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Cannabis use, pain and prescription opioid use in people living with chronic non-cancer pain: Findings from a four-year prospective cohort

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Abstract

Background: There has been growing interest in the use of cannabis and cannabinoids to treat chronic non-cancer pain (CNCP). Cannabis and cannabinoids have attracted attention because of their greater safety compared with opioids, and the possibility that their use can reduce opioid dose requirements via an opioid-sparing effect. Both factors have been proposed to contribute to fewer opioid-related deaths.

Methods: We used The Pain and Opioids IN Treatment (POINT) study, a national cohort of 1,514 people living with CNCP prescribed opioids, to examine relationships between cannabis use, opioid use and pain outcomes over four years.

Outcomes: Cannabis use was common, and by four-year follow-up, 24.3% had used cannabis for pain. Interest in using cannabis for pain doubled from 33% (baseline) to 60% (four years). We found that patients who had used cannabis had greater pain severity and interference, lower pain self-efficacy, and greater GAD severity than patients who had not used cannabis. We found no

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Contributors

GC conceived of the paper with LD, NL, WH and RB. Data analysis was undertaken by GC and GC. GC, TD and RB provided oversight for all statistical analyses. All authors made substantial concepts to critical review, editing and revision of the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

TD declares no competing interests.

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 living with CNCP prescribed opioids, but we found no evidence that cannabis use improved patient outcomes. Those 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.

Introduction

The use of prescribed opioids in the treatment of chronic non-cancer pain (CNCP) is controversial, due to a lack of evidence of their long-term effectiveness[1,2] and increased opioid harms in countries as opioid prescribing for CNCP has increased[3,4].

Alternatives to opioids are increasingly being debated and considered. Recent reviews of cannabinoids suggest they may have some efficacy in some CNCP conditions[5–7]. In Australia[8], the United States (U.S.)[9], Canada[10] and the Netherlands[11], CNCP is the most commonly cited reason for using cannabis for medicinal purposes. There has also been increasing discussion about the potential opioid-sparing effects of cannabinoids[12]. Changes in regulations mean that it is likely that there will be an increase in use of cannabinoid products for CNCP.

Longitudinal studies of cannabis use among people with CNCP are limited. Randomised controlled studies typically exclude those with complex physical, substance use and mental health comorbidities, which comprises a substantial number of people living with CNCP[16]. There is limited evidence on efficacy in the most common CNCP conditions, namely back or neck problems, arthritis and migraine[7,13]There is a lack of long-term follow-up in prospective studies, with the majority being 12-months or less[17–19]. Discussion about the opioid-sparing effects of cannabinoids has often been confined to ecological studies or cross-sectional surveys, which are poorly suited for testing causal hypotheses.

We used The Pain and Opioids IN Treatment (POINT) study, a national cohort of people living with CNCP prescribed opioids, to examine cannabis use and pain outcomes over four years. We aimed to examine:

1. Cannabis use over four years in people living with CNCP and who had been prescribed opioids, including their reasons for use and perceived effectiveness of cannabis;
2. Associations between level of cannabis use in the past month and pain, mental health and opioid-use;
3. The impact of cannabis use on pain severity and interference over time, while controlling for potential confounding of demographic and clinical variables;
4. Potential opioid-sparing effects of cannabis, controlling for potential confounding variables.

Method

The study was approved by the Human Research Ethics Committee of the University of New South Wales (HREC reference: #HC12149 and #HC16916). Full details of the study design and measure included have been published elsewhere[16,20].

Participants

POINT participants were recruited through community pharmacies across Australia (see Appendix Figure B1 for more details). They were: 18 years or older; living with CNCP (defined in this study as pain lasting longer than three months); taking prescribed Schedule 8 opioids (including morphine, oxycodone, buprenorphine, methadone and hydromorphone) for CNCP for greater than six 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 for cancer were not eligible. Of 2,091 people assessed for eligibility, 90% (n=1,873) were eligible and 1,514 completed the baseline interview (n=359 refused after being deemed eligible and 74 could not be contacted, see Appendix FigureB2). At each follow-up wave, at least 80% of the original participants completed the interview (Figure 1). Details of the interview procedure are located in Appendix B1. Figure 1 here

. Baseline interviews were conducted in 2012–2014, wave 1 interviews in 2013–2014, wave 2 in 2015, wave 3 in 2016 and Wave 4 in 2017.

Measures

The measures, tools, and data domains were based on recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT)[21,22].

Demographics—Data on age, gender, relationship status and current work status were collected.

Pain and pain-related measures—Participants were asked about lifetime and past year chronic pain conditions, and duration of CNCP. Pain is only one of a range of core outcomes to consider when evaluating interventions for CNCP[21]; we used the pain severity and interference (how pain impacts on sleep, daily living, working ability and social interaction) subscales of the Brief Pain Inventory (BPI)[23], with higher scores indicating greater pain severity/interference (score range 0–10).

