Reduced urinary opioid levels from pain management patients associated with marijuana use

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Aim: Marijuana use has been postulated to modulate opioid use, dependence and withdrawal. Broad target drug testing results provide a unique perspective to identify any potential interaction between marijuana use and opioid use. Materials & methods: Using a dataset of approximately 800,000 urine drug test results collected from pain management patients over multiple years, creatinine corrected opioid levels were evaluated to determine if the presence of the primary marijuana marker 11-nor-carboxy-tetrahydrocannabinol (THC-COOH) was associated with statistical differences in excreted opioid concentrations. Results & conclusion: For each of the opioids investigated (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl and buprenorphine), marijuana use was associated with statistically significant lower urinary opiate levels than in samples without indicators of marijuana use.

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Recently much attention has been placed on the use and misuse of opioids in the USA. Approximately 50 million adults in the USA suffer from chronic pain [1]. Opioids are commonly utilized for managing chronic pain; however, opioids are also frequently misused. In 2017 opioids were misused by 11.4 million people in the USA over the age of 12, with most of the misused opioids obtained from a friend or family member prescribed opioids for treating pain [2]. Intentional and accidental opioid overdoses combined to result in 47,600 deaths in the USA in 2017 [3]. In 2016 an estimated 2.1 million people in the USA were diagnosed with opioid use disorder (OUD) [2]. Treatment of OUD is challenging. Within the first 30 days of treatment for OUD the dropout rate for the various treatment strategies is high, ranging between 31 and 70% [4], and perhaps as a result of the low success rate the overall use of medically assisted treatment for OUD declined in 2016 [4].

To aid in addressing the opioid crisis, new tools for combating both chronic pain and opioid addiction are sought after. Marijuana and individual cannabinoids have been discussed as potential analgesics, as replacements for opioids, and to aid in opioid withdrawal [5]. However, medical marijuana is controversial; and efficacy data are inconclusive. In support of potential public health benefits from marijuana, several reports suggest states with medical marijuana laws (MML) have lower opioid prescriptions, lower opioid use, fewer opioid-involved crashes and lower rates of opioid overdose cases compared with states that do not have MML [6–10]. Additionally, a double-blind study including patients in long-term opioid therapy for pain were given placebo, 10 mg or 20 mg of dronabinol (synthetic, purified Δ9-THC); participants reported being more satisfied with their pain management when given dronabinol over placebo [11]. Likewise, healthy volunteers given placebo or oxycodone with or without cannabis then exposed to pain reported that a low dose of oxycodone was only effective when co-administered with cannabis, suggesting potential synergistic effects between cannabis and opioids [12]. Additionally, a study of patients taking morphine or oxycodone for chronic pain reported a decrease in pain level with vaporized cannabis use [13].

In another survey medical cannabis patients reported decreasing the amount of opioids needed for chronic pain by an average of 64% when using cannabis [14]. Further survey studies indicated medical cannabis was utilized
as a substitute for prescription drugs in 69% of the patients surveyed; 35% of the replaced prescriptions were opioid prescriptions [15]. In another survey of 2897 medical cannabis patients, one-third had used opioid-based prescriptions in the last 6 months, and nearly all (97%) agreed/strongly agreed that they were able to limit the amount of opioids needed when cannabis was also used [16]. 87% agreed that cannabis use alone was effective at treating their condition [16]. In a survey of 1500 patients with chronic pain 16% reported using cannabis in addition to opioid treatment due to greater pain relief [17].

Yet, not all studies support a potentially positive role for cannabis in pain management. Other studies suggest that MML increase the risk of opioid misuse and overdose based on self-reports and inconsistent urine drug testing [18–20].

Varied results have also been observed in studies of cannabinoid use for opioid withdrawal. Cannabis smoking provided no difference in opioid withdrawal symptoms during a methadone dose taper [21]. Dronabinol did improve withdrawal symptoms during the induction phase of a naltrexone treatment; however, it did not significantly change the treatment completion rate compared with placebo [22]. In contrast participants who elected to smoke cannabis (containing a naturally diverse spectrum of cannabinoids and terpenes) during the trial were more likely to complete the program [22]. Similar results were observed by Socias et al.; study participants were 21% more likely to continue opioid agonist treatment when cannabis was used at least daily [23].

