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Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study

Gabrielle Campbell  
*University of New South Wales*

Wayne Hall  
*University of Queensland*

Amy Peacock  
*University of New South Wales*

Nicholas Lintzeris  
*University of Sydney*

Raimondo Bruno  
*University of Tasmania*

*See next page for additional authors*

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Abstract

Background Interest in the use of cannabis and cannabinoids to treat chronic non-cancer pain is increasing, because of their potential to reduce opioid dose requirements. We aimed to investigate cannabis use in people living with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time; and potential opioid-sparing effects of cannabis. Methods The Pain and Opioids IN Treatment study is a prospective, national, observational cohort of people with chronic non-cancer pain prescribed opioids. Participants were recruited through community pharmacies across Australia, completed baseline interviews, and were followed up with phone interviews or self-complete questionnaires yearly for 4 years. Recruitment took place from August 13, 2012, to April 8, 2014. Participants were asked about lifetime and past year chronic pain conditions, duration of chronic non-cancer pain, pain self-efficacy, whether pain was neuropathic, lifetime and past 12-month cannabis use, number of days cannabis was used in the past month, and current depression and generalised anxiety disorder. We also estimated daily oral morphine equivalent doses of opioids. We used logistic regression to investigate cross-sectional associations with frequency of cannabis use, and lagged mixed-effects models to examine temporal associations between cannabis use and outcomes. Findings 1514 participants completed the baseline interview and were included in the study from Aug 20, 2012, to April 14, 2014. Cannabis use was common, and by 4-year follow-up, 295 (24%) participants had used cannabis for pain. Interest in using cannabis for pain increased from 364 (33%) participants (at baseline) to 723 (60%) participants (at 4 years). At 4-year follow-up, compared with people with no cannabis use, we found that participants who used cannabis had a greater pain severity score (risk ratio 1·14, 95% CI 1·01-1·29, for less frequent cannabis use; and 1·17, 1·03-1·32, for daily or near-daily cannabis use), greater pain interference score (1·21, 1·09-1·35; and 1·14, 1·03-1·26), lower pain self-efficacy scores (0·97, 0·96-1·00; and 0·98, 0·96-1·00), and greater generalised anxiety disorder severity scores (1·07, 1·03-1·12; and 1·10, 1·06-1·15). We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation. Interpretation Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.

Keywords
prescribed, cohort, opioids:, effect, findings, 4-year, prospective, cannabis, study, people, chronic, non-cancer, pain

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Gabrielle Campbell, Wayne D Hall, Amy Peacock, Nicholas Lintzeris, Raimonda Bruno, Briony Larance, Suzanne Nielsen, Milton Cohen, Gary Chan, Richard P Mattick, Fiona Blyth, Marian Shanahan, Timothy Dobbins, Michael Farrell, Louisa Degenhardt

Summary

Background Interest in the use of cannabis and cannabinoids to treat chronic non-cancer pain is increasing, because of their potential to reduce opioid dose requirements. We aimed to investigate cannabis use in people living with chronic non-cancer pain who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis; associations between amount of cannabis use and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time; and potential opioid-sparing effects of cannabis.

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Findings 1514 participants completed the baseline interview and were included in the study from Aug 20, 2012, to April 14, 2014. Cannabis use was common, and by 4-year follow-up, 295 (24%) participants had used cannabis for pain. Interest in using cannabis for pain increased from 364 (33%) participants (at baseline) to 723 (60%) participants (at 4 years). At 4-year follow-up, compared with people with no cannabis use, we found that participants who used cannabis had a greater pain severity score (risk ratio 1·14, 95% CI 1·01–1·29, for less frequent cannabis use; and 1·17, 1·09–1·32, for daily or near-daily cannabis use), greater pain interference score (1·21, 1·09–1·35; and 1·14, 1·03–1·26), lower pain self-efficacy scores (0·97, 0·96–1·00; and 0·98, 0·96–1·00), and greater generalised anxiety disorder severity scores (1·07, 1·03–1·12; and 1·10, 1·06–1·15). We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.

Interpretation Cannabis use was common in people with chronic non-cancer pain who had been prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. People who used cannabis had greater pain and lower self-efficacy in managing pain, and there was no evidence that cannabis use reduced pain severity or interference or exerted an opioid-sparing effect. As cannabis use for medicinal purposes increases globally, it is important that large well designed clinical trials, which include people with complex comorbidities, are conducted to determine the efficacy of cannabis for chronic non-cancer pain.