Pain self-efficacy relates to a person's beliefs about the extent to which they can carry out daily activities despite their pain; this was measured using the Pain Self-Efficacy Questionnaire (PSEQ)[24] (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)".

Opioid treatment—Daily oral morphine equivalent (OME) doses of opioids, in mg per day, were estimated using conversion units established through synthesis of clinical references[25], using the medication diary. At each follow-up, there was confirmation of whether participants were still taking a Schedule 8 opioid.

Cannabis use—Participants were asked about lifetime and past 12-month use, 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 cannabis use' (1–19 days) and 'near daily/daily cannabis use' (20+ days of cannabis use, approximately five times a week or more frequently).

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 (See Appendix B). All participants were asked 'if you had access to cannabis, would you want to use it?' at each wave (excluding the one-year follow-up). Based on a similar question in the BPI, we asked participants to rate the effectiveness of cannabis on their pain on a scale of 0 ('no relief') to 10 ('complete relief').

Mental health—Current depression and generalised anxiety disorder were measured by the PHQ-9 and GAD-7 modules of the Patient Health Questionnaire[26,27]. Moderate-severe depression was defined as PHQ-9 score ≥10 [26]; moderate-severe anxiety was defined as GAD-7 score ≥10 [27]. The Composite International Diagnostic Interview 3.0 (CIDI) substance use module assessed lifetime ICD-10 harmful use and dependence[28].

Statistical analysis

Analyses were conducted using STATA, version 15.0 (Stata Corporation, College Station, TX, USA). For descriptive statistics, means and standard deviations were computed where data were normally distributed; medians and inter-quartile ranges where data were skewed.

[29]Cross-sectional associations with cannabis use frequency—Multinomial logistic regression models were also used for univariate comparisons of people at each wave who reported 'less frequent cannabis use' and 'near daily/daily cannabis use' (cf. people who had not used cannabis). Variables included in the multinomial regressions were selected in the same manner as above. For interpretability, RRR's for OME are reported per 100 units.

Additional analysis on the demographic and clinical associations between prevalent and incident cannabis use are presented and discussed in Appendix C pages 14–15.

Prospective associations between cannabis use and outcomes—Lagged mixed-effects models examined temporal associations between cannabis use and pain severity and interference and OME, incorporating a random-intercept for individuals to account for the repeated measures design. We examined unadjusted and adjusted associations between cannabis use (the exposure) and three outcomes: pain severity, pain interference and OME. We analysed data from four annual waves, with outcomes for the following year compared with people who used cannabis ('less frequent cannabis use' and 'near daily/daily cannabis

use') and people who had 'never used cannabis'. Variables identified in previous research as related to the outcomes were included in adjusted models[29]. We conducted four models. In the first model, we adjusted for previous wave outcome; in the second, we adjusted for age, gender, duration of pain, GAD severity and history of substance use. Additionally, for the analysis on pain severity we also controlled for OME; for pain interference we adjusted for pain severity and OME; for OME we adjusted for pain severity. In the third model, we further adjusted for PSEQ (we had some missing data, since the PSEQ was not collected at the one-year interview). We utilised the Stata command *margins* (or *mimrgns* for multiple imputation) to obtain adjusted means. Details of sensitivity analysis are located in Appendix D

Role of the funding source—The funder had no role in the design, conduct, analysis, interpretation of findings, or decision to publish this work. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Characteristics of the cohort at baseline

At baseline, the cohort (n=1,514) was 44% male (IQR 42–47) with a median age of 58 years (IQR 48–67) (Table 1). Just under half were unemployed (48.8%) and 31% had retired from work. Participants had been living with CNCP for a median of 10 years (IQR 4.5–20) and had been prescribed a strong opioid for a median of four years (IQR 1.5–10). The median OME taken was 75mg per day (IQR 36–150). The most common types of pain reported at baseline was back/neck pain (76.6%) followed by arthritis (61.6%), and comorbid pain was common, with participants reporting a median of 2 (IQR 2–3) chronic pain conditions at baseline in the preceding 12 months. Approximately two-thirds (61.9%) reported neuropathic pain at baseline.

Cannabis use

At baseline, two-fifths of the cohort (43.2%) reported ever using cannabis, 12.9% reported use in the past 12-months, and 8.7% reported past month use. Both past 12-month and past-month use increased steadily from baseline to the four-year timepoint (15.8% and 12.9%, respectively; see Table 1).

Approximately one-in-six (15.6%) reported that they had used cannabis for their pain in their lifetime. Past 12-month and past month reporting of cannabis use for pain also increased steadily over time. The percentage reporting use between 1 and 19 days ('less frequent cannabis use') in the month preceding interview remained relatively stable. The percentage reporting use 20+ days in the past month-31 (approximately five days a week or more, i.e. 'near-daily/daily cannabis use') increased from 3.3% at baseline to 6.5% at the 4-year follow-up.

At baseline, participants who had used cannabis for pain rated its mean effectiveness for their pain as around seven 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 doubled from 33% at baseline to 60% at the four-year follow-up.

