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Featured Article

Real-Time Monitoring of Cannabis and Prescription Opioid Co-Use Patterns, Analgesic Effectiveness, and the Opioid-Sparing Effect of Cannabis in Individuals With Chronic Pain

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Abstract: **Despite a rapid expansion of cannabis use for pain management, how cannabis and prescription opioids are co-used and whether co-use improves analgesia and promotes reduction of opioid use in the daily lives of individuals with chronic pain is poorly understood. Based upon ecological momentary assessment (EMA), the present study examined 1) how pain and use of opioids and/or cannabis in the previous moment is associated with individuals' choice of opioids and/or cannabis in the next moment, 2) the effects of co-use on pain severity and pain relief, and 3) whether daily total opioid consumption differs on days when people only used opioids versus co-used. Adults with chronic pain (N = 46) using both opioids and cannabis who were recruited online completed a 30-day EMA. Elevated pain did not increase the likelihood of co-use in subsequent momentary assessments. Switching from sole use of either opioids and cannabis to co-use was common. Neither co-use nor sole use of either cannabis or opioids were associated with reductions in pain in the next moment. However, participants reported the highest daily perceived pain relief from co-use compared to cannabis and opioid use only. Post hoc analysis suggested recall bias as a potential source of this discrepant findings between momentary versus retrospective assessment. Lastly, there was no evidence of an opioid-sparing effect of cannabis in this sample. The present study shows preliminary evidence on cannabis and opioid co-use patterns, as well as the effects of co-use on pain and opoid dose in the real-world setting.**

Perspective: ***This article presents the overall patterns and effects of co-using cannabis and prescription opioids among individuals with chronic pain employing ecological momentary assessment. There were conflicting findings on the association between co-use and analgesia. Co-use was not associated with a reduction in daily opioid consumption in this sample.***

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Key words: *Chronic pain, cannabis, cannabinoids, opioids, opioid-sparing, ecological momentary assessment.*

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The social demand for cannabis products in the midst of opioid epidemic and COVID-19 pandemic is rising to unprecendeted levels in the U.S.[16,25] Chronic pain is the number one reported reason for the medical use of cannabis.[29] To date, more than half of U.S. states have legalized cannabis for either medicinal or recreational use.

Cannabis has shown promise as a possible *opioid-sparing agent* (ie, use of a non-opioid medication to facilitate a reduction in opioid dose for analgesia)[19] in pre-clinical studies. For instance, a recent meta-analysis of 19 pre-clinical studies revealed that combining the opioids morphine and codeine with delta-9- tetrahydrocannabinol (THC) allowed opioid doses to be reduced by 3.6- and 9.5-times, respectively, and produced an analgesic effect equivalent to that produced by higher doses of morphine or codeine alone.[22]

Human laboratory studies, on the other hand, provide overall less compelling evidence for opioid-sparing effects of cannabis.[13] Most of the laboratory studies to date show either attenuation of opioid analgesia or no significant improvement of analgesia when THC and opioids are combined.[1,21,24] THC enhancement of opioid effects in humans has thus far been observed only in low opioid dose conditions, while combining THC with an opioid has led to increased negative outcomes, such as increased ratings on abuse potential measures, dysphoric effects, and adverse events, suggesting a narrow therapeutic window.[9,12] However, these studies were all conducted in healthy research volunteers, rather than individuals with chronic pain, and mostly examined synthetic THC (ie, dronabinol)[1,12,21,24] with small dose ranges, limiting our understanding of cannabis-opioid interactions among patients with chronic pain who use an array of cannabis products and doses presently available through medical and recreational markets.

These human laboratory studies also do not align with repeated anecdotal reports from individuals with chronic pain who report that co-use of opioids and varied cannabis products is an important strategy for their personal pain management. In fact, the real-world potential for the opioid-sparing properties of cannabis is partially supported by epidemiological studies, which have found that cannabis legalization was associated with reduced opioid prescriptions, doses, and overdose deaths.[2,5] However, these studies are not definitive, and other recent data have been unable to replicate these associations.[13,26] Similarly, longitudinal studies that have examined the effects of medical cannabis use on pain and opioid use over time (≥6 months) have shown largely mixed results.[13]

To date, we lack sensitive data on *how* cannabis and opioids are co-used in the daily lives of individuals with chronic pain, whether cannabis-opioid co-use is a useful pain management strategy, and whether daily cannabis use has an 'opioid sparing' effect in a naturalistic setting. The current study contributes to closing those gaps based upon ecological momentary assessment (EMA) data. Specifically, our study had 4 aims: First, we examined how pain experiences assessed in the previous moment are associated with individuals' choice of medication (ie, opioids only versus cannabis only versus co-use) in the next assessment. Second, we also examined whether the choice of medication varies by cannabis and/or opioids use in the previous moment. Third, we investigated the effects of opioid, cannabis, and their co-use on changes in momentary pain severity, as well as associations between use and perceived pain relief reported during the previous day. Lastly, we examined whether daily total opioid consumption differs on days when people only used opioids versus co-used both cannabis and opioids.

Methods

We recently published a study based upon the current data which focuses on testing the feasibility and acceptability of using smartphone-based EMA for assessing prescription opioid and cannabis use among individuals with chronic pain.[15] The present study is a primary outcome paper and the aims of this study do not overlap with those in the previous publication.

Participants

Participants were recruited from December 2019 to June 2020 from Washington D.C. and 11 states that had legalized recreational cannabis use at the time of recruitment (ie, Alaska, California, Colorado, Illinois, Maine, Massachusetts, Michigan, Nevada, Oregon, Vermont, and Washington). Recruitment was conducted using paid Facebook and Instagram advertisements and via social media posts by Realm of Caring Foundation, a non-profit organization based in Colorado. The advertisements included a link that directed individuals to an online study eligibility questionnaire and an informed consent form. Inclusion criteria for the present study were individuals who 1) were at least 18 years of age, 2) had a current prescription for opioid medication for pain symptoms, 3) used their prescribed opioid medication in the past 30 days, 4) had a medical cannabis recommendation, 5) used cannabis in the past 30 days, 6) had a chronic pain condition, 7) reported pain severity of at least 3 on a scale of 0 to 10 on at least 10 days of each month for the past 3 months or longer, 8) had a smartphone (either iPhone or Android-based phones), and 9) currently lived in a state with legalized access to retail cannabis for adults. The exclusion criterion was currently having a severe mental or neurological disorder (eg., schizophrenia, psychotic disorder, dementia).