In response to the intriguing, seemingly contradictory reports of marijuana use increasing and decreasing opioid use/abuse, we retrospectively mined through urine drug testing data looking at opioid levels and the presence of 11-nor-carboxy-THC (THC-COOH) in samples from pain management programs. A decrease in excreted opioid levels could strengthen the hypothesis that marijuana use can reduce opioid consumption.

Methods

Ultra high-pressure liquid chromatography-tandem mass spectrometry urinalysis

An aliquot of urine (200 μl) was fortified with internal standard, 1 M acetate hydrolysis buffer (pH 5), and β-glucuronidase (Red abalone, Kura Biotech, Puerto Varas, Chile). The sample was incubated at 50°C for 1 h to hydrolyze Phase II conjugated metabolites. Following hydrolysis, samples were clarified by the addition of methanol (600 μl) and subsequent centrifugation. The supernatant was diluted 1:1 with 80% water/20% methanol prior to ultra high-pressure liquid chromatography-tandem mass spectrometry analysis. The method utilized a Waters Acquity® UPLC (MA, USA), a gradient consisting of 10 mM ammonium acetate with 0.1% formic acid and acetonitrile at a flow rate of 0.350 ml/min, and a Waters Acquity HSS T3 (2.1 × 50 mm, 1.8 μm) column maintained at 40°C. A Sciex 5500™ MS (Sciex, MA, USA) operated in scheduled MRM mode was utilized to monitor 413 transitions for 195 analytes and 11 internal standards. A single point calibrator was utilized for quantitation. Data from nine of the monitored analytes (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl, buprenorphine and THC-COOH) were utilized for the current study.

Sample set

The pain management department at Medtox Laboratories, a Labcorp Specialty Testing Group in MN, USA routinely analyzes over 25,000 urine samples per week utilizing the analytical test method described above. The test is designed to assist clinics and physicians in pain management, and samples are received from treatment centers throughout the country. Quantitative data from 1 month per each quarter ranging from July 2016 to July 2018 were pulled for eight opioids (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl, buprenorphine). A central month from each quarter was utilized to keep the size of the datasets manageable while representing the quarter of each year. Opioid concentrations were creatinine corrected to account for normal variations in the hydration state of the donors. Opioid datasets were further bisected for the presence of the metabolic marker indicative of marijuana, THC-COOH. The final dataset had 16 categories: each of the eight opioids with and without THC-COOH. The mining of results was performed under an institutional review board exemption covering preexisting data from subjects which cannot be identified, directly or through identifiers linked to the subjects.

Statistical analysis

The paired datasets of opioid concentrations were statistically analyzed to determine whether or not the mean concentrations of specific opioids differed dependent on the presence of THC-COOH. Creatinine corrected opioid concentrations were natural-log transformed allowing the data to more closely follow a Gaussian distribution. For
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Table 1. Survey sample set.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>THC</th>
<th>n</th>
<th>Prevalence of THC (%)</th>
<th>Ln transformed mean concentration (range)</th>
<th>( \Delta x )</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>+</td>
<td>1917</td>
<td>17.7</td>
<td>6.1809 (2.1972–11.7563)</td>
<td>-0.7355</td>
<td>-0.8129, -0.6582</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>8912</td>
<td></td>
<td>6.9164 (2.7081–11.9083)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>+</td>
<td>5869</td>
<td>15.0</td>
<td>6.9382 (2.0794–12.2503)</td>
<td>-0.4572</td>
<td>-0.5069, -0.4076</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>33,157</td>
<td></td>
<td>7.3964 (2.1972–13.7120)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>+</td>
<td>12,869</td>
<td>9.2</td>
<td>6.3814 (2.5649–12.4464)</td>
<td>-0.1893</td>
<td>-0.2127, -0.1659</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>+</td>
<td>14,288</td>
<td>10.2</td>
<td>5.3327 (2.1972–11.8717)</td>
<td>-0.1446</td>
<td>-0.1644, -0.1247</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>126,144</td>
<td></td>
<td>5.4773 (2.0794–12.0135)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxycodone</td>
<td>+</td>
<td>18,917</td>
<td>12.2</td>
<td>6.8461 (2.4849–11.8195)</td>
<td>-0.1895</td>
<td>-0.2095, -0.1695</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>136,044</td>
<td></td>
<td>7.0356 (2.3026–13.6322)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxymorphone</td>
<td>+</td>
<td>20,784</td>
<td>12.7</td>
<td>6.5769 (2.0794–12.2849)</td>
<td>-0.1883</td>
<td>-0.2077, -0.1689</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>143,389</td>
<td></td>
<td>6.7652 (2.1918–13.0624)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>+</td>
<td>3252</td>
<td>13.7</td>
<td>2.9041 (0–7.3544)</td>
<td>-0.4097</td>
<td>-0.4698, -0.3495</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>20,516</td>
<td></td>
<td>3.1318 (0–10.4133)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>+</td>
<td>13,652</td>
<td>20.8</td>
<td>4.2965 (0–11.3022)</td>
<td>-0.1893</td>
<td>-0.2150, -0.1635</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>52,133</td>
<td></td>
<td>4.4857 (0–11.4648)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