At the three and four-year follow-ups, participants who reported past month cannabis use were asked whether it influenced their use of opioid medication. The majority reported that cannabis had no effect on their use of opioid medication (3-year 77%; 4-year71%); one-quarter reported that they 'sometimes' or 'regularly' reduced their opioid medication when using cannabis (3 year 21%; 4 year 29%) see Figure Appendix C, page 11). There were no differences in age, gender, pain severity/interference or OME between cannabis users who reported cannabis 'sometimes' or 'regularly' reduced their opioid use, compared with those who said it had no such effect.

Of those currently using cannabis, the most common reasons for use at both the three-year and four-year follow-up were to relieve pain (82% at each year) and pain-related distress (3 year 64; 4 year 73%), to improve sleep (3 year 66%; 4 year 63%) and for general relaxation (3 year 72% and 4 year 64%) (see Figure Appendix C, page 12). 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 28%; 4 year 23%), legal concerns 3 year 26%; 4 year 18%), difficulties accessing cannabis (3 year 18%; 4 year 20%) and its ineffectiveness in relieving pain (3 year 22%; 4 year 12%) (Figure Appendix C, page 13).

Cross-sectional associations of pain-related factors with cannabis use

Table 2 presents univariate analyses of associations between level of involvement in cannabis use and a range of clinical variables. With few exceptions, at each wave, people who were using cannabis (less frequent or daily/near daily use) reported greater pain severity and pain interference, lower pain self-efficacy and higher levels of GAD than those not using cannabis (Table 2). The associations were consistent for less frequent and near daily users (Table 2). For example, at the 4 year interview, compared to people with no cannabis use, less frequent and daily/near daily had greater pain severity score (RRR 1.14, 95%CI 1.01–1.29; RRR 1.17 95%CI 1.03–1.32), greater pain interference score (RRR1.21 95%CI 1.09–1.35; RRR 1.14, 95%CI 1.03–1.26), lower pain self-efficacy scores (RRR 0.97, 95%CI 0.96–1.00; RRR 0.98, 95%CI 0.96–1.00) and greater GAD severity scores (RRR 1.07, 95%CI 1.03–1.12; RRR 1.10, 95%CI 1.06–1.15)

There were very few differences in OME consumption or rates of opioid discontinuation between those using cannabis at different frequencies. The exception was that people who reported 'less frequent' cannabis use had lower opioid discontinuance rates at 4 years (9%) than those reporting no use (21%), despite no difference in OME at the 4-year.

Temporal associations between prior cannabis use and current pain severity, pain interference and oral morphine equivalent (OME) consumption

Lagged mixed effect models examined the effect of past cannabis use on current pain severity (Table 3), current pain interference (Table 4) and current OME consumption (Table 5) in people using cannabis compared with those not using cannabis (complete case analysis; for multiple imputation analysis see Appendix C). In the unadjusted model, near daily or

daily cannabis users had significantly *greater* pain severity (β 0.53, 95%CI 0.27–0.80) than people who had not used cannabis (difference of 0.5 on a 10-point scale). This difference, though still significant, was mediated by the inclusion of previous pain severity score (β 0.21, 95%CI 0.01–0.40). In adjusted models, including clinical covariates and pain self-efficacy there was no association between past cannabis use and current pain severity.

People who had used cannabis in the previous wave had *greater* pain interference in the subsequent wave than those who had not used cannabis (for less frequent use β 0.38, 95%CI 0.11–0.66; for near daily/daily β 0.46, 95%CI 0.15–0.77). In adjusted models, after controlling for age, gender, previous pain interference, pain factors (e.g., duration of pain, pain severity and pain self-efficacy) and OME, prior cannabis use was not independently associated with current pain interference.

We also failed to detect an association between cannabis use in the previous wave and reduced OME in the subsequent wave. A complete case analysis of the effect of past cannabis use on current OME using is presented in Table 5 (for analysis based on multiple imputation, which found similar results, see Appendix D, pages 16–18)). There was no association in the univariate model and no independent association after controlling for other variables (Table 5).

Sensitivity analysis—To examine the robustness of the findings we conducted the following sensitivity tests. Sensitivity analyses that used log transformations of OME (Appendix D, pages 19) and used OME in categories (0, 1–20mg, 21–90mg, 91–199mg and 200+ greater mg, Appendix D, pages 20) found similar results to those presented here. Post-hoc, we ran the mixed-effects models among participants who self-reported neuropathic pain (Appendix D, pages 21–23) and also adjusting for neuropathic pain (see Appendix D, pages 24–25) and found no significant effect of past cannabis use on pain severity, interference or OME.

Discussion

To our knowledge, this is one of the longest in-depth prospective studies of a community cohort of people with CNCP that examines the impacts of cannabis use on pain and prescribed opioid use. Cannabis use was common in the cohort, patients reported that it reduced their pain and the proportion interested in using cannabis for pain doubled over the four-year follow up. We found that patients who had used cannabis had greater pain severity and interference, lower pain self-efficacy, and greater GAD severity than 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 rates of 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[32], highlight growing community interest in using cannabis for pain.