Among 3,853 individuals who completed the screening questionnaire, a total of 115 participants were eligible for the study. The most frequent reasons for being ineligible (not mutually exclusive) were no current opioid prescription (67.0%), not having used prescription opioids in the past 30 days (62.4%), or not having a medical cannabis recommendation (48.2%). Of those eligible, 65 people provided identification and were verified for study participation. Among these 65 individuals, 51 completed the baseline survey and were invited to the EMA phase. Finally, 46 participants

completed the 30-day EMA and were included in the current analyses.

Procedures

After completing the initial screening and consent procedures, participants completed a baseline survey that assessed socio-demographic characteristics, substance use behavior and history, and chronic pain. Participants were also asked to identify from a list of long- and/or short-acting oral and non-oral opioid medication (s), as well as all cannabis products (ie, flower, oil, concentrates, edibles, topicals, and prescription medications) they had used in the past month.

Following the baseline survey, participants started the EMA phase of the study. EMA data collection was conducted using the PiLR EMA smartphone application (MEI Research Ltd., Minnesota, USA), on participants' personal smartphones. Prior to starting EMA data collection, participants completed a 3-day demo period during which they received remote support from study staff on how to use the app. After the demo period, participants began the 30-day EMA phase in which they were asked to respond to prompted surveys about their opioid and cannabis use and pain-related experiences on the study app. On each day, participants received notifications to complete 5 different surveys, 4 of which were prompted at random times between 8 am and 11 pm (participant device local time), assessed opioid and cannabis use as well as pain during the previous hour, and had to be completed within a 1-hour time window. As opioids and cannabis can produce drug effects for several hours,[14,28] we decided to conduct the random prompt assessments approximately every 3 to 4 hours. The fifth survey was a retrospective daily diary that was always prompted between 10 am and 11 am and asked about participants' experiences on the previous day. This daily diary had a 12-hour time window for completion.

For each participant, EMA surveys were pre-populated with the prescription opioid(s) and cannabis product(s) that she or he had reported currently using on the baseline survey. Each EMA survey took approximately 2 minutes to complete and participants could communicate questions or concerns to research staff via email and text message. During the EMA phase, research staff sent participants text messages on days 3, 4, 14, and 21 to inform their cumulative EMA survey completion rate. The staff also regularly monitored participants' EMA survey activities and conducted check-ins to troubleshoot issues.

Each participant received $2 for each day of participation in the EMA surveys (a maximum possible $60 for a 30-day EMA) plus a bonus of $60 if they achieved at least 75% completion rate of all EMA surveys over the entire 30-day data collection period. Participant incentives were provided by electronic gift cards, which were emailed to participants at the end of the study. All of the study procedures were approved by the Institutional Review Board at Johns Hopkins Bloomberg School of Public Health.

Measures

Baseline Assessment

Sociodemographic characteristics. The baseline survey assessed sociodemographic information, including age, sex, race/ethnicity, and education.

Brief pain inventory–short form. Baseline pain severity and pain interference were assessed by the Brief Pain Inventory–Short Form (BPI[7]). For assessing pain severity, participants rated their current pain and average, least, and worst pain in the past 24 hours, using a scale ranging from 0 ("*no pain*") to 10 ("*pain as bad as you can imagine*"). For assessing pain interference, participants indicated the extent to which pain interfered with 7 domains of function (eg., general activity, mood, sleep, etc.) using a scale ranging from 0 ("*does not interfere*") to 10 ("*completely interferes*"). We computed mean composite scores for each subscale by averaging ratings within each of the severity and interference sections. Cronbach's alphas for pain severity and pain interference were .73 and .91, respectively.

Graded chronic pain scale. To assess the severity of chronic pain at baseline, the Graded Chronic Pain Scale (GCPS[18]) was administered. GCPS includes 7 items that measure pain intensity and related disability with daily activities. Based upon these items, GCPS allows for classifying participants into 1 of 5 chronic pain severity grades: 1) No Pain, 2) Low Disability-Low Intensity, 3) Low Disability-High Intensity, 4) High Disability-Moderately Limiting, and 5) High Disability-Severely Limiting. Cronbach's alphas for the GCPS pain intensity and disability subscales, which were used for categorization, were .77, and .86, respectively.

Cannabis use. Cannabis use was assessed using select questions from the Quantity of Cannabis Use Inventory (DFAQ-CU).[10] We also administered questions our research team has developed in order to quantify patterns of cannabis use (eg., frequency of cannabis use, quantity used, methods of administration, and type and potency of cannabis used). Cronbach's alphas for the DFAQ-CU factors for frequency, cannabis quantity, and cannabis concentrates were .95, .88, and .76, respectively. Cannabis use data from the baseline assessment were used to uniquely pre-populate the EMA surveys for each participant. Each EMA survey also provided an option to report any additional cannabis products participants may not have reported at baseline.

Opioid use. Opioid use was assessed through self-reported data of opioid use in the past 30 days. Participants selected opioid medications used in the past month from a list of 1) oral long-acting opioid medications, 2) non-oral long-acting opioid medications, and 3) oral short-acting opioid medications. For each selected oral medication (long- or short-acting), data were collected on the dose quantity (eg., in milligrams) and daily dose amount (eg, number of pills per day). For each selected non-oral long-acting medication, data

were collected on the dose quantity (eg., in micrograms) and the number of consecutive days of medication use. Opioid use from the baseline assessment was used to uniquely pre-populate the EMA surveys for each participant. Each EMA survey also provided an option to report any additional opioid products participants may not have reported at baseline.