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Introduction

The use of prescribed opioids in the treatment of chronic non-cancer pain is controversial because of insufficient evidence for their long-term effectiveness13 and increased harms as opioid prescribing for chronic non-cancer pain has increased.14 Alternatives to opioids are increasingly being debated and considered. Reviews of cannabinoids suggest they might have efficacy in some chronic non-cancer pain conditions. In the USA, Canada, and the Netherlands, chronic non-cancer pain is the most commonly cited reason for use of cannabis for medicinal purposes.
Evidence before this study
The potential use of cannabinoids in chronic non-cancer pain has raised substantial interest. We did a literature review by searching MEDLINE, Embase, PsycINFO, CENTRAL, and ClinicalTrials.gov in July, 2017, with no language restrictions, for randomised controlled trials (RCTs) and observational studies relating to all cannabinoid types and specific chronic non-cancer pain conditions and pain-related outcomes. We used the following search terms: “Cannabinoids”, “Cannabis”, “cannabid”, “marijuana”, “marijinal”, “dronabinol”, “nabilone”, “levonantradol”, “delta-9-tetrahydrocannabinol”, “cesamet”, “drona-9-THC”, “delta-9-tetrahydrocannabinol”, “nabiximols”, “sativex”, “cannabidiol”, “therapeutic use”, “analgesics”, “medical marijuana”, “medicinal cannabis”, “pain”, “chronic pain”, “Neuralgia”, and “neuropathic pain”. We identified 91 publications, containing 104 studies, which included 47 randomised control trials and 57 observational studies. We found the pooled change in pain intensity (standardised mean difference −0.14, 95% CI −0.20 to −0.08) was equivalent to 3 mm on a 100 mm visual analogue scale greater than placebo.

We graded the quality of evidence as moderate using an adapted version of the standard Grades of Recommendation, Assessment, Development and Evaluation tool. Existing clinical studies of the effects of cannabinoids on chronic non-cancer pain mainly consisted of RCTs done using a restricted range of cannabinoid conditions and lacking clarity in reporting of pain outcomes.

Added value of this study
To our knowledge, our study is one of the longest, in-depth, prospective studies of a community cohort of people with various types of chronic non-cancer pain that examined the effects of cannabis use on pain and prescription opioid use during 4 years of follow-up. Cannabis use was common in our cohort, patients reported that it reduced their pain, and interest in using cannabis for pain doubled in the cohort during the 4-year follow-up. Nonetheless, patients who had used cannabis had greater pain severity and interference, lower pain self-efficacy, and greater generalised anxiety disorder severity than did patients who had not used cannabis. Unlike recent reviews that suggested a positive effect of cannabinoids on pain and a reduction in opioid use, we found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased rates of opioid discontinuation.

Implications of all the available evidence
Previous systematic reviews suggested there is moderate evidence that cannabinoids are effective for certain types of pain. Previous evidence has been scarce because of studies with short duration and exclusion of participants with complex clinical profiles. In our 4-year prospective cohort of people prescribed opioids for chronic non-cancer pain, we did not find evidence supporting claims that cannabis and cannabinoids improved outcomes in chronic non-cancer pain, nor that they reduced prescription opioid use. To date, evidence that cannabinoids are effective for chronic non-cancer pain and aid in reducing opioid use is lacking. Large, well designed clinical trials are required to evaluate in which patients cannabinoids might be effective in reducing pain severity, interference, and opioid doses.
Articles

study as pain lasting longer than 3 months), taking prescribed schedule 8 opioids (including fentanyl, morphine, oxycodone, buprenorphine, methadone, and hydromorphone) for chronic non-cancer pain for longer than 6 weeks, competent in English, mentally and physically able to participate in telephone and self-complete interviews, and did not have any serious cognitive impairments, as determined by the interviewer at the time of screening. A history of injecting drug use was not an exclusion criterion, but people currently prescribed pharmaceutical opioids for opioid substitution therapy for heroin dependence or cancer were not eligible for inclusion.

Written informed consent was obtained from participants. This study was approved by the Human Research Ethics Committee of the University of New South Wales (reference #HCI12149 and #HCI16916).

Measures
The measures, tools, and data domains were based on recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials. Details of the interview procedure are provided in the appendix. Baseline interviews comprised a phone interview and self-complete survey and were done from Aug 20, 2012, to April 14, 2014. 3-month self-complete surveys were done as close to 3 months after baseline interview as possible and occurred from Nov 15, 2012, to Nov 1, 2014. The 3-month self-complete questionnaire was a reduced questionnaire with a smaller number of measures included and is therefore not included in the current analysis as many of the measures used, such as the Pain Self-Efficacy Questionnaire (PSEQ) and questions regarding cannabis use, were not included. Furthermore, for consistency in analyses, we used interviews which were 12 months apart. 12-month self-complete questionnaires occurred 12 months after baseline interviews, between Aug 28, 2013, and Dec 4, 2015. 2-year interviews were done from Aug 12, 2014, to March 23, 2016. The 3-year interview was part of a new funding grant and all participants were interviewed annually by calendar year. 3-year interviews took place between Jan 11, 2016, and Jan 3, 2017. 4-year follow-ups were done from Jan 9, 2017, to Dec 12, 2017.