It is possible that perceptions of efficacy and safety will increase in Australia after a recent legislative change[33] allowing medicinal use. Specifically, amendments to the federal Narcotic Drugs Act 1967 decriminalising medicinal use and supply of cannabis and cannabinoids came into effect on 30 October 2016[13]. Only a minority of the data in the 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. It is not surprising, then, that two of the main reasons for discontinuing cannabis use for pain were access difficulties and legal concerns, similar to previous findings[8]. The increased availability of medicinal cannabinoids may increase use among people living with CNCP in Australia, though there is still limited accessibility and licensed cannabinoid medications are expensive. Additionally,it is unlikely cannabis was consumed under the guidance of a medical practitioner. Expectancies around cannabis reducing pain and opioid use may be different from participants using medicinal cannabis. High quality double-blind, randomised, placebo-controlled trials, which also examine expectancy effects, which are lacking for most CNCP conditions, may shed further light.

There were 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 seven out of a possible score of 10, in unadjusted cross-sectional and longitudinal analysis, people who used cannabis in the past month reported greater pain severity and inference than those who had not used cannabis in the past month. In adjusted longitudinal analyses, there was no association between cannabis and pain severity or interference. This finding is inconsistent with previous studies that have found cannabis reduced pain severity[17–19].

In our cohort, CNCP patients 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 more conventional treatments[34,35]. Those using cannabis with the intent of relieving their pain may comprise 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 may be that in the absence of cannabis use, pain severity and interference may have been worse. Importantly, however, this study supports recent research which suggests cannabis use is associated with reduced self-efficacy in managing [36]depression and anxiety[36]. Although previous reviews have found moderate support for cannabis use in reducing pain in CNCP[5–7,9], they have mainly relied on RCT studies in which people with complex comorbidities have been excluded. In light of the recent findings of Wilson[36] and the current study, it is important future research focuses on self-efficacy and the complexity of patients with CNCP in order to better understand which type of CNCP patients might benefit from using cannabinoids.

Previous cross-sectional studies have suggested cannabis may have ‘opioid-sparing’ effects in people with CNCP[37,38], though a systematic review revealed a lack of high-quality clinical studies testing potential opioid-sparing effects[39]. In the current 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.

Strengths and Limitations

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 CNCP. We collected data from a random sample of 71 pharmacies on the characteristics of all customers obtaining opioids during their six-week recruitment window, which showed important similarities between the cohort we recruited and customers overall. Among all customers recorded purchasing opioids in these pharmacies, 52% were female (vs. 55% in the POINT cohort); and 7% were 18–34 years, 55% 35–64 years and 38% 65+ years (vs. 5%, 62% and 33% respectively, in the POINT cohort). Two thirds (63%) were prescribed oxycodone (vs. 62% in the POINT cohort), 16.5% prescribed morphine (vs. 15% in the POINT cohort), and 24% prescribed buprenorphine patches (vs. 21% in the POINT cohort).

Although data were self-reported, this method of collection is reasonably reliable[41], particularly when there are no disincentives for being honest[42]. All participants were assured of confidentiality and that the data would be de-identified, however, we performed no independent checks of participant reports of cannabis use. Due to the illegality of cannabis during the study period, it is possible that cannabis use has been underreported. We also note however, that other epidemiological studies that have reported that cannabis use reduces opioid use also depend upon self-reported cannabis and opioid use [37,38,43,44].

Additionally, we recorded frequency of cannabis use, rather than quantity and type of cannabis, but there are major complexities in reliably measuring this, given variations in THC content and amounts consumed in a session of use[45,46]. Finally, although we found no significant association between cannabis use and pain, it is difficult to understand completely the effects of cannabis on pain in an observational study design.

Conclusion

Cannabis use is common in people living with CNCP 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. We found no evidence that cannabis use reduced pain interference or exerted an opioid-sparing effect.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Evidence before this study

There has been substantial interest in the potential utility of cannabinoids for use in chronic non-cancer pain (CNCP). We conducted and literature review using MEDLINE, Embase, PsycINFO, CENTRAL and clinicaltrials.gov were searched in July 2017 for and RCT and observational studies relating to all cannabinoid types and specific CNCP conditions and pain-related outcomes. We identified 91 publications, containing 104 studies, which included 47 randomised control trials and 57 observational studies. We found pooled change in pain intensity (standardised mean difference: −0.14, 95%CI −0.20, −0.08) was equivalent to 3mm on a 100mm visual analogue scale greater than placebo. Evidence was graded as moderate. Existing clinical studies of the effects of cannabinoids on CNCP mainly comprised RCTs conducted using a limited range of cannabinoids in a limited range of CNCP conditions and a lack of clarity in reporting of pain outcomes.