History of alcohol and drug use problems and mental health conditions. To assess for history of alcohol and drug use problems, participants were asked if they ever had a problem with drugs or alcohol (yes/no). To assess for mental health conditions, participants self-reported past or current diagnosis and/or treatment of depression, bipolar disorder, panic disorder, and posttraumatic stress disorder.

EMA Measures

Momentary cannabis and/or opioid use. In each randomly prompted momentary EMA survey, participants were asked if they used the cannabis product(s) and/or prescription opioid(s) in the past hour. These data were used to assign participants to 1 of the following 4 nominal categorical variables for each momentary assessment: 1) cannabis use only, 2) opioid use only, 3) cannabis and opioid co-use, and 4) neither use of cannabis or opioids (ie, "no use").

Momentary pain severity. In each EMA survey, participants were asked to rate their average pain level in the past hour based upon a numerical rating scale (NRS) that ranges from 0 ("*no pain*") to 10 ("*worst pain imaginable*").[17]

Daily Diary Measures

Daily perceived pain relief. In each daily diary survey, when participants reported using cannabis or opioids, they were asked about percentage of perceived pain relief from using each of these substances. When participants reported using both cannabis and opioids on the previous day, they were also asked if they used these substances together (ie, within the same hour). If they reported using together, they were subsequently asked how much pain relief using cannabis and opioids together provided. For all of these items, perceived pain relief was recorded on a 11-point scale ranging from 0 ("*0% - No relief*") to 10 ("*100% - Complete relief*"). Items were adapted from the BPI.[7]

Daily morphine milligram equivalents for short- and long-acting opioid use. To standardize opioid intake across different prescription opioids we computed morphine milligram equivalents (MMEs) for short- and long-acting opioid use, respectively. For the calculation we used the information that was provided by participants about their opioid prescriptions (ie, generic name and dose), as well as the frequency of their prescribed opioid(s) they reported in each daily diary survey. The oral MMEs were created based on a 2018 compilation of opioid analgesic MME conversion factors from the Centers for Disease Control's National Center for Injury Prevention and Control[23] and were based upon the following equation: strength per unit*(number of units/h)*MME conversion factor = MME/h.

Power Analysis

We have conducted a multi-level model power analysis based upon the MLPowSim program[4] using 1,000 simulation data sets with $\alpha = 0.05$. The simulation suggested that one can reach sufficient statistical power (>80%) to detect a small level-1 (moment-level) effect (ie, fixed effect estimate of .03) when the level-3 cluster size (ie total sample size) is 20, level-2 cluster size (ie the number of days) is 17 and level-1 cluster size (ie the number of random prompts per day) is 3. The present study, in which 46 participants completed the EMA 4 times a day for 30 days, was therefore adequately powered to detect small moment-level effects.

Data Analytic Plan

All analyses were conducted with R software. First, we provided a descriptive summary of socio-demographic and clinical characteristics of the study participants, characteristics of cannabis and prescription opioid use (eg., product types, routes of administration, dose, and etc.), and study retention. Second, we a estimated mixed-effects multinomial logistic regression model to examine 1) how pain experienced in the previous moment is associated with the likelihood of using cannabis and/or opioids (Aim 1), and 2) how cannabis and/or opioid use in the previous moment is associated with the likelihood of using cannabis and/or opioids in the next moment (Aim 2). The mixed-effects multinomial logistic model adequately handles the nested nature of the data (ie, moments nested within days, and days nested within persons) and nominal categorical outcomes. Third, linear mixed-effects models were employed to examine the lagged effects of momentary use of cannabis, opioids, and co-use on pain severity (Aim 3). We estimated a series of models by switching the reference predictor category from "no use" to "co-use." For these models, pain severity reported in the previous observation was included as a covariate to reflect the momentary changes in pain. In terms of testing differences in perceived pain relief from using only opioids, only cannabis, or co-using opioids and cannabis, we present both descriptive statistics and results of a mixed-effects linear regression model (Aim 3). Days of co-use was set as a reference group and was compared to days of only using opioids and days of only using cannabis. Lastly, we tested the difference in total daily short- and long-acting opioid consumption between days when participants used only opioids and days when participants used both cannabis and opioids (Aim 4).

All level-1 predictor variables were cluster-mean centered (eg., for moment-level predictor variables, we

subtracted the day's mean from the original random-prompt rating) so as to evaluate pure level-1 effects. Mixed-effects models included random intercepts, along with a set of fixed effects. For the lagged effect model, because the time interval between 2 adjacent observations were different across random prompt occasions, we included the difference in observation time interval as a covariate. In terms of effect sizes, odds ratios are reported for the mixed-effects multinomial logistic regression model, and Cohen's d estimates are reported for linear mixed-effects models. Note that for calculating Cohen's d in linear mixed-effects models, we used a modified mathematical equation developed by Westfall, Judd, and Kenny.[30] The *lme4* and *nlme* R packages were used for the above-mentioned mixed-effects analyses.

Results

Socio-Demographic and Clinical Characteristics

The majority of participants were women (78.3%), non-Hispanic (91.3%), and White (93.5%). The average age was 44.8 years (SD = 12.9), more than half of the participants had either a college or graduate degree (58.7%), and more than half (54.3%) reported not living with a partner. Average pain severity in the past 30 days at baseline was 6.0 (SD = 1.2) on the 0 to 10 NRS. More than half of participants (56.5%) reported pain that was in the "high disability-severely limiting" category according to the GCPS. Specific pain disorders were not systematically assessed or verified due to the remote nature of the data collection. Only 4 (8.7%) participants reported a lifetime history of either alcohol or drug use problems. In terms of mental health conditions, 39.1% individuals reported having depression, 13.0% reported having bipolar disorder, 32.6% reported having PTSD, and 26.1% reported having panic disorder. Table 1 provides a more detailed summary of socio-demographic and clinical characteristics of the sample.