We collected data on age, sex, relationship status, and current work status. Relationship status and work status data were collected at all timepoints. Sex and age data were collected only at baseline.

Participants were asked about chronic pain conditions in their lifetime and during the past year, and duration of chronic non-cancer pain. As pain is only one of several core outcomes to consider when evaluating interventions for chronic non-cancer pain, we used the pain severity and interference (how pain affects sleep, daily living, working ability, and social interaction) subscales of the Brief Pain Inventory (BPI), with higher scores indicating greater pain severity or interference (score range 0–10).

Pain self-efficacy relates to an individual’s beliefs about the extent to which they can do daily activities despite their pain; this was measured using the PSEQ9 (score out of 60, higher scores indicating greater self-efficacy). Participants were asked at baseline “Is your pain neuropathic? That is, pain that burns or tingles (either diagnosed by self or doctor).”

Daily oral morphine equivalent doses of opioids, in mg per day, were estimated using conversion units established through synthesis of clinical references, using a medication diary. At each follow-up, we confirmed whether participants were still taking a schedule 8 opioid. Participants were asked about lifetime and past 12-month use of cannabis, and number of days used in the past month, in general and for pain specifically. Frequency of cannabis use in the past month was categorised as no use (0 days), less frequent use (1–19 days), and near-daily or daily use (≥20 days of cannabis use, approximately five times a week or more).

Figure: Study flow chart
Patient flow and reasons for exclusion between study referral and baseline interview are provided in the appendix.
Participants who reported lifetime use of cannabis for pain but had discontinued use were asked their reasons for doing so. Those who reported past 12-month cannabis use were asked further questions about reasons for use (appendix). All participants were asked “If you had access to cannabis, would you want to use it?” at each wave (excluding the 1-year follow-up). Based on a similar question in the BPI, we asked participants to rate the effectiveness of cannabis for their pain on a scale of 0 (no relief) to 10 (complete relief).

Current depression and generalised anxiety disorder were measured by the Patient Health Questionnaire 9 (PHQ-9) and Generalized Anxiety Disorder 7-Item Scale (GAD-7).23,24 We defined moderate to severe depression as a PHQ-9 score of 10 or greater.23 We defined moderate to severe anxiety as a GAD-7 score of 10 or greater.24 We used the Composite International Diagnostic Interview for specific diagnoses (GAD-7),23,24 We defined moderate to severe depression as a PHQ-9 score of 10 or greater.23 We defined moderate to severe anxiety as a GAD-7 score of 10 or greater.24 We used the Composite International Diagnostic Interview for specific diagnoses (GAD-7).23,24 We defined moderate to severe depression as a PHQ-9 score of 10 or greater.23 We defined moderate to severe anxiety as a GAD-7 score of 10 or greater.24 We used the Composite International Diagnostic Interview for specific diagnoses (GAD-7).23,24 We defined moderate to severe depression as a PHQ-9 score of 10 or greater.23 We defined moderate to severe anxiety as a GAD-7 score of 10 or greater.24 We used the Composite International Diagnostic Interview for specific diagnoses (GAD-7).23,24 We defined moderate to severe depression as a PHQ-9 score of 10 or greater.23 We defined moderate to severe anxiety as a GAD-7 score of 10 or greater.24 We used the Composite International Diagnostic Interview for specific diagnoses (GAD-7).