Added value of this study

To our knowledge, this is one of the longest in-depth prospective studies of a community cohort of people with a variety of different types of CNCP that examined the impacts of cannabis use on pain and prescribed opioid use over four years of follow up. Cannabis use was common in the cohort, patients reported that it reduced their pain, and interest in using cannabis for pain doubled in the cohort over the four-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 patients who had not. Unlike recent reviews which suggest a positive impact of cannabinoids on pain and reduction in opioid use, we found there was 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 have suggested that there is moderate evidence that cannabinoids are effective for certain types of pain. Previous evidence has been limited due to studies with limited duration and excluding participants with complex clinical profiles. In our current 4-year prospective cohort of people prescribed opioids for CNCP, we did not find evidence supporting claims that cannabis and cannabinoids improve outcomes in CNCP, nor that they reduce prescription opioid use. To date, evidence that cannabinoids are effective for CNCP and aid in reducing opioid use is limited. Large, well-designed clinical trials are required to evaluate in which patients, cannabinoids may be effective in reducing pain severity, interference and opioid doses.

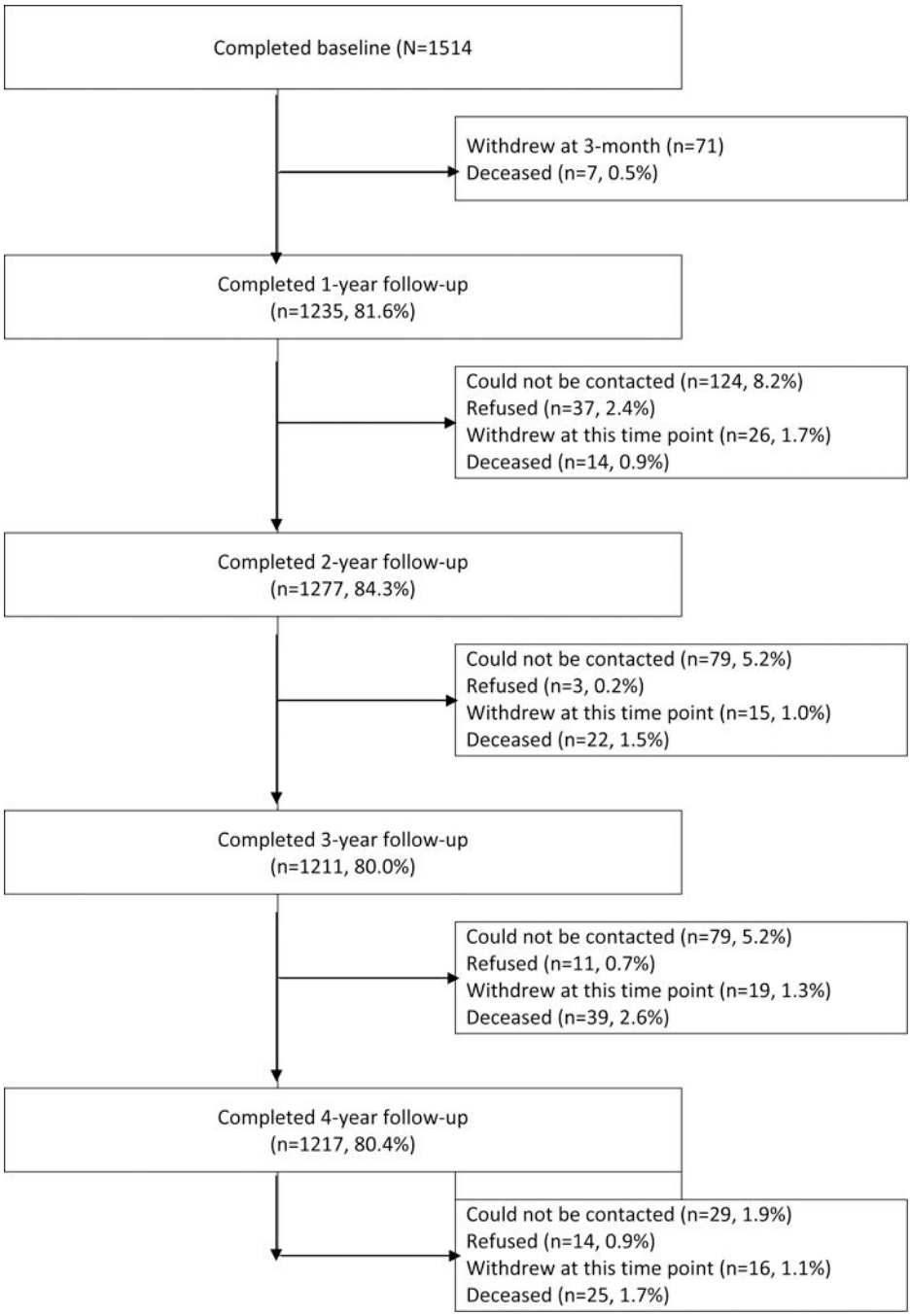

Figure 1:
POINT study flow chart

Table 1:

