MME (mean = 37.8, range = 0:320), representing an average decrease of 24% compared to the day of certification. Among those who purchased medical cannabis, 105 (42%) stopped or reduced their prescription opioid use during the first six months following certification, with a mean reduction of 22.8 MME/day (SD=66.4; range = 1.2 - 130). Among those who purchased medical cannabis, 38% achieved a clinically-significant reduction in opioid use during the study period (± 30%; Buonora, Perez, Heo, Cunningham, & Starrels, 2018; Henry, Wilsey, Melnikow, & Iosif, 2015), with (26%) of these patients discontinuing use.

Changes in Prescription Opioid Use as a Function of Medical Cannabis Use

Regression models indicated no association between filling a medical cannabis certification at least once, total medical cannabis purchases, or total dosages and the likelihood of stopping/reducing (vs. stable/increasing) prescription opioid use (*p*s > .05, 95% CIs ± 0). Follow-up analyses indicated that nearly half (46%) of patients who purchased medical cannabis at or above the median purchase frequency (i.e., 3) reduced or stopped their prescription opioid use. In

contrast, only 36% of patients who filled below the median number of times reduced or stopped their use of prescription opioids. This difference was not statistically significant ($\chi^2 = 2.8$; $p = .09$).

Medical Cannabis Use and Changes in Prescription Opioids as a Function of Age and Sex

In terms of the type of products used, female (vs. male) patients purchased greater daily doses of equal ratio THC:CBD products $t(253) = 3.43$, $p = .001$ 95% CI = 4.07:15.05 (Female; M = 19.8, SD = 31.2, Male; M = 10.3, SD = 14.7). Neither age nor sex was associated with the odds of purchasing (vs. not purchasing) medical cannabis during the study period (*p*s > .05, 95% CIs ± 0), the total number of separate purchase instances period (*p*s > .05, 95% CIs ± 0), nor total dosages purchased during the study period (*p*s > .05, 95%CIs ±0). In terms of the likelihood of having an active product at follow-up, no differences were observed as a function of age or sex (*p*s > .05, 95%CIs ±0). However, an interaction effect was observed among those who purchased product at least once. Specifically, age was positively associated with greater log odds of having an active product at follow-up among males but not among females ($\chi^2 = 8.7$, $df = 1$, $p < .01$). Among those who purchased medical cannabis, neither age nor sex was associated with odds of stopping/reducing (vs. stable/increasing) prescription opioid use (*p*s > .05, 95%CIs ±0), or changes in daily MME (*p*s > .05, 95%CIs ±0). See tables 5 and 6 for details of regression models.

Discussion

The current study is the largest EMR and PDMP-based retrospective examination of medical cannabis and prescription opioid use among a sample of treatment-seeking chronic pain patients following initial certification. Consistent with hypotheses, the majority (91%) of patients

filled their medical cannabis certification at least once and nearly half (45%) had an active product at follow-up. The frequency of medical cannabis purchases was heterogenous, exhibited a positively skewed distribution, and a median of three transactions over the six-month study period. Among patients who purchased medical cannabis, 42% reduced their prescription opioid use by six months post-certification with 26% of these patients discontinuing use entirely. The proportion of opioid reduction/elimination was 10% greater among patients who purchased medical cannabis at least three times (vs.< 3 times). Female (vs. male) patients purchased greater dosages of equal ratio THC:CBD products, and age was positively associated with greater odds of having an active product at follow-up among males but not among females. Contrary to hypotheses, no further associations were observed between age, sex, or other indices of medical cannabis consumption, nor subsequent changes in prescription opioid use.

The majority of patients in the current study (91%) purchased medical cannabis at least once. This is 27% higher than observed in another cohort of chronic pain patients that also used a six month observation period (O'Connell et al., 2019), which could be a result of numerous factors including sampling criteria (i.e., co-use of benzodiazepines; O'Connell et al, 2019). The frequency of purchases was positively skewed (skew = 1.96) and patients purchased a wide range of dosage days (range = 5:417, mean = 64.5, SD = 67.2). Heterogeneity in medication use can be influenced by a variety of factors, including complexity of the medication regimen/lack of patient education, lack of efficacy/unfavorable side-effects, as well as cost (Fishman et al., 2000). Thus, at least three interrelated reasons may explain current findings. First, unlike prescription medications the dosing, timing of use, and method of administration is not standardized for medical cannabis (Brooks, Gundersen, Flynn, Brooks-Russell, & Bull, 2017; Fischer et al., 2017b; Fletcher, 2013). Instead, guidelines for administration have focused on

general diagnostic considerations (i.e., chronic pain) and not product variables (Kansagara, Becker, Ayers, & Tetrault, 2019). In the absence of specific guidance from providers, patients may rely on dispensary staff for advice. For example, only 2.6% of medical cannabis patients choose products based on advice from a medical professional and about half rely on dispensary employees (54.9%; Boehnke, Scott, Litinas, Sisley, Clauw, et al., 2019), who do not always provide evidence-based recommendations (Haug et al., 2016).

