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

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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.

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.

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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 effectiveness[1,2] and increased harms as opioid prescribing for chronic non-cancer pain has increased.[3,4]

Alternatives to opioids are increasingly being debated and considered. Reviews of cannabinoids suggest they might have efficacy in some chronic non-cancer pain conditions.[5–7] In the USA,[8] Canada,[9] and the Netherlands,[10] chronic non-cancer pain is the most commonly cited reason for use of cannabis for medicinal purposes.

Research in context

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", "cannab*", "marijuana", "marinol", "dronabinol", "nabilone", "levonantradol", "tetrahydrocannabinol", "cesamet", "delta-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 cannabinoids in a small range of chronic non-cancer pain conditions and lacked 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 prescribed 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.

Furthermore, there is increasing discussion about the potential opioid-sparing effects of cannabinoids.[11] Changes in regulations mean that there could be an increase in use of cannabinoid products for chronic non-cancer pain.

Longitudinal studies of cannabis use among people with chronic non-cancer pain are scarce. Randomised controlled studies typically exclude individuals with complex physical, substance use, and mental health comorbidities, who represent a substantial proportion of people living with chronic non-cancer pain.[12] Evidence on efficacy in the most common causes of chronic non-cancer pain—namely, back or neck problems, arthritis, and migraine, is scarce.[7,13] Long-term follow-up in prospective studies is insufficient, with most being 12 months or less.[14–16] 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.

See Online for appendix

We used the Pain and Opioids IN Treatment (POINT) study, a national cohort of people with chronic non-cancer pain who had been prescribed opioids, to examine cannabis use and pain outcomes over 4 years. We aimed to investigate the following: cannabis use during a 4-year period in people 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 in the past month and pain, mental health, and opioid use; the effect of cannabis use on pain severity and interference over time, controlling for potential confounding of demographic and clinical variables; and potential opioid-sparing effects of cannabis, controlling for potential confounding variables.

Methods

Study design and participants

Full details of the study design and measures included have been published elsewhere.[12,17] POINT participants were recruited through community pharmacies across Australia (appendix). We did not have a planned period of recruitment, but aimed to recruit until we reached 1500 participants. Recruitment took place from August 13, 2012, to April 8, 2014. Participants were aged 18 years or older, living with chronic non-cancer pain (defined in this

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 #HC12149 and #HC16916).

Measures

The measures, tools, and data domains were based on recommendations made by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[18,19] 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 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,[18] 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),[20] 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 PSEQ[21] (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,[22] 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).

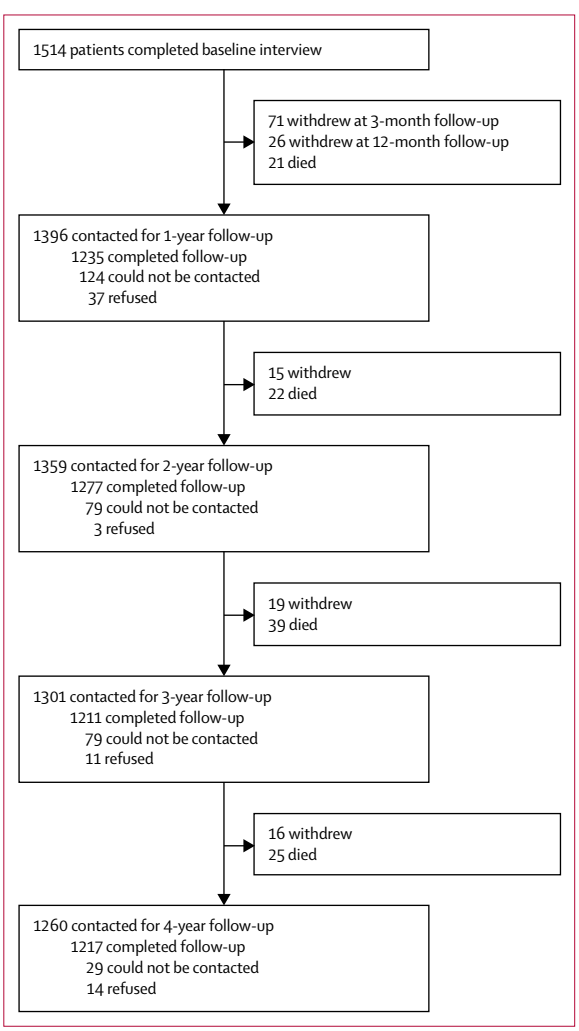

Figure: **Study flow chart**
Patient flow and reasons for exclusion between study referral and baseline interview are provided in the appendix.