<table>
<thead>
<tr>
<th>Demographics (n=1514)</th>
<th>Baseline (n=1235)</th>
<th>1-year follow-up (n=1211)</th>
<th>2-year follow-up (n=1217)</th>
<th>3-year follow-up (n=1277)</th>
<th>4-year follow-up (n=1217)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>58 (48–67)</td>
<td>58 (49–68)</td>
<td>59 (50–69)</td>
<td>60 (50–69)</td>
<td>60 (50–70)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>672 (44%)</td>
<td>542 (44%)</td>
<td>555 (43%)</td>
<td>524 (43%)</td>
<td>524 (43%)</td>
</tr>
<tr>
<td>Female</td>
<td>842 (56%)</td>
<td>693 (56%)</td>
<td>722 (57%)</td>
<td>687 (57%)</td>
<td>693 (57%)</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BPI pain interference score</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
</tr>
<tr>
<td><strong>Prescribed opioid use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral morphine equivalent, mg/day</td>
<td>75 (36–150)</td>
<td>61 (24–135)</td>
<td>6 (25–135)</td>
<td>60 (22–126)</td>
<td>57 (15–125)</td>
</tr>
<tr>
<td>Discontinued opioids</td>
<td>119 (91%)</td>
<td>108 (91%)</td>
<td>105 (90%)</td>
<td>107 (89%)</td>
<td>104 (86%)</td>
</tr>
<tr>
<td><strong>Cannabis use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifetime use</td>
<td>64 (43%)</td>
<td>66 (45%)</td>
<td>64 (43%)</td>
<td>68 (47%)</td>
<td>68 (47%)</td>
</tr>
<tr>
<td>Past 12 months</td>
<td>195 (33%)</td>
<td>154 (25%)</td>
<td>170 (30%)</td>
<td>171 (30%)</td>
<td>192 (30%)</td>
</tr>
<tr>
<td>Past month use</td>
<td>126 (8%)</td>
<td>112 (9%)</td>
<td>123 (10%)</td>
<td>132 (11%)</td>
<td>155 (13%)</td>
</tr>
<tr>
<td>Frequency of use in the past month*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>35 (91%)</td>
<td>33 (91%)</td>
<td>35 (90%)</td>
<td>34 (90%)</td>
<td>35 (90%)</td>
</tr>
<tr>
<td>1–19 days (less frequent)</td>
<td>78 (5%)</td>
<td>65 (5%)</td>
<td>70 (5%)</td>
<td>70 (6%)</td>
<td>78 (6%)</td>
</tr>
<tr>
<td>20–31 days (near-daily or daily)</td>
<td>48 (3%)</td>
<td>47 (4%)</td>
<td>53 (4%)</td>
<td>62 (5%)</td>
<td>79 (6%)</td>
</tr>
<tr>
<td>Ever used for pain relief</td>
<td>227 (16%)</td>
<td>220 (18%)</td>
<td>260 (20%)</td>
<td>267 (22%)</td>
<td>295 (24%)</td>
</tr>
<tr>
<td>Used for pain relief in the past 12 months</td>
<td>123 (10%)</td>
<td>151 (12%)</td>
<td>145 (12%)</td>
<td>168 (14%)</td>
<td>168 (14%)</td>
</tr>
<tr>
<td>Used for pain relief in the past month†</td>
<td>85 (6%)</td>
<td>111 (9%)</td>
<td>121 (10%)</td>
<td>134 (11%)</td>
<td>134 (11%)</td>
</tr>
<tr>
<td>Effectiveness of cannabis for pain (out of 10)</td>
<td>6 (2.9)</td>
<td>5 (3.5)</td>
<td>7 (3.2)</td>
<td>7 (2.2)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Would use it if had access†</td>
<td>364 (33%)</td>
<td>562 (44%)</td>
<td>649 (54%)</td>
<td>723 (60%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are median (IQR), n (%), or mean (SD). BPI=Brief Pain Inventory. *Data were missing for some patients. †Data not collected at 1-year timepoint. ‡Data missing for 396 patients.

Table 1: Sociodemographic characteristics, pain, prescribed opioid use, and cannabis use among the Pain and Opioids IN Treatment sample, by study wave.

Statistical analysis

We aimed to recruit 2000 participants, but then limited this number to 1500 because of funding and time constraints. For descriptive statistics, means and SDs were computed when data were normally distributed, and medians and IQRs when data were skewed.26

To investigate cross-sectional associations with cannabis use, we used multinomial logistic regression models for univariate comparisons of people at each wave who reported less frequent cannabis use and near-daily or daily cannabis use (compared with people who had not used cannabis). Variables identified in previous research as related to the outcomes were included. For interpretability, risk ratios (RRs) for oral morphine equivalent doses are reported per 100 units. Additional analyses of the demographic and clinical associations between prevalent and incident cannabis use are presented and discussed in the appendix.

For prospective associations between cannabis use and outcomes, we used lagged mixed-effects models to examine temporal associations between cannabis use (the exposure) and pain severity, pain interference, and oral morphine equivalent doses (the outcomes), incorporating a random intercept for individuals to account for the repeated measures design and examining unadjusted and adjusted associations. We analysed data from baseline interviews and the four annual follow-up waves, with outcomes for the following year, and constructed four models. In the first model, we compared the outcome of interest in people who used cannabis (less frequent use, and near-daily or daily use) versus those who had never used cannabis. In the second, we adjusted for the outcome at the previous wave. In the third, we additionally adjusted for clinical covariates identified in previous research as related to the outcomes (age, sex, duration of pain, generalised anxiety disorder severity, and history of substance use).26 Furthermore, for analysis of pain severity, we also adjusted for oral morphine, for pain interference, we adjusted for pain severity and oral morphine equivalent, and for oral morphine equivalent, we adjusted for pain severity. In the final model, we further adjusted for PSEQ results (we had some missing data as the PSEQ was not completed at the 1-year interview).