Second, inconsistency in the effects of cannabinoids and possible side effects might have contributed to the heterogenous pattern of use observed here (Lotsch, Weyer-Menkhoff, & Tegeder, 2018; Mun et al., 2020). For example, patients may trial multiple products in an attempt to titrate dosing to meet the narrow therapeutic window for analgesic effects (Khan, Pickens, & Berlau, 2019; Wallace et al., 2007). Presence of side-effects may also have driven some patients to discontinue use. Indeed, high THC:low CBD formulations were the most commonly purchased in the current sample (M = 41 dosage days), and unwanted side-effects are most common with high THC products (Martin-Sanchez, Furukawa, Taylor, & Martin, 2009). Third, the cost of medical cannabis may have led patients to use less than needed for adequate efficacy or have led some to ration their dosing (O'Connell et al., 2019). Medical cannabis patients spend a mean of over $3,000 per year on these products (Piper et al., 2017), and almost 30% of dispensary patients with chronic pain cite cost as a problem (Piper et al., 2017). The expense associated with medical cannabis has been hypothesized as a reason that nearly half of medical cannabis patients in Minnesota did not re-enroll in the program (Philbrick, 2019).

Vaporization-based products were the most purchased method of administration among the current sample. One possible explanation for this finding is that vaporization allows patients to rapidly self-titrate dosing, which is preferred by the majority of medical cannabis users

(Shiplo, Asbridge, Leatherdale, & Hammond, 2016). Vaporized products also produce a more robust analgesic response compared to tinctures and edibles (Mun et al., 2020). Furthermore, recent findings indicate that non-inhalation-based products from licensed dispensaries often do not contain the advertised amounts of active ingredients (i.e., CBD, THC; Vandrey et al., 2015). Despite these potential advantages of vaporized products, other methods of administration (i.e., tinctures, edibles) were purchased by 33% to 55% of patients in the current study. These patients may have prioritized avoiding the potential health risks associated with inhalation-based products (Fischer et al., 2017a). Indeed, even non-combustible vaporization confers possible health problems (Fischer et al., 2017a). Most notably, incidences of e-cigarette or vaping associated lung injury (EVALI) have been associated with use of THC-containing vape products (Moritz et al., 2019), perhaps a result of contamination with vitamin E acetate (Blount et al., 2019).

Regarding changes in opioid use, nearly half (42%) of all patients reduced or stopped filling their opioid prescriptions during the study period. Furthermore, nearly 40% of patients reached a clinically significant decrease in prescription opioid dosage as defined by ≥ 30% MME reduction (Buonora et al., 2018; Henry et al., 2015). This is the first study to test for differences in opioid reduction between those who purchased (vs. did not purchase) medical cannabis. Both groups evinced a reduction in prescription opioid use (42% vs. 46%, respectively). This difference was not statistically significant, yet an unexpectedly small number of patients did not purchase medical cannabis (n = 24). Given the small sample of non-users and the positive skew of medical cannabis purchase frequency, further analysis was conducted based on median purchase frequency. These analyses revealed that patients who purchased medical cannabis above (vs. below) the median frequency evinced a 10% greater incidence of opioid reduction or

elimination. This is a novel finding as previous studies have not tested for a relationship between medical cannabis purchases and changes in prescription opioid use (Vigil et al., 2017). This signal, albeit it limited, could be reflective of a dose-response relationship between medical cannabis use and prescription opioid use.