Socio-demographic characteristics, pain, prescribed opioid use and cannabis use amongst the POINT sample, by wave

	Baseline (N=1514) % (n)	1-year (N=1216) % (n)	2-year (N=1277) % (n)	3-year (N=1211) % (n)	4 year (N=1214) % (n)
Demographics					
Age MDN (IQR)	58 (48–67)	58 (49–68)	59 (50–69)	60 (50–69)	60 (50–70)
% Male	44 (672)	44 (542)	44 (555)	43 (524)	43 (524)
Pain					
BPI pain severity (M, SD)	5.1 (1.79)	5.3 (1.9)	5.0 (1.9)	4.9 (1.9)	4.8 (1.9)
BPI pain interference (M, SD)	5.7(2.3)	5.7 (2.4)	5.4 (2.4)	5.5 (2.4)	5.4 (2.4)
Prescribed opioid use					
OME (MDN, IQR)	75 (36–150)	61 (24–135)	63 (25–135)	60 (22–126)	56.8 (15–125)
% Discontinued opioids	-	10.7 (131)	13.7 (174)	16.7 (162)	20.2 (246)
Cannabis use					
% Lifetime use	43.2 (649)	-	-	-	-
% Past 12 months	12.9 (195)	11.1 (135)	13.3 (170)	14.3 (173)	15.8 (190)
% Past month use	8.7 (126)	9.4 (112)	9.7 (123)	10.9 (132)	12.9 (155)
Proportion past month use: None 1–19 days 20–31 days	91.3 (1319) 5.4 (78) 3.3 (48)	90.6 (1085) 5.4 (65) 3.9 (47)	90.4 (1151) 5.5 (70) 4.2 (53)	89.1 (1078) 5.8 (70) 5.1 (62)	87.1 (1047) 6.4 (78) 6.5 (79)
% Ever used for pain relief	15.6 (237)	18.0 (220)	20.4 (260)	22.0 (267)	24.3 (295)
% Used for pain relief past 12 months	-	9.8 (123)	11.8 (151)	12.0 (145)	14.0 (168)
% Used for pain relief past month	5.6 (85)	-	8.7 (111)	10.0 (121)	11.1 (134)
Effectiveness of cannabis for pain (out of 10) (M, SD)	6.5 (2.9)	5.0 (3.5)	7.3 (2.2)	7.0 (2.2)	7.2 (2.3)
% Would use it if had access	32.6 (364)	-	44.1 (562)	53.6 (649)	60.1 (723)

Note. BPI: Brief Pain Inventory; OME: oral morphine equivalent; MDN: median; IQR: interquartile range; CI: confidence interval; M: mean; SD: standard deviation, -data not collected

Table 2.

Bivariate cross-sectional associations between level of cannabis use in the past month (days of use) and pain, anxiety and medication use in the POINT cohort, by wave