Analyses were done using Stata version 15.0. We used the Stata command margins (or mimrgrns for multiple imputation) to obtain adjusted means. For details of sensitivity analyses see the appendix.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to
all the data in the study and had final responsibility for the decision to submit for publication.

**Results**

Of the 2091 people we assessed for eligibility, 1873 (90%) were eligible for inclusion and 1514 (81%) completed the baseline interview (appendix p 7). At each follow-up wave, at least 80% of the original participants completed the assessment (figure).

At baseline, 44% of the cohort were male, and the median age was 58 years (IQR 48–67; table 1). 737 (49%) participants were unemployed and 469 (31%) had retired.

### Results

At baseline, 44% of the cohort were male, and the median age was 58 years (IQR 48–67; table 1). 737 (49%) participants were unemployed and 469 (31%) had retired.

#### Table 2: Bivariate cross-sectional associations between amount of cannabis use in the past month (days of use) and pain, anxiety, and medication use in the Pain and Opioids IN Treatment cohort, by study wave

<table>
<thead>
<tr>
<th>Duration of pain, years</th>
<th>No cannabis use, &lt;20 (&lt;20)</th>
<th>Daily or near-daily cannabis use, &lt;20 (&lt;20)</th>
<th>Unadjusted</th>
<th>Less frequent cannabis use, &lt;20 (&lt;20) vs no cannabis use</th>
<th>Daily or near-daily cannabis use, &lt;20 (&lt;20) vs no cannabis use</th>
<th>p value</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 5.1 (1.8)</td>
<td>3.1 (1.9)</td>
<td>2.1 (1.4)</td>
<td>1.09 (0.96–1.24)</td>
<td>0.19</td>
<td>1.00 (0.86–1.19)</td>
<td>0.906</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year 5.3 (2.0)</td>
<td>3.0 (1.6)</td>
<td>2.0 (1.6)</td>
<td>1.03 (0.90–1.17)</td>
<td>0.703</td>
<td>1.09 (0.93–1.27)</td>
<td>0.27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-year 5.6 (1.9)</td>
<td>3.1 (1.6)</td>
<td>1.1 (0.98–1.27)</td>
<td>0.090</td>
<td>1.20 (1.00–1.39)</td>
<td>0.020</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-year 4.8 (1.9)</td>
<td>1.4 (1.4)</td>
<td>1.1 (0.94–1.36)</td>
<td>0.111</td>
<td>1.21 (1.05–1.40)</td>
<td>0.0081</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-year 4.7 (1.9)</td>
<td>1.3 (1.8)</td>
<td>1.2 (1.01–1.29)</td>
<td>0.031</td>
<td>1.17 (1.02–1.32)</td>
<td>0.023</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are median (IQR) or mean (SD), unless otherwise indicated. RR=risk ratio. BPI=Brief Pain Inventory. PSEQ=pain self-efficacy questionnaire. *Only asked at baseline. †Data on PSEQ not collected at 1-year timepoint. ‡RR based on per 100 units.

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**Tables and Figures:**

- **Table 2:** Bivariate cross-sectional associations between amount of cannabis use in the past month (days of use) and pain, anxiety, and medication use in the Pain and Opioids IN Treatment cohort, by study wave.
from work. Participants had been living with chronic non-cancer pain for a median of 10 years (IQR 4–5–20–0) and had been prescribed a strong opioid for a median of 4 years (1–5–10–0). The median oral morphine equivalent taken was 75 mg/day (36–150). The most common types of pain reported at baseline were back or neck pain (1159 [77%] participants), followed by arthritis (933 [62%] participants), and comorbid pain was common, with participants reporting a median of two (IQR 2–3) chronic pain conditions at baseline in the preceding 12 months. 937 (62%) participants reported neuropathic pain at baseline.

Using a random sample of 71 pharmacies, we compared the characteristics of all customers obtaining opioids during the 6-week recruitment window with the study cohort overall. Among 800 customers who recorded purchasing opioids in these pharmacies, 418 (52%) were aged 18–34 years (vs 284 [55%] in the POINT cohort) and 58 (7%) were aged 65 years or older (vs 842 [55%] in the POINT cohort). At baseline, approximately one in six participants reported that they had used cannabis for pain in their lifetime. Past 12-month and past-month reporting of cannabis use for pain also increased over time. The proportion of participants reporting cannabis use on 1–19 days (categorised as less frequent use) in the month before interview remained relatively stable. The proportion reporting use on 20–31 days in the past month (categorised as near-daily or daily use) increased from 3% at baseline to 7% at 4-year follow-up (table 1).