In terms of changes in prescription opioid use, a few differences were observed compared to previous retrospective studies (O'Connell et al., 2019; Vigil et al., 2017). Vigil et al. (2017) reported a higher percentage of prescription opioid reduction (84%) and discontinuation (40%) compared to the current study (42% and 26%, respectively). One possible explanation is that the longer follow-up period of 21 months captured pateints who took longer to titrate down their prescription opioids (Vigil et al., 2017). Indeed, O'Connell et al. (2019) reported that no patients discontinued prescription opioid use by six months post-medical cannabis certification, despite a statistically significant reduction in total opioid dosage (O'Connell et al., 2019). No change in NRS pain ratings was observed between time of certification and six months post-certification in the present study, which is consistent with prior findings and suggests analgesic response was maintained (O'Connell et al., 2019). However, a second study reported a statistically significant reduction in NRS ratings at 12 months post-certification (Vigil et al., 2017). One posssible explanation for these findings is that a reduction in opioids is more likley with lower initial doses, which are perhaps reflective of less severe pain. Indeed, medical cannabis users in the current study were prescribed higher mean doses of opioids at time of certification (47 MME) compared to the study that observed a reduction in NRS scores (24 MME; Vigil et al., 2017). One method to compare samples maintained on varying doses of prescription opioids is to test for the clinical signifigance of opioid dose reduction, which is typically defined as $\geq$ 30% MME (Buonora et al., 2018). In the current study 37% of patients evinced a clinically-significant

reduction in opioid dosage, which reflects the majority of patients who reduced/discontinued at all. This is especially notable given that prescription opioid dosing is often stable over time among chronic pain patients (Henry et al., 2015).

Collectively, it appears that a portion of medical cannabis patients may evince clinically significant reductions in prescription opioid use after initiating medical cannabis, without reporting a change in pain intensity. One tentative possibility is that this reflects the opioid-sparing effects seen in experimental studies (Chen et al., 2019; Nielsen et al., 2017). Regardless of the specific mechanism involved, reductions in prescription opioids following medical cannabis use could mitigate risk of deadly overdose (Guy et al., 2017) and decrease both the frequency and severity of side effects that are common with chronic administration of opioids (Anastassopoulos et al., 2013).

In terms of age and sex distribution, the mean age of the current sample was 56.3 and skewed female (60% female), which is broadly consistent with previous studies (Degenhardt et al., 2015; O'Connell et al., 2019; Vigil et al., 2017). Female (vs. male) patients purchased greater total daily dosages of high CBD:low THC products, and age was positively associated with greater log odds of having an active medical cannabis product at follow-up among males but not among females. Contrary to hypotheses, no further age or sex differences were observed in terms of medical cannabis use or changes in prescription opioid dosage. These hypotheses were based on theories of prescription medication use (Rottman et al., 2017) and findings often among patients using cannabis for therapeutic purposes without a certification (e.g., Cuttler, Mischley, & Sexton, 2016). Thus, one possibility that hypotheses were not supported is that the relationships typically observed for prescribed medication do not generalize to medical cannabis (Degenhardt et al., 2015). Males (vs females) are more likely to seek a medical cannabis

certification (Pedersen, Tucker, Seelam, Rodriguez, & D'Amico, 2019) and have prior experience with cannabis (Cooper & Craft, 2018). On the other hand, meta-analysis indicates that women (vs. men) are more likely to use prescription opioids (Serdarevic, Striley, & Cottler, 2017). Thus, one tentative explanation for current findings is that males experience with cannabis translates to a more typical pattern of medication taking behavior. The interaction between age and sex is suggested by initial experimental research (Britch et al., 2020; Craft et al., 2019) but more research is required to confirm current results.

The present study raises several clinical implications. First, providers might consider ongoing monitoring of medical cannabis patients' motivation and intention to reduce their prescription opioids for at least six months following initial certification. Early identification and support for patients who are trying to reduce their use of prescription opioids could help mitigate iatrogenic effects of prescription opioids (Darnall, Mackey, et al., 2019). Importantly, such a patient-centered approach must also consider the potential benefits of prescription opioids and avoid forced tapering of these medications (Darnall, et al., 2019; Darnall et al., 2018). Second, providers might consider ways to reduce the overall cost of medical cannabis, perhaps by minimizing certification fees for the large proportion of patients on a fixed income (i.e., use of Medicare/Medicaid). Indeed, 61% of the current sample was covered primarily by a government funded insurance program. Helping patients afford adequate dosing of medical cannabis could mitigate wasted financial resources and reduce the burden on healthcare systems (Briesacher, Gurwitz, & Soumerai, 2007).