	No cannabis use (A)	Less frequent cannabis use (<20 days) (B)	Daily/near daily cannabis use (20+ days) (C)	Unadjusted[1]			
				B vs A		C vs A	
				RRR	p	RRR	p
Duration of pain + (years; MDN, IQR)	10 (4–20)	12.5 (6–21)	13 (5–21.5)	1.00 (0.99–1.02)	0.484	1.00 (0.98–1.02)	0.901
BPI Pain Severity score (M, SD)							
Baseline	5.1 (1.8)	5.3 (1.9)	5.1 (1.4)	1.09 (0.96–1.24)	0.19	1.00 (0.86–1.19)	0.906
1-year	5.3 (2.0)	5.4 (1.8)	5.6 (1.6)	1.03 (0.90–1.17)	0.703	1.09 (0.93–1.27)	0.27
2-year	5.0 (1.9)	5.4 (1.9)	5.6 (1.9)	1.12 (0.98–1.27)	0.090	**1.20 (1.03–1.39)**	**0.020**
3-year	4.8 (1.9)	5.4 (1.8)	5.5 (1.6)	**1.19 (1.04–1.36)**	**0.011**	**1.21 (1.05–1.40)**	**0.0081**
4-year	4.7 (1.9)	5.2 (1.9)	5.3 (1.8)	**1.14 (1.01–1.29)**	**0.031**	**1.17 (1.03–1.32)**	**0.013**
BPI Pain Interference score (M, SD)							
Baseline	5.6 (2.3)	6.0 (2.2)	6.2 (1.5)	1.08 (0.98–1.21)	0.13	1.13 (0.99–1.30)	0.078
1-year	5.6 (2.4)	6.2 (2.2)	6.4 (2.0)	1.11 (0.99–1.24)	0.076	**1.15 (1.01–1.31)**	**0.039**
2-year	5.3 (2.4)	6.2 (2.3)	6.2 (1.8)	**1.18 (1.05–1.31)**	**0.0035**	**1.18 (1.04–1.33)**	**0.010**
3-year	5.4 (2.4)	6.5 (2.0)	6.4 (2.0)	**1.23 (1.10–1.38)**	**<0.001**	**1.22 (1.08–1.38)**	**0.0011**
4-year	5.3 (2.4)	6.3 (2.3)	6.0 (2.3)	**1.21 (1.09–1.35)**	**<0.001**	**1.14 (1.03–1.26)**	**0.0091**
PSEQ Pain self-efficacy score (M, SD)							
Baseline	29.7 (13.6)	26.4 (12.7)	25.6 (9.8)	**0.98 (0.97–1.00)**	**0.039**	**0.98 (0.96–1.00)**	**0.048**
1-year[b]	-	-	-	-	-	-	-
2-year	33.7 (13.4)	27.8 (11.2)	29.6 (11.4)	**0.97 (0.95–0.99)**	**<0.001**	**0.98 (0.96–1.00)**	**0.029**
3-year	34.4 (13.2)	28.1 (12.3)	28.6 (13.1)	**0.96 (0.95–0.98)**	**<0.001**	**0.97 (0.95–0.99)**	**0.0008**
4-year	34.2 (13.9)	30.2 (12.7)	30.6 (13.3)	**0.97 (0.96–1.00)**	**0.015**	**0.98 (0.96–1.00)**	**0.026**
GAD-7 severity score (M, SD)							
Baseline	5.3 (5.3)	7.2 (5.5)	8.0 (5.5)	**1.06 (1.02–1.10)**	**0.0023**	**1.09 (1.04–1.14)**	**0.0007**
1-year[a]	5.1 (5.3)	7.4 (5.3)	8.9 (7.2)	**1.07 (1.03–1.12)**	**0.0012**	**1.11 (1.06–1.16)**	**<0.001**
2-year	4.5 (4.8)	7.5 (5.5)	6.9 (5.8)	**1.11 (1.06–1.15)**	**<0.001**	**1.09 (1.03–1.14)**	**<0.001**
3-year	4.5 (4.8)	6.7 (5.5)	8.1 (5.9)	**1.08 (1.03–1.13)**	**<0.001**	**1.12 (1.07–1.17)**	**<0.001**
4-year	4.3 (4.9)	6.4 (5.1)	7.3 (6.1)	**1.07 (1.03–1.12)**	**<0.001**	**1.10 (1.06–1.15)**	**<0.001**
OME (MDN, IQR)							
Baseline	70 (35–140)	84 (38–188)	90 (33–171)	**1.21 (1.01–1.44)****	**0.040**	1.05 (0.80–1.37)	0.72
1-year	60 (23–135)	88 (44–152)	90 (31–240)	1.05 (0.85–1.30)	0.64	**1.39 (1.18–1.63)**	**<0.001**
2-year	60 (24–135)	87 (52–191)	80 (30–165)	1.12 (0.98–1.27)	0.082	1.14 (0.99–1.30)	0.063
3-year	60 (22–120)	71 (39–180)	60 (23–138)	1.15 (0.89–1.29)	0.072	1.07 (0.89–1.29)	0.47
4 year	55 (15–124)	63 (23–135)	49 (8–135)	1.04 (0.88–1.22)	0.65	1.01 (0.85–1.21)	0.89

	No cannabis use (A)	Less frequent cannabis use (<20 days) (B)	Daily/near daily cannabis use (20+ days) (C)	Unadjusted[1]			
				B vs A		C vs A	
				RRR	p	RRR	p
% discontinued opioids							
1-year	10.8 (9.1–12.8)	9.2 (4.1–19.4)	10.6 (4.3–23.8)	0.59 (0.21–1.65)	0.31	0.88 (0.31–2.52)	0.81
2-year	13.8 (11.9–15.9)	7.1 (2.9–16.3)	18.9 (10.2–32.1)	0.48 (0.19–1.21)	0.12	1.44 (0.71–2.94)	0.304
3-year	16.8 (14.7–19.1)	15.7 (8.8–26.5)	16.1 (8.7–27.8)	0.92 (0.48–1.79)	0.81	0.95 (0.48–1.91)	0.89
4-year	20.9 (18.6–23.5)	9.0 (5.1–19.4)	21.5 (13.7–32.2)	**0.38 (0.17–0.83)**	**0.016**	1.05 (0.60–1.84)	0.85

Note. Table 1 provides n for each wave.

[+] only asked at baseline

[–] not asked at this wave.

[**] RRR based on per 100 unit

Values highlighted in bold where p<.05.

BPI: Brief Pain Inventory; PSEQ: Pain Self-Efficacy Questionnaire; OME: oral morphine equivalent; GAD-7: Generalized Anxiety Disorder 7-item scale.

[a] Data on PSEQ not collected at 1-year timepoint

[1.] Results of multivariate are provided in the appendix.