At baseline, participants who had used cannabis for pain rated its mean effectiveness for their pain as 6·5 out of 10 (with 10 being extremely effective; table 1). The percentage of participants reporting that they would use cannabis if they had access to it increased from 33% at baseline to 60% at 4-year follow-up.

At the 3-year and 4-year follow-up waves, participants who reported cannabis use in the past month were asked whether it influenced their use of opioid medication. Most participants reported that cannabis had no effect on their use of opioid medication (3-year follow-up 103 [78%] of 132 participants; 4-year follow-up 105 [70%] of 151 participants). At 3-year follow-up, 29 (22%) of 132 participants, and at 4-year follow-up, 46 (30%) of 151 participants reported that they sometimes or regularly reduced their opioid medication when using cannabis (appendix). There were no differences in age, sex, pain severity or interference, or oral morphine equivalent between cannabis users who reported cannabis sometimes or regularly reduced their opioid use, compared with those who said it had no such effect (data not shown).

Of participants currently using cannabis, the most common reasons for use at both 3-year and 4-year follow-up were to relieve pain (3-year follow-up 142 [83%] of 174 participants; 4-year follow-up 157 [83%] of 190 participants) and pain-related distress (3-year follow-up 124 [65%] of 192 participants; 4-year follow-up 140 [73%] of 192 participants), to improve sleep (3-year follow-up 116 [67%] of 174 participants; 4-year follow-up 122 [64%] of 190 participants), and for general relaxation (3-year follow-up 126 [72%] of 174 participants; 4-year follow-up 124 [65%] of 192 participants; appendix). Participants who had previously used cannabis for pain, but were no longer doing so, were asked about their reasons for stopping. The most common reasons were side-effects (3-year follow-up 46 [28%] of 166 participants; 4-year follow-up 31 [23%] of 134 participants), legal concerns (3-year follow-up 43 [26%] of 166 participants; 4-year follow-up 24 [18%] of 134 participants), difficulties accessing cannabis (3-year follow-up 30 [18%] of 166 participants; 4-year follow-up 27 [20%] of 166 participants; 4-year follow-up 16 [12%] of 134 participants; appendix).

### Table 3: Lagged mixed-effects linear regression examining the effect of cannabis use on pain severity at the following wave (complete case analysis)

<table>
<thead>
<tr>
<th>Current level of pain severity</th>
<th>Adjusted mean (SE)</th>
<th>β 95% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannabis use at previous study wave</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cannabis use (ref)</td>
<td>5.0 (0.05)</td>
<td>-</td>
</tr>
<tr>
<td>Less frequent use</td>
<td>5.1 (0.13)</td>
<td>0.16</td>
</tr>
<tr>
<td>Near-daily or daily use</td>
<td>5.5 (0.13)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

### Adjusted for pain severity at previous study wave

<table>
<thead>
<tr>
<th>Cannabis use at previous study wave</th>
<th>Adjusted mean (SE)</th>
<th>β 95% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cannabis use (ref)</td>
<td>5.0 (0.02)</td>
<td>-</td>
</tr>
<tr>
<td>Less frequent use</td>
<td>5.0 (0.10)</td>
<td>0.06</td>
</tr>
<tr>
<td>Near-daily or daily use</td>
<td>5.2 (0.10)</td>
<td>0.21</td>
</tr>
</tbody>
</table>

### Adjusted for previous pain severity and clinical covariates*

<table>
<thead>
<tr>
<th>Cannabis use at previous study wave</th>
<th>Adjusted mean (SE)</th>
<th>β 95% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cannabis use (ref)</td>
<td>4.9 (0.03)</td>
<td>-</td>
</tr>
<tr>
<td>Less frequent use</td>
<td>5.0 (0.13)</td>
<td>0.35</td>
</tr>
<tr>
<td>Near-daily or daily use</td>
<td>5.1 (0.14)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

### Adjusted for previous pain severity and clinical covariates* and Pain Self-Efficacy Questionnaire

<table>
<thead>
<tr>
<th>Cannabis use at previous study wave</th>
<th>Adjusted mean (SE)</th>
<th>β 95% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cannabis use (ref)</td>
<td>4.9 (0.03)</td>
<td>-</td>
</tr>
<tr>
<td>Less frequent use</td>
<td>5.1 (0.13)</td>
<td>0.37</td>
</tr>
<tr>
<td>Near-daily or daily use</td>
<td>5.2 (0.14)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