Third, providers might consider ongoing use of state prescription drug monitoring systems to monitor adherence and identify increases in use which might suggest development of tolerance to analgesic effects (D'Souza et al., 2016; MacCallum & Russo, 2018; Wakley, Wiley,

& Craft, 2014). Tracking patient's use of medical cannabis might also be used to improve patient-centered care by reinforcing treatment goals (Moore et al., 2004). For example, personalized feedback using data from drug monitoring programs and delivered using a motivational enhancement therapy (MET) approach might facilitate accurate perceptions of medication effects and improve adherence (Palacio et al., 2016; Rottman et al., 2017).

Fourth, mixed findings with regard to age and sex indicate the need for further tests to identify predictors of medical cannabis utilization (Gast & Mathes, 2019), and dissuade providers from generalizing findings from prescription medication use to medical cannabis (Kansagara et al., 2019). For example, common co-morbid psychiatric problems among those with chronic pain such as depression and anxiety-related disorders (Feingold, Brill, Goor-Aryeh, Delayahu, & Lev-Ran, 2017; Hooten, 2016) may evince nonintuitive relationships to medical cannabis use. Indeed, recent meta-analysis indicates that anxiety (50%), and depression/mood (34%) are common reasons for medical cannabis use (Kosiba, Maisto, & Ditre, 2019), yet chronic exposure to cannabis may exacerbate certain psychiatric symptoms (National Academies of Sciences, 2017). Taken together, an idiographic approach to the use of medical cannabis comprised of substantial patient education, collaboration, and monitoring of treatment goals seems warranted (Beaulieu, Boulanger, Desroches, & Clark, 2016; Kahan et al., 2014; MacCallum & Russo, 2018; Sutherland, Nicholls, & Clarke, 2017). Theoretical models of medication adherence posit that patients rely on beliefs derived from initial personal experiences with medications to make decisions regarding their use in pursuit of a desired health outcome (Rottman et al., 2017). Thus, any additional support from providers may be especially impactful as patients are adjusting their medications (Alison Phillips, Leventhal, & Leventhal, 2013).

The current study follows calls for examining associations between medical cannabis and opioid use among individuals with chronic non-cancer pain (Brooks et al., 2017; Carlini, Garrett, & Carter, 2017; Hill, Palastro, Johnson, & Ditre, 2017; St-Amant, Ware, Julien, & Lacasse, 2015) and has several strengths. First, the use of a venue-based sample is a recommended approach that allowed for the recruitment of a highly specific population of critical interest (Rothman, Gallacher, & Hatch, 2013; Thomas & Freisthler, 2016). This approach also builds on studies among online convenience samples (Bonn-Miller, Boden, Bucossi, & Babson, 2014), which are often biased representations of the larger population (Jeong et al., 2019). The use of a retrospective design is also a recommended approach to studying relationships between medical cannabis and prescription opioids (McCarty, 2018), as it minimizes potential for provider bias in prescribing practices associated with a prospective design (Verheij, Curcin, Delaney, & McGilchrist, 2018). The current study also extends prior self-report studies (e.g., Boehnke et al., 2016) by including objective data on opioid and medical cannabis purchases. This helps to minimize reporting bias and loss of follow-up, which have been as high as 60% in previous samples (Vigil, Stith, & Reeve, 2018; Zolotov et al., 2016). Lastly, this is the first study to examine age and sex in relation to medical cannabis use and subsequent prescription opioid use.

The current results must be interpreted in the context of specific methodological limitations. First, while the retrospective design extends previous cross-sectional research, no causal relationships can be inferred. Future research might use a control group matched on key variables that would be prohibited in randomized experimental designs (i.e., length of opioid use; Scherrer & Pace, 2017). Second, the current study did not collect data on the concomitant use of cannabis obtained without a certification, use of cannabis for non-therapeutic purposes, cost/affordability of medical cannabis, or other interventional pain treatments during the study

period. Use of non-medical cannabis is one possible explanation for the changes in prescription opioid use observed among those who did not purchase medical cannabis. Thus, research is needed to examine these variables as potential confounds and modifiers of observed associations. Third, the current study used a single follow-up interval of six months, which was chosen to be consistent with theories of medication behavior change (Rottman et al., 2017), existing data among medical cannabis users (Zolotov et al., 2016), and to facilitate comparison across other studies (O'Connell et al., 2019; Vigil et al., 2017). However, reductions in MME may not be fully realized until up to 12 months following certification (Vigil et al., 2017)..