Table 3:

Lagged mixed-effects linear regression examining the impact of cannabis use in the previous wave on pain severity in the following wave (complete case analysis)

	Current level of pain severity			
	Adjusted mean (SE)	**β**	**95% CI**	**P value**
Cannabis use in previous wave				
No cannabis use (ref)	5.0 (0.05)	-	-	-
Less frequent use	5.1 (0.12)	0.16	−0.07–0.39	0.18
Near daily/daily use	5.5 (0.13)	**0.53**	**0.27–0.80**	**<0.001**
…adjusted for pain severity in previous wave				
No cannabis use (ref)	5.0 (0.02)	-	-	-
Less frequent use	5.0 (0.10)	0.06	−0.12–0.26	0.51
Near daily/daily use	5.2 (0.10)	**0.21**	**0.01–0.40**	**0.037**
…adjusted for previous pain severity and clinical covariates[1]				
No cannabis use (ref)	4.9 (0.03)	-	-	-
Less frequent use	5.0 (0.13)	0.35	−0.01–0.71	0.061
Near daily/daily use	5.1 (0.14)	0.45	−0.21–1.11	0.18
…adjusted for previous pain severity and clinical covariates[1] **and PSEQ**				
No cannabis use (ref)	4.9 (0.03)	-	-	-
Less frequent use	5.1 (0.13)	0.37	−0.01–0.75	0.056
Near daily/daily use	5.2 (0.14)	0.43	−0.23–1.10	0.201

[1]Covariates include: previous wave BPI severity, age, gender duration of pain, OME, GAD severity, baseline lifetime ICD10 substance use disorder, time. PSEQ: Pain Self-Efficacy Questionnaire

Table 4:

Lagged mixed-effects linear regression examining the impact of cannabis use in the previous wave on pain interference in the following wave (complete case analysis)

	Current level of pain interference			
	Adjusted mean (SE)	**β**	**95% CI**	**P value**
Cannabis use in previous wave				
No cannabis use (ref)	5.4 (0.06)	-	-	-
Less frequent use	5.8 (0.14)	**0.38**	**0.11–0.66**	**0.0065**
Near daily/daily use	5.9 (0.15)	**0.46**	**0.15–0.77**	**0.0034**
…adjusted for pain interference in previous wave				
No cannabis use (ref)	5.4 (0.03)	-	-	-
Less frequent use	5.8 (0.12)	**0.32**	**0.08–0.55**	**0.0087**
Near daily/daily use	5.6 (0.11)	0.15	−0.08–0.37	0.20
…adjusted for previous OME and clinical covariates[1]				
No cannabis use (ref)	5.3 (0.03)	-	-	-
Less frequent use	5.6 (0.14)	0.33	−0.23–0.89	0.25
Near daily/daily use	5.2 (0.15)	−0.56	−1.41–0.28	0.19
…adjusted for previous OME and clinical covariates[1] **and PSEQ**				
No cannabis use (ref)	5.4 (0.04)	-	-	-
Less frequent use	5.7 (0.16)	0.35	−0.22–0.92	0.23
Near daily/daily use	5.2 (0.19)	−0.63	−1.46–0.19	0.13

[1]Covariates include: previous wave BPI interference, age, gender, duration of pain, BPI severity score, OME, GAD severity, baseline lifetime ICD10 substance use disorder, time. PSEQ: Pain Self-Efficacy Questionnaire

Table 5:

Lagged mixed-effects linear regression examining the impact of cannabis use in the previous wave on level of opioid use in the following wave (complete case analysis)

	Current opioid morphine equivalent (OME) mg use per day			
	Adjusted mean (SE)	**β**	**95% CI**	**P value**
Cannabis use in previous wave				
No cannabis use (ref)	97.5 (2.77)	-	-	-
Less frequent use	100.7 (7.46)	3.31	−11.74–18.36	0.67
Near daily/daily use	105.3 (13.44)	7.84	−18.75–34.44	0.56
…adjusted for OME in previous wave				
No cannabis use (ref)	96.3 (1.32)	-	-	-
Less frequent use	91.7 (5.15)	−4.56	−15.13–6.01	0.40
Near daily/daily use	100.3 (7.43)	4.08	−10.79–18.95	0.59
…adjusted for previous OME and clinical covariates[1]				
No cannabis use (ref)	91.2 (1.45)	-	-	-
Less frequent use	88.2 (6.78)	1.05	−31.25–33.35	0.95
Near daily/daily use	91.5 (8.88)	27.64	−28.87–84.15	0.34
…adjusted for previous OME and clinical covariates[1] **and PSEQ**				
No cannabis use (ref)	85.5 (1.74)	-	-	-
Less frequent use	95.1 (8.85)	7.00	26.97–40.96	0.69
Near daily/daily use	97.1 (12.66)	32.76	−25.04–90.57	0.27

[1]Covariates include: previous wave OME, age, gender, duration of pain, BPI severity score, GAD severity, baseline lifetime ICD10 substance use disorder, time. PSEQ: Pain Self-Efficacy Questionnaire