Table 1. Socio-Demographic and Clinical Characteristics

Characteristic	n (%) or Mean (SD) N = 46
Age	44.8 (12.9)
Sex	
Female	36 (78.3%)
Race	
Black/African American	2 (4.3%)
White	43 (93.5%)
Other (i.e., Asian, American Indian, Alaska Native, and other race)	1 (2.2%)
Ethnicity	
Hispanic	4 (8.7%)
Education	
High school graduate/GED	3 (6.5%)
Some college	16 (34.8%)
2-y college	6 (13.0%)
4-y college	9 (19.6%)
Graduate degree	12 (26.1%)
Marital Status	
Living with partner	8 (17.4%)
Married	13 (28.3%)
Single	13 (28.3%)
Divorced	7 (15.2%)
Separated	2 (4.3%)
Widow/widower	3 (6.5%)
Average Pain Severity	6.0 (1.2)
Graded Chronic Pain Scale Category	
High disability-severely limiting	26 (56.5%)
High disability-moderately limiting	14 (30.4%)
Low disability-high intensity	5 (10.9%)
Low disability-low intensity	1 (2.1%)
History of alcohol or drug use problem	4 (8.7%)
Depression	18 (39.1%)
Bipolar Disorder	6 (13.0%)
Panic Disorder	12 (26.1%)
Post-Traumatic Stress Disorder (PTSD)	15 (32.6%)

Prescription Opioid Products and Dose

Table 2 provides a summary of daily dose for each opioid product category. On average, participants were consuming approximately 2 different types of opioids (M = 1.7, SD = 1.0) at baseline, and use patterns were a mix of short and long-acting opioid medications. The overall daily short- and long-acting dose (morphine equivalent) across the 30-day EMA period was 15.8 mg (SD = 30.1) and 8.7 mg (SD = 23.4), respectively.

Cannabis Products, Dose, Potency, and Routes of Administration

Table 3 provides detailed information on cannabis daily dose and percentage of THC and/or CBD potency for each cannabis product category. Some of the most commonly used cannabis products among participants were cannabis flower with high THC (54.3%), cannabis flower with equal THC and cannabidiol (CBD) levels (39.1%), and cannabis edibles with high THC (39.1%). On average, participants reported using more than 3 different cannabis products (M = 3.5, SD = 2.1) at baseline. Table 4 summarizes participants' characteristics of cannabis use. The 3 most common routes of cannabis ingestion were vaporizer (33.3%), joints (15.6%), and bong (13.3%). In terms of the frequency of cannabis use, participants reported that they use on average 3.1 times/d (SD = 2.5) during weekday and 3.3 times/d (SD = 2.7) on weekends.

EMA Compliance

A total of 6,888 prompts were sent to participants, of which 5,511 (80%) were random prompt surveys and 1,377 (20%) were once daily diaries. Participants had 70% compliance (3845 observations out of 5511 prompts) for random prompt surveys and 92% compliance (1263 observations out of 1377 prompts) for daily diaries.

Table 2. Prescription Opioid Products and Dose

Cannabis Products	Use at Baseline n (%)	Daily Mean Dose (SD)
Oral Long-Acting Opioids		
Oxycodone (OxyContin)	9 (19.6%)	18.9 mg (23.6)
Hydrocodone 12 h (Zohydro)	5 (10.9%)	106.1mg (220.3)
Morphine Sulfates (MS Contin)	5 (10.9%)	21mg (8.2)
Tramadol (Ultram)	5 (10.9%)	65mg (77.8)
Tapentadol (Nucynta)	1 (2.2%)	50mg (0)
Methadone	1 (2.2%)	5mg (0)
Hydrocodone 24 hour (Hysingla)	0 (0%)	—
Hydromorphone (Exalgo)	0 (0%)	—
Morphine Sulfate 24 hour (Kadian)	0 (0%	—
Oxymorphone Hydrochloride	0 (0%	—
Non-Oral Long-Acting Opioids		
Buprenorphine Patch (Butrans)	2 (4.3%)	6.2mcg (1.8)
Buprenorphine Film (Belbuca)	0 (0%)	—
Fentanyl Patch (Duragesic)	0 (0%)	—
Oral Short-Acting Opioids		
Hydrocodone with paracetamol (acetaminophen)	21 (45.7%)	69mg (127.3)
Oxycodone (OxyContin)	7 (15.2%)	8.6mg (2.4)
Tramadol	7 (15.2%)	44.3mg (15.1)
Oxycodone with paracetamol (acetaminophen)	6 (13.0%)	18.8mg (27.8)
Codeine	4 (8.7%)	21.2mg (11.8)
Hydromorphone (Dilaudid)	2 (4.3%)	3mg (1.4)
Oxycodone with ibuprofen	1 (2.2%)	10mg (0)
Demerol (Meperidine)	0 (0%)	—
Dihydromorphine	0 (0%)	—
Nicomorphine	0 (0%)	—
Oxycodone with aspirin	0 (0%)	—
Oxymorphone	0 (0%)	—
Tapentadol	0 (0%)	—

NOTE. The opioid doses described in the table are not morphine equivalents, but rather doses of specific medications.

Cannabis and/or Opioid Use Over EMA Phase

Among participants' daily diary assessments, 30.2% of the observations were cannabis use only, 12.2% were opioid use only, and 50.0% were opioid and cannabis co-use. On co-use days, participants reported using both cannabis and opioid within 1 hour of each other on 49.2% days. Only 7.6% of the days were indicated as "no use." In terms of participants' momentary measurements of use during the past hour, 23.8% of the observations were cannabis use only, 14.8% were opioid use only, and 7.6% were co-use. Close to half (53.8%) of the random prompt assessments were indicated as "no use." We also tried to capture the potential use of illicit opioids using both EMA and daily diaries. We found that there were no reports (ie, 0 case) of using street or synthetic opioids (eg., heroin, opium, fentanyl, etc.) in both EMA and daily diaries.

In the retrospective daily diary, we assessed if participants used any other opioid medication or cannabis product (that were not pre-populated) in the previous day. They were also asked to indicate what other opioid medications and/or cannabis products they used based upon free text entries. We found that among days participants indicated using opioids, only 3.2% (24 out of 742 days) of them were different from the opioid medications they identified using at baseline. Similarly, in terms of cannabis, among days participants indicated using cannabis, only 6.7% (64 out of 957 days) of them were different from their identified cannabis products.