Fourth, the current study did not examine core elements of co-occurring psychiatric disorders (i.e., transdiagnostic factors) that might influence medical cannabis use and subsequent changes in prescription opioids. For example, discomfort intolerance has been positively associated with cannabis use among persons with chronic pain (Kosiba, Mitzel, Zale, Zvolensky, & Ditre, 2020), and both distress (in)tolerance and pain-related anxiety have been associated with prescription opioid misuse among those with chronic pain (LaRowe et al., 2018; McHugh et al., 2016). Future research might also examine coping motives for medical cannabis use (K. M. Bohnert et al., 2018), expectancies for drug effects (Metrik et al., 2009), and the role of co-morbid psychological disorders (Demyttenaere et al., 2007). For example, research is needed that assesses whether or not patients are motivated to reduce their prescription opioid use prior to the initiation of medical cannabis.

Studies are needed which can examine the course of changes in medical cannabis use and prescription opioid use at multiple time points and over a longer follow-up period (i.e., $\geq$ 12 months). The use of a venue-based sample has been recommended for studying medical cannabis use (Kepple & Freisthler, 2017), yet this necessarily limits generalizability to other

geographic/legislative regions. A sampling strategy that makes use of multi-level modeling could test for different patterns of medical cannabis and prescription opioid use across treatment facilities nested within geographic regions (Keyes et al., 2016). Indeed, rapidly evolving legislation governing the use of medical cannabis has resulted in substantial geographic differences in the legality, availability, and acceptance of medical cannabis (Klieger et al., 2017). Future studies must keep up with these changes to produce timely, clinically relevant findings (Frieden, 2017; Ware, 2018).

This retrospective study is an essential first step in a programmatic line of research aimed at improving our understanding of medical cannabis and prescription opioid use among chronic pain patients. Most patients (91%) purchased medical cannabis at least once within the first six months following certification. Clinically significant reductions in prescription opioid use were observed among 37% of those who purchased medical cannabis, despite substantial variability in products and dosages purchased. Future research is needed to test the possible role of psychosocial factors and examine why some patients do not purchase medical cannabis following certification.