THC: Tetrahydrocannabinol.

Each of the eight datasets, a 95% confidence interval for the difference in the concentration means between THC positive and THC negative results was estimated using the following expression [24]:

\[
\Delta x + / - 1.96 \times \sqrt{\left( \frac{S^2_T}{n(T)} + \frac{S^2_O}{n(O)} \right)}
\]  
(Eq. 1)

Where \( \Delta x \) is the observed difference of the two means, 1.96 is the 97.5th percentile of a standard normal distribution with a mean of 0 and standard deviation of 1, and the square root term represents the standard error of the difference. \( S^2_T, S^2_O, n(T), \) and \( n(O) \) represent the variances and samples sizes of THC positive and THC negative results [24].

Results

Over a two year span starting in July 2016, data from pain management urine drug testing was mined for samples containing the following opioids: codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl and buprenorphine. Each dataset was subsequently bifurcated based on the presence or absence of the THC metabolite, THC-COOH. Paired datasets were statistically analyzed for differences in excreted opioid concentration. For each of the eight opioids monitored, lower mean concentrations were observed when THC-COOH was also present in the sample (Table 1). The differences in opioid concentrations between the THC positive and THC negative groups were statistically significant at a 95% confidence interval. The largest shift was seen in codeine positive samples, \( \Delta x = -0.7355 \), followed by morphine \( (-0.4572) \) and fentanyl \( (-0.4097) \). The results are presented graphically in Figure 1 where the natural log transformed, creatinine corrected opioid concentrations are plotted against the percent distribution. While not visually dramatic, a larger portion of samples are consistently distributed at lower concentrations in the THC positive samples compared with THC negative samples. Each of the datasets used in this evaluation are large; oxymorphone, oxycodone, hydromorphone and hydrocodone were the most prevalent with between 140,207 to 164,173 positive results. Codeine was least prevalent at 10,829 positive results. The buprenorphine positive group had the highest percentage of samples containing THC (20.8%), and hydrocodone had the lowest THC positive rate, 9.2% (Table 1).

Discussion

A retrospective analysis looking at the potential impact of known marijuana use on urinary opioid concentrations from pain management patients is presented. Mean opioid concentrations were significantly lower in samples which also contained the THC metabolite THC-COOH. The largest difference was seen in codeine, morphine and fentanyl samples (Figure 1A). Other opioids were also found at lower concentrations when THC-COOH was present, but to a lesser extent (Figure 1B). The differences in the concentrations of the evaluated opioids associated
Figure 1. Distribution of opioid concentrations among tetrahydrocannabinol-positive and tetrahydrocannabinol-negative urine samples. (A) Codeine, morphine and fentanyl, (B) hydrocodone, hydromorphone, oxycodone, oxymorphone and buprenorphine. Solid lines indicate the mean creatinine corrected concentration (ng/ml), natural log transformed; values presented in Table 1. Dotted lines (••••) represent first and third quartiles. THC: Tetrahydrocannabinol.
with marijuana use are not dramatic when viewed individually. However, the finding is strengthened as statistical significance was seen for each opioid evaluated.