Table 3. Cannabis Products, Dose, and Potency

Cannabis Products	Use at Baseline *n* (%)	Daily Mean Dose (SD)	Mean % Potency (SD)
Cannabis flowers (marijuana, dried plant) - High THC	25 (54.3%)	2g (2.2)	33.6% (24) – THC
Cannabis/hemp flowers (marijuana, dried plant) - High CBD	7 (15.2%)	0.9g (1.2)	51.4% (33.9) – CBD
Cannabis flowers (marijuana, dried plant) - Equal THC and CBD	18 (39.1%)	0.8g (0.9)	39.5% (29.3) – THC 32.9% (29.3) – CBD
Cannabis flowers (marijuana, dried plant) - Unknown THC/CBD	9 (19.6%)	1g (1.4)	—
Cannabis oil - High THC	14 (30.4%)	8.6mL (9)	60.8% (29.6) – THC
Cannabis/hemp oil - High CBD	12 (26.1%)	18.4mL (18.3)	57.5% (30.3) – CBD
Cannabis oil - Equal THC and CBD	6 (13.0%)	16.2mL (23.1)	— *
Cannabis oil - Unknown THC/CBD	5 (10.9%)	8.8mL (9.3)	—
Cannabis concentrates (e.g., hash, dab, wax, shatter, glass)	14 (30.4%)	7.8 puffs (9.8)	64.9% (22.1) – THC 11.9% (18.8) – CBD
Cannabis edibles - High THC	18 (39.1%)	10.3mg (6.2)†	100%
Cannabis edibles - High CBD	9 (19.6%)	11.7mg (6.1)†	100%
Cannabis edibles - Equal THC and CBD	17 (37.0%)	—‡	—
THC patch/gel	1 (2.2%)	1 time (0)	74% (0) – THC
CBD patch/gel	1 (2.2%)	1 time (0)	20% (0) – CBD
Dronabinol (Marinol)	1 (2.2%)	2.5 mg (0)	—

*Due to an oversight in the baseline assessment, potency for this product category was not assessed.
†Cannabis dose for edibles was assessed as mg of THC and mg of CBD.
‡Due to an oversight in the baseline assessment, dose for this product category was not assessed.

Table 4. Routes of Administration for Cannabis

Variables	% or Mean (SD) $N = 46$
Primary method of ingestion	
Vaporizer (eg., Volcano, Vape pen)	15 (33.3%)
Joints (cigar-sized)	7 (15.6%)
Bong (water pipe)	6 (13.3%)
Hand pipe	5 (11.1%)
Edibles	3 (6.7%)
Blunts	2 (4.4%)
Hookah	0 (0%)
Other (eg., 1 hitter, dabs, suppository)	7 (15.6%)

The Effect of Pain Severity in the Previous Moment on Medication Choice

Detailed parameter estimates of the lagged mixed-effects multinomial logistic regression model are presented in Table 5 (Aim 1 section). First, greater momentary pain severity was associated with greater likelihood of using opioids (OR = 1.27, 95% CI: 1.01 – 1.58), compared to no use at the next momentary assessment. For a one-unit increase in the score for momentary pain (from 0–10 NRS), there was a 27% increase in the odds of using only opioids over no use at the next assessment. However, there was no significant association between pain severity and cannabis only use (OR = 1.05, 95% CI: .89 – 1.24) or co-using cannabis and opioids (OR = 1.33, 95% CI: .98 – 1.80), compared to no use. We also found that greater momentary pain severity in the previous momentary assessment was not significantly associated with greater likelihood of co-using cannabis and opioids in the next assessment relative to opioid use only (OR = 1.04, 95% CI: .71 – 1.52) or cannabis use only (OR = 1.35, 95% CI: .96 – 1.89).

The Effect of Cannabis and/or Opioid Use in the Previous Moment on Medication Choice

Detailed parameter estimates of the lagged mixed-effects multinomial logistic regression model are presented in Table 5 (Aim 2 section). First, when individuals reported using only opioids (OR = .01, 95% CI: .01 – .03) or co-using cannabis and opioids (OR = .25, 95% CI: .07 – .87) in the previous momentary assessment, they were less likely to use only opioids in the next assessment compared to no use. Use of cannabis only in the previous assessment was not significantly associated with individuals' choice of opioids only or no use in the next assessment (OR = 1.17, 95% CI: .57 – 2.40).

Second, when participants reported using only opioids (OR = .21, 95% CI: .12 – .36) or cannabis (OR = .10, 95% CI: .06 – .15) in the previous momentary assessment, they were less likely to use cannabis, relative to no use, in the next assessment. Co-use in the previous momentary assessment was not significantly associated with individuals' choice of cannabis only or no use in the next assessment (OR = .47, 95% CI: .21 – 1.07).

Third, when individuals reported using only opioids (OR = .09, 95% CI: .03 – .25) or both cannabis and opioids (OR = .001, 95% CI: .0003 – .01) in the previous momentary assessment, they were less likely to co-use, relative to no use, in the next assessment. Cannabis only use in the previous momentary assessment was not significantly associated with individuals' choice of co-use or no use in the next assessment (OR = .54, 95% CI: .23 – 1.30).

Fourth, when individuals reported using only opioids in the previous momentary assessment, they were far more likely to engage in co-use, relative to opioid-only use, in the next assessment compared to using only opioids (OR = 10.64, 95% CI: 3.47 – 32.61). On the other hand, when individuals had co-used in the previous momentary assessment, they were far less likely to co-use in the next assessment (OR = .01, 95% CI: .001 – .03). Cannabis only use in the previous momentary assessment was not significantly associated with individuals' choice of co-use or opioid use only in the next assessment (OR = .58, 95% CI: .18 – 1.86).

Lastly, when co-use was compared directly with cannabis use only, individuals who reported using only cannabis in the previous momentary assessment were more likely to co-use in the next assessment as compared to when they reported using cannabis only (OR = 2.90, 95% CI: 1.30 – 6.44). In contrast, when individuals co-used in the previous momentary assessment, they were far less likely to co-use in the next assessment as compared to cannabis only (OR = .01, 95% CI: .001 – .02). Opioid only use in the previous momentary assessment was not significantly associated with individuals' choice

Table 5. Prospective Momentary Associations Between Previous Moment Pain Severity (Aim 1) and Cannabis and/or Opioid use (Aim 2) and Choice of Medications (Cannabis and/or Opioids).