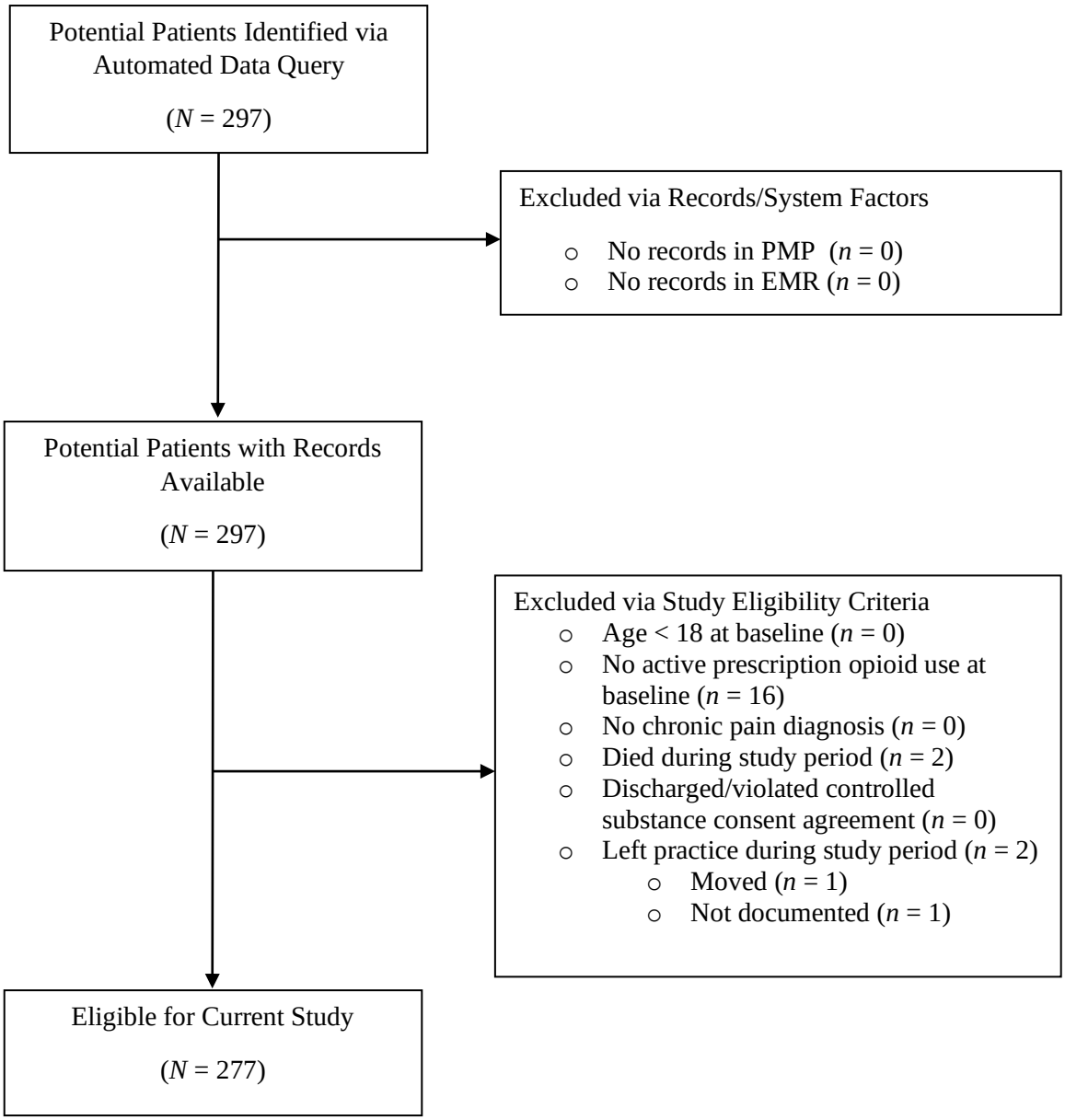

Figure 1. Eligibility Flowchart

Table 1

Sociodemographic Variables

	Purchased Medical Cannabis (*n* = 253)	No Medical Cannabis Purchased (*n* = 24)	Entire Sample (*N* = 277)
	n (%)	*n* (%)	*n* (%)
Biological Sex			
Female	156 (61.7)	12 (50)	168 (60.6)
Male	97 (38.3)	12 (50)	109 (39.4)
Ethnicity			
Hispanic/Latino	4 (1.6)	2 (8.3)	6 (2.2)
Non-Hispanic/Latino	228 (90.1)	21 (87.5)	249 (89.9)
Declined to report	21 (8.3)	1 (4.2)	22 (7.9)
Race			
White	228 (90.1)	23 (95.8)	251 (90.6)
Black/African American	6 (2.4)	0 (0)	6 (2.2)
Asian	0 (0)	0 (0)	0 (0)
American Indian/Alaskan Native	1 (0.4)	0 (0)	1 (0.4)
Hawaiian/Pacific Islander	0 (0)	0 (0)	0 (0)
More than one Race	9 (3.6)	0 (0)	9 (3.2)
Declined to report	9 (3.6)	1 (4.2)	10 (3.6)
Marital Status			
Single	51 (20.2)	6 (25)	57 (20.6)
Married	151 (59.7)	12 (50)	163 (58.8)
Divorced	18 (7.1)	1 (4.2)	19 (6.9)
Widowed	3 (1.2)	1 (4.2)	4 (1.4)
Not documented or not reported	30 (11.9)	4 (16.7)	34 (12.3)
Primary Insurance[1]			
Private	97 (40.3)	5 (21.7)	102 (38.8)
Medicare	123 (51.2)	12 (52.2)	135 (51.3)
Medicaid	20 (8.3)	6 (26.1)	26 (9.9)
	M (*SD*) (range)	*M* (*SD*) (range)	*M* (*SD*) (range)
Age	56.2 (13.0) 27-91	58 (15.2) 29-89	56.3 (13.2) (27-91)

Note. [1]*N* = 264 available due to missing data, valid percentages reported.