All samples were de-identified; therefore, it is unknown whether the measured opioids indicate compliance with prescribed pain medication or if the opioids were consumed outside of the purview of a physician. Likewise, sample blinding removes the ability to determine if any specific sample was from a state with legal recreational or medical marijuana.

Any attempt to assign causation to the noted difference would be speculative as numerous potential theories could be presented. The discussed data and the elucidated differences are correlative and cannot scientifically support any theories of the mechanism underlying the finding. However, this finding is consistent with data from self-report surveys of medical cannabis patients in which nearly half claimed they substituted cannabis for their prescription medications, which were typically opiates/opioids [14–16,25].

The potential role for cannabis in pain management and opioid addiction treatment is alluring. Any evidence indicating a path to reduce opioid use/misuse and to reduce opioid overdoses should be explored. Further studies will hopefully elucidate if cannabis can or should play a role in pain management through the anti-nociceptive properties of THC and any potential interaction with opioids. From the perspective of opioid addiction treatment, it is interesting that the highest rate of THC use was seen in buprenorphine-positive samples as buprenorphine is frequently utilized as a component of medication assisted treatment for opioid dependency. Further studies are also needed to determine if THC/cannabis use alone or in combination with other medical treatments may help combat OUD in a manner similar to one published dronabinol–naltrexone and methadone–cannabis study [17,26].

Limitations

All sample demographics and prescription information was de-identified; therefore, it is unknown whether the measured THC metabolite was from medicinal/recreational use of marijuana or extracted THC products. It’s also not known if the measured opioids were a result of compliant prescription use or misuse. The dataset was also limited to the samples received and tested at one location in Minnesota; while the laboratory receives samples from throughout the country, it is not a national survey of samples uniformly distributed from throughout the country.

This study specifically looked for a potential interaction between opioids and THC. THC is a marker of marijuana use, but it is not the only interesting cannabinoid in cannabis. Potential interactions with other cannabinoids such as cannabidiol which are present in hemp and hemp products without significant levels of THC would not be detected.

Summary points

- Literature suggests cannabis may aid in the opioid epidemic as a substitute for opioids.
- Cannabis may also play a role in opioid use dependence.
- Data from 800,000 pain management patients was analyzed for trends in urinary opioid levels in the presence/absence of the tetrahydrocannabinol (THC) metabolite, THC-COOH.
- A trend of lower opioid urinary levels was observed for each of the opioids investigated (codeine, morphine, hydrocodone, hydromorphone, oxycodone, oxymorphone, fentanyl and buprenorphine) when 11-nor-carboxy-THC was also present compared with urinary levels when 11-nor-carboxy-THC was not detected.
- The greatest variances in opioid concentration between THC positive / THC negative sets was observed for codeine (-0.7355), morphine (-0.4572) and fentanyl (-0.4097).
- Buprenorphine samples had the greatest prevalence of THC (20.8% of 65,785 samples).
- Further research is needed to determine the efficacy of cannabis use for pain management and opioid use dependence.

Financial & competing interests disclosure

G Janis, M Goggin and B Shahriar are paid employees of Laboratory Corporation of America. Andy Stead is an independent statistical contractor employed by Laboratory Corporation of America. Laboratory Corporation of America (Labcorp) performs clinical laboratory testing services. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.
Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and that the mining of results was performed under an institutional review board approval exemption covering preexisting data from subjects which cannot be identified, directly or through identifiers linked to the subjects.

References

Papers of special note have been highlighted as: ● of interest

● Double-blind study suggesting cannabis–oxycodone synergism for analgesia. Low-dose oxycodone was only effective when cannabis was also used.
14. Boehnke KF, Litinas E, Claw DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J. Pain 17(6), 739–744 (2016).
● A survey of more than 2800 medical cannabis users; the majority of individuals also taking opioids agreed that a lower dose of opioid was need when cannabis was also used.
Presented data from nationally representative sample of adults surveyed 3 years apart from the National Epidemiologic Survey on Alcohol and Related Conditions. Data suggest cannabis use at initial time point was associated with increased opioid use disorder at three-year survey.