		Opioids Only versus No Use ($_{t+1}$)			Cannabis Only versus No Use ($_{t+1}$)			Co-Use versus No Use ($_{t+1}$)			Co-Use versus Opioids Only ($_{t+1}$)			Co-Use versus Cannabis Only ($_{t+1}$)		
	Predictors	Odds Ratios	95% CI	P	Odds Ratios	95% CI	P	Odds Ratios	95% CI	P	Odds Ratios	95% CI	P	Odds Ratios	95% CI	P
Aim 1	Momentary Pain$_t$	1.27	1.01 – 1.58	.038	1.05	.89 – 1.24	.587	1.33	.98 – 1.80	.070	1.04	.71 – 1.52	.852	1.35	.96 – 1.89	.085
	Opioid Use$_t$	.01	.01 – .03	< .001	0.21	.12 – .36	< .001	.09	.03 – .25	< .001	10.64	3.47 – 32.61	< .001	.42	.14 – 1.29	.131
Aim 2	Cannabis Use$_t$	1.17	.57 – 2.41	.661	0.10	.06 – .15	< .001	.54	.23 – 1.30	.172	.58	.18 – 1.86	.359	2.90	1.30 – 6.44	.009
	Co-Use$_t$	.25	.07 – .87	.029	0.47	.21 – 1.07	.074	.001	.0003 – .01	< .001	.01	.001 – .03	< .001	.01	.001 – .02	< .001
	Time Interval	.25	.92 – 1.07	.836	1.13	1.07 – 1.19	< .001	1.15	1.03 – 1.29	.012	1.23	1.08 – 1.41	.002	1.09	.97 – 1.22	.146

NOTE. Co-use = cannabis and prescription opioid co-use; No use = neither using cannabis or opioids. 't' indicates measurement occasion and 't+1' indicates next measurement occasion. If the odds ratio is greater than 1, then that particular category is 'more likely' than the reference category. If the odds ratio is less than 1, then that particular category is 'less likely' than the reference category.

of co-use or cannabis use only in the next assessment (OR = .42, 95% CI: .14 − 1.29).

The overall summary of these lagged mixed-effects multinomial logistic regression findings are as follows: 1) use of cannabis in the previous assessment did not significantly lower the likelihood of using opioids in the next assessment; 2) individuals were more likely to report co-use following an occasion during which a single medication (ie, cannabis or opioids) was used; and 3) repeated co-use was unlikely.

The Effect of Cannabis and/or Opioid use on Changes in Momentary Pain Severity

Table 6 also provides the detailed summary of the lagged linear mixed-effects model findings. On average there was a 226−minute (3.8-hour) difference between 2 subsequent momentary assessments (ie, first-order lag). There was a significant pain severity autocorrelation (ie, pain severity at the previous measurement occasion predicting pain severity measured at the next measurement occasion). We found that after controlling for pain severity in the previous assessment, using cannabis only (B = -.06, 95% CI: -.19 − .07, Cohen's d = -.03), opioids only (B = .07, 95% CI: -.07 − .21, Cohen's d = .03), or co-use (B = -.15, 95% CI: -.37 − .07, Cohen's d = -.08) were not more effective in reducing pain severity in the next assessment compared to those assessments when people used neither substance. We also found that after controlling for pain severity in the previous assessment, co-use was not more effective in reducing pain severity in the next assessment, compared to those moments when people used either opioids only (B = .09, 95% CI: -.14 − .32, Cohen's d = .05) or cannabis only (B = .22, 95% CI: -.02 − .46, Cohen's d = .11). Overall, these data indicate that using cannabis or opioids, either alone or in combination, did not on average yield substantial reductions in pain severity in the next assessment, approximately 4 hours later.

Table 6. Prospective Momentary Association Between Cannabis and/or Opioid Use and Pain Severity

Predictors	Estimates	SE	95% CI	P
Cannabis Only versus No Use$_t$	-.06	.07	-.19 − .07	.347
Opioids Only versus No Use$_t$	.07	.07	-.07 − .21	.345
Co-Use versus No Use$_t$	-.15	.11	-.37 − .07	.182
Cannabis Only versus Co-Use$_t$	.09	.12	-.02 − .32	.452
Opioids Only versus Co-Use$_t$	.22	.12	-.02 − .46	.072
Pain Severity$_t$	-.22	.03	-.27 − -.17	< .001
Time interval	.002	.01	-.02 − .02	.852
Random Effects				
σ^2	.72			
τ_{u0}^2	2.64			
τ_{v0}^2	.00			

NOTE. Co-use = cannabis and prescription opioid co-use; No use = neither using cannabis or opioids. 't' indicates measurement occasion and 't+1' indicates next measurement occasion. σ^2 = level-1 residual variance, τ_{u0}^2 = level-2 intercept variance, and τ_{v0}^2 = level-3 intercept variance.

Daily Perceived Pain Relief by Opioids and/or Cannabis Use

Perceived pain relief from using only opioids, only cannabis, or opioids and cannabis together were assessed in daily morning diaries, which covered the entire previous day. On average, participants reported highest pain relief from using cannabis and opioids together (M = 6.9, SD = 2.0; range: 0−10), followed by pain relief from cannabis on days when they only used cannabis (M = 5.4, SD = 2.7, range: 0−10), and pain relief from opioids on days when they used opioids only (M = 4.5, SD = 2.1, range: 0-10). Linear mixed-effects analysis further support the descriptive results, such that pain relief from using cannabis only was significantly smaller than that from co-use (B = -1.74, SE = .16, P < .001, 95% CI: -2.05, -1.43, Cohen's d = -.74), and pain relief from using opioids only was also significantly smaller than that from co-use (B = -1.65, SE = .20, P < .001, 95% CI: -2.04, −1.26, Cohen's d = -.70). Of note, there was no significant difference in perceived pain relief between days when people used opioids only and cannabis only (B = -.09, SE = .22, P = .683, 95% CI: -.04, .34, Cohen's d = -.04).