Table 2

Pain Locations, Pain Diagnoses, and Pain Intensity

	Purchased Medical Cannabis (*n* = 253)	No Medical Cannabis Purchased (*n* = 24)	Entire Sample (*N* = 277)
	n (%)	*n* (%)	*n* (%)
Pain Locations[1]			
Head/Cervical	118 (46.6)	10 (41.7)	128 (46.2)
Back (Lumbar and Thoracic)	220 (87)	21 (87.5)	241 (87.0)
Lower Extremity	94 (37.2)	5 (20.8)	99 (35.7)
Upper Extremity	48 (19)	3 (12.5)	51 (18.4)
Chest	3 (1.2)	0 (0)	3 (1.1)
Stomach	1.4 (5.5)	0 (0)	14 (5.1)
Pain Quality and Diagnoses[1]			
Nerve Involvement/Nerve Pain	202 (79.8)	18 (75)	220 (79.4)
Fibromyalgia	22 (8.7)	1 (4.2)	23 (8.3)
Chronic Regional Pain Syndrome	5 (2)	0 (0)	5 (1.8)
	M (*SD*) (Range)	*M* (*SD*) (Range)	*M* (*SD*) (Range)
Number of Pain Locations	2 (0.9) 0-5	1.6 (0.8) 0-3	1.9 (0.9) 0-5
Pain Intensity[2]			
Prior to Certification[3]	5.8 (2.1) 0-10	6.3 (2.5) 0-10	5.9 (2.1) 1-10
Six-Months Post-Certification[4]	5.7 (2.1) 0 -10	5.4 (2.6) 1-10	5.7 (2.1) 0-10

Note. [1]Active clinical diagnosis/conditions recorded in the electronic medical record, Patients may have had multiple diagnoses; [2]numerical rating scale for pain intensity.[3]Based on appointment data recorded ≤ date of certification; [4]Based on appointment data recorded ≥ six months post-certification.

Table 3

Medical Cannabis Use[1]

Method of Administration Purchased	Number of patients *n* (%)
Vaporizer	155 (61.3)
Tincture	139 (54.9)
Oral Spray	83 (32.8)
Capsules/Powder	117 (46.2)
Active product at six months post-certification	113 (44.7)
Type of Product	**Dosage days purchased *M (SD) Range***
High CBD and Low THC	5.5 (14.2) *0 – 106*
Equal Ratio CBD and THC	17.5 (27) *0 - 150*
Low CBD and High THC	41.4 (50.5) *0 – 292*
Aggregated Purchase Data	***M (SD) Range***
Number of separate days purchased	4.16 (3.19) *1 - 20*
Total dosages purchased	64.5 (67.25) *5 - 417*

Note. [1]Among those who purchased medical cannabis at least once (N = 253).

Table 4

Prescription Opioid Dosages at Certification and Six-Months Post-Certification

	Purchased Medical Cannabis (n = 253)	No Medical Cannabis Purchased (n = 24)	Entire Sample (N = 277)
	M (*SD*)	*M* (*SD*)	*M* (*SD*)
At certification date	49.69 (74.29)	47.16 (45.32)	47.38 (48.34)
At six-month follow-up	40.62 (75.37)	37.56 (45.37)	37.82 (48.52)
Mean change in MME	-9.06 (15.89)	-9.6 (27.3)	-9.55 (26.49)
Mean % change in MME	-34.3 (49.77)	-22.85 (66.45)	-23.85 (65.18)

Note. All prescription opioid dosages in Morphine Milligram Equivalents (MME)

Table 5

Variables Associated with Medical Cannabis Use: Dichotomous Criterion

	Criterion: Purchased medical cannabis (yes/no)					
	R^2	β	SE	Wald's χ^2	95% CI	*p*
Age	0.00	-0.01	0.02	0.43	-0.05:0.03	.51
Sex	0.01	-0.47	0.45	1.20	-1.38:0.43	.27
Pain Intensity[1]	0.01	-0.1	0.13	0.97	-0.38:0.13	.4
	Criterion: Active medical cannabis at follow-up (yes/no)					
	R^2	β	SE	Wald's χ^2	95% CI	*p*
Age	0.02	0.02	0.01	3.52	-0.003:0.04	.07
Sex	0.00	-0.05	0.25	0.04	-0.55:0.45	.85
Pain Intensity[1]	0.02	-0.11	0.06	3.63	-0.23:0.004	.05

Note. Sex: 0 = female, 1 = male; [1]numerical rating scale for pain.

Table 6

Sex as a Moderator of Age on Odds of Active Medical Cannabis at Follow-Up

Path		***Coeff.***	**SE**	***z***	***p***	**95% CI**
Constant	*c*	-0.11	0.69	-0.16	.87	-1.48:1.25
Age (X)	b_1	-0.00	0.01	-0.33	.73	-0.03:0.02
Sex (M)	b_2	-3.81	1.26	-3.01	< .01	-6.29:-1.33
Age x Sex (X*M)	b_3	0.07	0.02	3.11	< .01	0.02:0.11

Note. Sex: 0 = female, 1 = male.