* Covariates were Brief Pain Inventory severity at previous study wave, age, sex, duration of pain, oral morphine equivalent, generalised anxiety disorder severity, baseline lifetime International Statistical Classification of Diseases and Related Health Problems, Tenth Revision substance use disorder, and time.
With a few exceptions, at each follow-up, people who were using cannabis (less frequent or daily or near-daily use) reported greater pain severity and pain interference, lower pain self-efficacy, and higher generalised anxiety disorder score than those not using cannabis (table 2). The associations were consistent for less frequent and near-daily users (table 2). For example, the 4-year interview, compared with people with no cannabis use, those with less frequent and daily or near-daily use had greater pain severity scores, greater pain interference scores, lower pain self-efficacy scores, and greater generalised anxiety disorder severity scores.

Few differences were reported in oral morphine equivalent consumption or the proportion of participants with discontinued opioids between those using cannabis at different frequencies. However, people who reported less frequent cannabis use were less likely to discontinue opioids at 4 years (9%) than those reporting no use (21%), despite no difference in oral morphine equivalent at subsequent follow-up; we found no association between past cannabis use and current pain severity.

People who had reported use of cannabis at the previous wave had greater pain interference at subsequent follow-up than did those who had not used cannabis (difference of 0.5 on a 10-point scale; table 3). This difference, although still significant, was reduced by inclusion of previous pain severity score. In adjusted models that included clinical covariates and pain self-efficacy, we found no association between past cannabis use and current pain severity.

In the unadjusted model, near-daily or daily cannabis users had significantly greater pain severity than did people who had not used cannabis (difference of 0.5 on a 10-point scale; table 3). This difference, although still significant, was reduced by inclusion of previous pain severity score. In adjusted models that included clinical covariates and pain self-efficacy, we found no association between past cannabis use and current pain severity.

We did not detect an association between cannabis use in the previous wave and reduced oral morphine equivalent at subsequent follow-up; we found no association in the univariate model and no independent

<table>
<thead>
<tr>
<th>Cannabis use in previous study wave</th>
<th>Current amount of pain interference</th>
<th>Adjusted mean (SE)</th>
<th>β</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cannabis use (ref)</td>
<td>$4 (0.06)$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>Less frequent use</td>
<td>$8 (0.14)$</td>
<td>$0.38$</td>
<td>$0.11$ to $0.66$</td>
<td>$0.0065$</td>
<td></td>
</tr>
<tr>
<td>Near-daily or daily use</td>
<td>$9 (0.15)$</td>
<td>$0.46$</td>
<td>$0.15$ to $0.77$</td>
<td>$0.0034$</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for previous oral morphine equivalent and clinical covariates

<table>
<thead>
<tr>
<th>Cannabis use in previous study wave</th>
<th>Current oral morphine equivalent use mg/day</th>
<th>Adjusted mean (SE)</th>
<th>β</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cannabis use (ref)</td>
<td>$97.5 (2.77)$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
</tbody>
</table>

Adjusted for oral morphine equivalent in previous study wave

*Covariates were Brief Pain Inventory interference at previous study wave, age, sex, duration of pain, Brief Pain Inventory severity score, oral morphine equivalent, generalised anxiety disorder severity, baseline lifetime International Statistical Classification of Diseases and Related Health Problems, Tenth Revision substance use disorder, and time.

Table 4: Lagged mixed-effects linear regression examining the effect of cannabis use at the previous study wave on pain interference at the following wave (complete case analysis)

Table 5: Lagged mixed-effects linear regression examining the effect of cannabis use at the previous study wave on amount of opioid use at the following wave (complete case analysis)
association after controlling for other variables (table 5; for analysis based on multiple imputation see appendix).

We did sensitivity tests to examine the robustness of the findings. Sensitivity analyses using log transformations of oral morphine equivalent in categories (0 mg, 1–20 mg, 21–90 mg, 91–199 mg, and ≥200 mg) found similar results to those presented here (appendix). We ran post-hoc mixed-effects models among participants who self-reported neuropathic pain and adjusted for neuropathic pain and found no significant effect of past cannabis use on pain severity, interference, or oral morphine equivalent (appendix).

Discussion
To our knowledge, this is one of the longest, in-depth, prospective studies of a community cohort of people with chronic non-cancer pain, examining the effects of cannabis use on pain and prescribed opioid use. Cannabis use was common in our cohort, patients reported that it reduced their pain, and the proportion interested in using cannabis for pain doubled over the 4-year follow-up. We found that patients who had used cannabis had greater pain severity and interference, lower pain self-efficacy, and greater generalised anxiety severity than did patients who had not used cannabis.