Findings of Post Hoc Analysis

To further identify a potential source of the discrepancy between momentary EMA versus retrospective daily diary findings in terms of the effect of cannabis and/or opioid use on pain severity relief, we conducted an additional analysis by creating day-level pain severity from the EMA random prompts. Then, we compared how the findings based upon this day-level pain severity derived from EMA random prompts differ from those based on the retrospective day measure of pain relief, which showed significant analgesic effects of cannabis and co-use of cannabis and opioid. Consistent with the findings of momentary pain severity (which showed no analgesic effects of cannabis, opioids, and their combination), the average of momentary pain severity (ie, daily pain severity) also showed no evidence of the analgesic effects of cannabis, opioids, and their combination.

We also conducted an extra analysis to further examine potential recall bias impacting this discrepancy. We created a variable that indicates how long it took for participants to complete the retrospective daily diary survey after the prompt was notified. This variable was included as a moderator in the model which compared the difference in pain relief for cannabis versus opioids versus the combination of the two. We found partial evidence that the longer delays in completing the retrospective daily diary prompt may be related to stronger recall bias. Specifically, we found a significant interaction effect indicating longer delays were associated with greater pain relief from co-use when compared to cannabis only use (B = -.002, SE = 0.001, P = .001). Other interactions were not significant, however.

The Comparison Between Co-Use Days and Opioids Only Use Days on Daily MME

There were no significant differences in total daily short- and long-acting opioid MME between days when people only used opioids and co-used (for short-acting opioid MME: $B = 3.59$, $SE = 2.29$, $P = .12$, 95% CI: -.89, 8.08, Cohen's d = .12; for long-acting opioid MME: $B = -.80$, $SE = 1.35$, $P = .55$, 95% CI: -3.44, 1.84, Cohen's d = -.03).

Sensitivity Analysis

To test whether the effect of time intervals between EMA random prompts were the same for all levels of the predictor variables in the lagged-effects models, we tested the moderating effects of time intervals (ie, Time Interval x Predictors). A number of Aims 1 and 2 models failed to converge (despite significantly increasing the number of iteration) after including the interaction terms. Models with opioid only versus no use and co-use versus cannabis only as outcomes converged without issues. However, none of the interaction terms were significant in these models (*P*-values ranging from .110 to .746). In the case of Aim 3 models, all of them converged successfully. However, again none of the Time Interval interactions were significant (*P*-values ranging from .122 to .357) indicating the effect of time interval may be the same for all levels of the predictor variables.

Discussion

Utilizing EMA data collected in participants' natural environment, the present study examined 1) how momentary pain experiences relate to individuals' choice of opioids, cannabis, and cannabis-opioid co-use; 2) how previous moment cannabis and/or opioid use shapes individuals' choice of cannabis and/or opioids in the next moment; 3) the effect of co-use on changes in pain severity and perceived pain relief; and 4) whether co-use is associated with lower daily short- and long-acting opioid MME among individuals with chronic pain. Our findings suggest that this population of persons who were prescribed opioid medications and reported using cannabis were not more likely to co-use both products when they experienced greater level of pain. Use of cannabis earlier in the day did not reduce the likelihood of using opioids at the next momentary assessment. Also, while consecutive use of opioids and cannabis was somewhat rare, switching from sole use of either opioids and cannabis to co-use was highly likely. In terms of the analgesic effect, the lagged effect analysis revealed weak and statistically non-significant effects of co-use on pain severity. On the other hand, when participants were asked about their perceived pain relief from use on the previous day, on average participants reported that using cannabis and/or opioids was quite helpful in relieving their pain, with use of opioids and cannabis together receiving the highest ratings of perceived pain relief. The quantity of opioids consumed on days when people only used opioids versus both cannabis and opioids, did not differ significantly, suggesting an absence of a cannabis-related "opioid-sparing" effect in this sample.

Findings from the lagged effect analysis at the momentary level shed light on a complex within-day process involved in individuals' choice of cannabis and/or opioids. First, in the face of experiencing elevated pain severity, participants were more likely to use opioids compared to not using either opioids or cannabis. Second, greater pain severity in the previous observation was not significantly associated with greater likelihood of co-use or cannabis only use compared to no use in the next observation. Repeated single medication (ie, cannabis or opioids) use was unlikely; rather, individuals were more likely to engage in co-use if they reported using cannabis or opioids at the preceding momentary assessment. We also found that repeated co-use of opioids and cannabis was uncommon. This is consistent with a recent qualitative study which showed that although patients with chronic pain reported benefits of co-using cannabis and opioids, they also expressed concerns about dosing and the addictive potential of using cannabis with other medications.[8] Based upon our findings, we speculate that individuals may be more likely to first try using a single medication to relieve pain, and preferentially selected the medication prescribed to them for that indication. However, if one medication alone does not produce significant improvements in pain, participants may be more likely to experiment with combining both cannabis and opioids to achieve analgesia.

In terms of the effects of cannabis and/or opioid use on pain severity, consistent with previous clinical studies suggesting that neither opioids or cannabis are universally effective analgesic agents for treating chronic pain,[6,20] the present findings suggest that neither cannabis nor opioids, used alone or together, were significantly associated with meaningful pain reduction in subsequent moments. These findings are in line with those of previous human laboratory studies on healthy adults reporting the limited analgesic improvement of combining both cannabis and opioids.[1,12,21,24] However, despite the fact that medications did not alter moment to moment pain ratings, patients retrospectively remembered each medication as having provided significant pain relief. For example, perceived pain relief from using opioids and cannabis together averaged approximately 70%. These seemingly conflicting findings highlight a discrepancy between the perception of pain in real time and attributions of pain relief assigned to opioids and cannabis in retrospect. Our additional post hoc findings suggest potential *recall bias* as a potential source of this discrepancy, demonstrating differences between what participants remembering having occurred (ie, retrospective assessment) versus what actually occurred (ie, momentary assessment). In fact, previous studies demonstrate people's tendency (ie, memory heuristic) to remember peak or salient pain experiences when asked to recall their overall pain experience given a certain period of time.[27] It is, therefore, possible that when participants are asked retrospectively about the

analgesic effect of a medication, they may be more likely to remember the peak or salient analgesic effect that was experienced during the day. This may be why we observed greater analgesic effects using the retrospective daily diary measure, but not from the moment-level measure. We believe that these findings may help contextualize prior conflicting results in the literature, whereby laboratory-based studies found limited evidence of analgesia following co-use of opioids and cannabis,[22] whereas retrospective data from an epidemiological study suggested that patients experienced perceived pain relief from adjunctive cannabis use compared to opioid use alone.[11]