Table 7

Variables Associated with Medical Cannabis Use: Linear Criterion

	Criterion: Total daily doses of medical cannabis purchased				
	β	*b* (SE)	R^2	95% CI	*t (p)*
Age	0.09	0.00 (0.00)	0.01	-0.00:0.01	1.38 (.17)
Sex	-0.02	-0.02 (0.06)	0.00	-0.13:0.09	-0.32 (.75)
Pain Intensity[1]	-0.04	-0.01 (0.01)	0.00	-0.04:0.02	-0.68 (.49)
	Criterion: Number of times medical cannabis was purchased				
	β	*b* (SE)	R^2	95% CI	*t (p)*
Age	0.08	0.00 (0.00)	0.01	-0.00:0.00	1.3 (.2)
Sex	-0.01	-0.01 (0.03)	0.00	-0.06:0.06	-0.15 (.88)
Pain Intensity[1]	-0.02	-0.00 (0.01)	0.00	-0.02:0.01	-0.34 (.73)

Note. Sex: 0 = female, 1 = male; [1]numerical rating scale for pain.

Table 8

Variables Associated with Prescription Opioid Use: Dichotomous Criterion

	Criterion: Reduced prescription opioid use (yes/no)					
	R^2	β	SE	Wald's χ^2	95% CI	*p*
Cannabis Purchases[1]	0.00	0.03	0.04	0.84	-0.04:0.1	.36
Cannabis Dosage[2]	0.00	0.02	0.27	0.49	-0.36:0.79	.5
Age	0.00	0.00	0.01	0.19	0.99:1.02	.67
Sex	0.00	-0.19	0.26	0.55	-0.73:0.3	.46
Pain Intensity[3]	0.01	-0.06	0.06	1.22	-0.18:0.05	.26

Note. [1]total number of medical cannabis purchases; [2]total dosages purchased; [3]numerical rating scale for pain.

Table 9

Variables Associated with Prescription Opioid Use: Linear Criterion

	Criterion: Raw change in MME				
	β	*b* (SE)	R^2	95% CI	*t (p)*
Cannabis Purchases[1]	-8.18	-8.18 (6.73)	0.01	-21.17:5.08	-1.2 (.23)
Cannabis Dosage[2]	-0.05	-3 (3.54)	0.001	-9.96:3.91	-0.83 (.41)
Age	-0.04	-.08 (0.12)	0.001	-0.31:0.15	-0.59 (.55)
Sex	0.1	5.54 (3.44)	0.01	-1.38:12.3	1.63 (.12)
Pain Intensity[3]	0.07	0.88 (0.78)	0.005	-0.64:2.42	1.1 (.27)
	Criterion: Percentage change in MME				
	β	*b* (SE)	R^2	95% CI	*t (p)*
Cannabis Purchases[1]	-0.02	-5.5 (14.9)	0.00	-35.33:23.1	-3.2 (.75)
Cannabis Dosage[2]	0.00	0.65 (8.5)	0.00	-16.86:16.58	0.07 (.94)
Age	0.02	0.10 (0.003)	0.00	-0.52:0.77	0.3 (.76)
Sex	-0.01	-1.88 (9.23)	0.00	-19.21:17.2	-0.22 (.83)
Pain Intensity[3]	0.11	3.47 (1.67)	0.01	0.3:6.86	1.73 (.09)

Note. Sex: 0 = male, 1 = female; [1]total number of medical cannabis purchases; [2]total dosages purchased; [3]numerical rating scale for pain.

Appendix A

Morphine Milligram Equivalents (MME) Calculations[1]

Opioid (in mg/day except as noted)	**Conversion Factor**
Codeine	0.15
Fentanyl Transdermal (mcg/hour)	2.4
Hydromorphone	4.0
Hydrocodone	1.0
Morphine	1.0
Methadone	≤ 20 = 4 > 20, ≤ 40 = 8 > 40, ≤ 60 = 10 ≥ 60 = 12
Oxycodone	1.5
Oxymorphone	3.0
Tramadol	0.1

[1]Adapted from www.cdc.gov/drugoverdose/prescribing/guideline.html; Accessed 6.26.2018

Appendix B

Numerical Rating Scale for Pain (NRS)

How would you rate your pain RIGHT NOW?

No Pain										Pain as bad as could be
0	1	2	3	4	5	6	7	8	9	10

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