We found no evidence of a temporal relationship between cannabis use and pain severity or pain interference, and no evidence that cannabis use reduced prescribed opioid use or increased opioid discontinuation. The most common reasons for discontinuing cannabis use included side-effects, lack of efficacy, access difficulties, and legal concerns. Nonetheless, our data and other population surveys highlight growing community interest in using cannabis for pain.

A legislative change on Oct 30, 2016, decriminalised medicinal use and supply of cannabis and cannabinoids; perceptions of efficacy and safety of cannabis for medical use might therefore increase in Australia, as they have done in other jurisdictions. Few data in our 4-year follow-up were collected after this change, and very few individuals nationally have accessed cannabinoids for medicinal purposes, so our cohort primarily used illicitly produced cannabis. Increased availability of medicinal cannabinoids might increase use among people living with chronic non-cancer pain in Australia, although access is still restricted and licensed cannabinoid medications are expensive. Additionally, in our study it is unlikely cannabis was consumed under the guidance of a medical practitioner. Expectations that cannabis will reduce pain and opioid use might differ for participants using medicinal cannabis compared with those using illicit cannabis. High-quality, double-blind, randomised, placebo-controlled trials examining expectancy effects, which are lacking for most chronic non-cancer conditions, might shed further light.

We found inconsistencies in our findings between what participants reported and our statistical assessment of associations. Although participants who used cannabis reported that the mean effectiveness of cannabis on pain was 7 out of a possible score of 10, in unadjusted cross-sectional and longitudinal analyses, people who used cannabis in the past month reported greater pain severity and interference than those who had not used cannabis in the past month. In adjusted longitudinal analyses, we found no association between cannabis and pain severity or interference. This finding is inconsistent with previous studies that have found cannabis reduced pain severity.

In our cohort, patients with chronic non-cancer pain who used cannabis reported significantly greater pain severity than those not using cannabis, consistent with surveys of medicinal users who report using cannabis because of a failure of conventional treatments. Those using cannabis with the intent of relieving their pain might represent a patient population with more distress and poorer coping mechanisms, as evidenced in our study by the lower pain self-efficacy scores for people who used cannabis. It could be that in the absence of cannabis use, pain severity and interference might have been worse. However, our study supports recent research that suggests cannabis use is associated with reduced self-efficacy in managing depression and anxiety. Although previous reviews have found moderate support for cannabis use in reducing chronic non-cancer pain, they have mainly relied on randomised controlled trials, in which people with complex comorbidities have been excluded. Considering recent findings and our study, it is important that future research focuses on self-efficacy and complexity of patients to better understand what types of patients with chronic non-cancer pain might benefit from using cannabinoids.

Previous cross-sectional studies have suggested cannabis might have opioid-sparing effects in people with chronic non-cancer pain, although a systematic review found a lack of high-quality clinical studies testing potential opioid-sparing effects. In our study, using both cross-sectional and longitudinal analytic approaches, we found no evidence that cannabis use was associated with reduced opioid use or opioid cessation. This finding needs to be qualified as participants had access only to illicit cannabis and were not taking cannabis as part of structured pain management under medical supervision.

To our knowledge, our study was unique in exploring temporal associations between cannabis use, pain, and opioid use in a large cohort with multiple assessment waves and low attrition. There might be concern that we did not recruit a representative sample of people prescribed opioids for chronic non-cancer pain. To appraise the generalisability of the study cohort, we collected data from a random sample of 71 pharmacies on the characteristics of all customers obtaining opioids during their 6-week recruitment window. These data showed important similarities between the cohort we recruited and customers overall in sex, age, and type of opioid prescribed.
Although our data were self-reported, this method of collection is reasonably reliable, particularly when there are no disincentives for being honest. All participants were assured of confidentiality and that the data would be de-identified; however, we did no independent checks of participant reports of cannabis use. Because of the illegality of cannabis during the study period, it is possible that cannabis use has been under-reported. However, other epidemiological studies that have reported cannabis use associated with reduced opioid use.

Additionally, we recorded reported cannabis use associated with reduced opioid use. It is possible that cannabis use has been under-reported. However, other epidemiological studies that have shown a significant association between cannabis use and pain, it is difficult to completely understand the effects of cannabis on pain in an observational study.

In conclusion, cannabis use is common in people with chronic non-cancer pain who have been prescribed opioids, and interest in medicinal use of cannabis is increasing. We found no evidence that cannabis use improved patient outcomes; those who used cannabis had greater pain and lower self-efficacy in managing pain. Furthermore, we found no evidence that cannabis use reduced pain interference or exerted an opioid-sparing effect.

References


37 Boenhake KF, Litinas E, Clawz DJ. Medical cannabis use is associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain 2016; 17: 739–44.