Contrary to the meta-analysis of pre-clinical studies demonstrating the robust opioid-sparing effects of cannabis,[19] the present study found no significant differences in daily use of long- and short-acting MMEs on days when only opioids were used versus days when participants reported co-using opioids and cannabis. One explanation for these null findings is perhaps that patients do not necessarily use cannabis in order to reduce the amount of opioids consumed. Rather, people may just titrate using cannabis in response to pain while maintaining their regular dose of opioids, or may be using cannabis to lesson adverse side effects that can occur following high dose or chronic opioid use (eg., nausea). Future studies should assess participant intentions for co-using cannabis and opioids to address this important question. Also, although the present findings do not support an opioid-sparing effect of cannabis in daily life with chronic pain, it should be noted that these results are based upon an observational study without experimental manipulation of drug conditions. To more precisely examine the opioid-sparing effects of cannabis, future randomized-controlled trials (RCTs) should include individuals with chronic pain, as well as a number of different opioid dose conditions in combination with cannabis.

Limitations

The present study has several limitations that need to be addressed in future studies. First, although EMA (4 times/day) and daily diaries (1 time/day) were collected for 30 days for each participant and allowed for adequate power to detect within-person effects, the sample size of the present study was still small for exploring some some potentially important cross-level interaction effects (eg., effects of sex, routes of cannabis administration, use of short- or long acting opioids). Second, our random prompt assessments covered only the past hour of pain medication use, and thus, may have missed some important use information throughout the day. We intentionally limited the reference recall time point to 1 hour for the random prompt to minimize retrospective bias for each assessment, though future studies should consider increasing the number of random prompt assessments and participant-initiated event contingent reports (ie, entering opioid or cannabis use data when a participant uses a substance). Third, the current study used a convenience sample of volunteers recruited online using social media platforms (eg., Facebook). The sociodemographic construction of the sample is mostly educated, white, and female. In terms of clinical characteristics, a large proportion of the sample reported high-disability pain that was at least moderately limiting, as well as depression and PTSD, which can all impact the experience, perception, and reporting of pain, as well as the use of opioids and cannabis. Thus, the generalizability of our findings may be limited. Future studies should replicate and extend the current findings based upon on more representative samples. Fourth, the present study did not measure diagnostic information on clinical conditions, such as chronic pain. Having this information may have provided us greater insight in our findings. For instance, it is an open question whether individuals with highly disabling idiopathic chronic pain (eg., fibromyalgia) respond better with cannabis and opioid co-use in terms of analgesia compared with those with chronic pain with an identifiable pathology (eg., osteoarthritis), or vice versa. Relatedly, the assessment of psychiatric and substance use disorder co-morbidity was not comprehensive in the present study. Future studies should more thoroughly evaluate these comorbidities and examine whether individuals with co-morbid chronic pain and psychiatric conditions exhibit different co-use patterns. Fifth, different types of cannabis products may have had an impact on the analgesic effect of co-use. Unfortunately, this was not testable in the present study, as the majority of participants were co-using multiple cannabis products (ie, mean of 3.5 different products), which prohibited us from testing the moderating effects of different cannabis products (eg., THC vs CBD vs THC/CBD). Sixth, the vast majority (89%) of our data were collected after the pandemic was declared by the WHO on March 11, 2020 and the COVID-19 pandemic may have impacted the overall patterns of cannabis, opioids, or their co-use in ways we do not yet understand. Seventh, prescription opioid and cannabis use assessments were entirely based upon participants' self-report. Thus, errors in reporting of products cannot be ruled out. Moreover, especially in the case of cannabis products, the product label may not accurately reflect the product content; a problem that is difficult to rule out in observational studies. Some creative approaches may be used in future studies to address this important limitation, however. For instance, by combining EMA with other mobile technologies, one may be able to have participants take a photo or a short video of the cannabis product and opioid medication prior to intake.[3] Lastly, we did not measure how long people have been co-using both cannabis and opioids. The opioid-sparing effects of cannabis could have been different between those who just started co-using cannabis and opioids and those who have been co-using them for a long time.

Conclusions

Based upon EMA, the present study investigated the complex association between pain and cannabis and

opioids co-use and vice versa, as well as the opioid-sparing potential of cannabis in the context of the daily lives of individuals with chronic pain. We believe that, despite limitations, findings of the present study provide a number of important take-home messages. First, our study demonstrates for the first time, to our knowledge, how experience of pain shapes patients' choice of cannabis, opioid, and co-use of both products within a day. Our findings shed further light on how patients decide to co-use opioids and cannabis in the context of chronic pain. Second, our findings also suggest that regardless of the reason patients co-use cannabis and opioids, cannabis intake does not seem to significantly reduce the amount of opioids consumed. This finding has important implications for the ongoing public and scientific debate on whether cannabis can be utilized to reduce or replace opioids. Lastly, there was a substantial difference in retrospective versus momentary assessment in evaluating analgesic effects. Our additional analyses suggest recall bias as a potential source of this discrepancy. Investigators evaluating analgesic efficacy in future studies should be mindful about the impact of retrospective recall bias on their assessment of analgesic efficacy. Replications and extensions of the current preliminary findings are required with a substantially larger sample size and more frequent objective assessment of opioid and cannabis use. Additionally, the potential opioid-sparing effect of cannabis should be examined comprehensively using RCTs.

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