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 3.0 substance use module to assess lifetime International Statistical Classification of Diseases and Related Health Problems, Tenth Revision diagnostic codes for harmful use and dependence.[25]

	Baseline (n=1514)	1-year follow-up (n=1235)	2-year follow-up (n=1277)	3-year follow-up (n=1211)	4-year follow-up (n=1217)
Demographics					
Age, years	58 (48–67)	58 (49–68)	59 (50–69)	60 (50–69)	60 (50–70)
Sex					
Male	672 (44%)	542 (44%)	555 (43%)	524 (43%)	524 (43%)
Female	842 (56%)	693 (56%)	722 (57%)	687 (57%)	693 (57%)
Pain					
BPI pain severity score	5·1 (1·79)	5·3 (1·9)	5·0 (1·9)	4·9 (1·9)	4·8 (1·9)
BPI pain interference score	5·7 (2·3)	5·7 (2·4)	5·4 (2·4)	5·5 (2·4)	5·4 (2·4)
Prescribed opioid use					
Oral morphine equivalent, mg/day	75 (36–150)	61 (24–135)	6 (25–135)	60 (22–126)	57 (15–125)
Discontinued opioids	..	131 (10·6%)	174 (13·6%)	202 (16·7%)	246 (20·2%)
Cannabis use					
Lifetime use	649 (43%)	..	..	..	..
Past 12 months	195 (13%)	135 (11%)	170 (13%)	173 (14%)	192 (16%)
Past month use	126 (8%)	112 (9%)	123 (10%)	132 (11%)	155 (13%)
Frequency of use in the past month*					
None	1319 (91%)	1085 (91%)	1151 (90%)	1078 (89%)	1047 (86%)
1–19 days (less frequent)	78 (5%)	65 (5%)	70 (5%)	70 (6%)	78 (6%)
20–31 days (near-daily or daily)	48 (3%)	47 (4%)	53 (4%)	62 (5%)	79 (6%)
Ever used for pain relief	237 (16%)	220 (18%)	260 (20%)	267 (22%)	295 (24%)
Used for pain relief in the past 12 months	..	123 (10%)	151 (12%)	145 (12%)	168 (14%)
Used for pain relief in the past month†	85 (6%)	..	111 (9%)	121 (10%)	134 (11%)
Effectiveness of cannabis for pain (out of 10)	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†	364 (33%)‡	..	562 (44%)	649 (54%)	723 (60%)

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 frequency, 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 mimrgns 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

	No cannabis use	Less frequent cannabis use (<20 days)	Daily or near-daily cannabis use (≥20 days)	Unadjusted			
				Less frequent cannabis use (<20 days) *vs* no cannabis use		Daily or near-daily cannabis use (≥20 days) *vs* no cannabis use	
				RR (95% CI)	p value	RR (95% CI)	p value
Duration of pain, years*	10·0 (4–20)	12·5 (6–21)	13·0 (5-22)	1·00 (0·99–1·02)	0·484	1·00 (0·98–1·02)	0·901
BPI pain severity score							
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							
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)	0·0003	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)	0·0004	1·14 (1·03–1·26)	0·0091
PSEQ score							
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†	..	..	..	..	..	..	..
2-year	33·7 (13·4)	27·8 (11·2)	29·6 (11·4)	0·97 (0·95–0·99)	0·0004	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)	0·0001	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
Generalized Anxiety Disorder 7-item scale severity score							
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	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)	<0·0001
2-year	4·5 (4·8)	7·5 (5·5)	6·9 (5·8)	1·11 (1·06–1·15)	<0·0001	1·09 (1·03–1·14)	0·0004
3-year	4·5 (4·8)	6·7 (5·5)	8·1 (5·9)	1·08 (1·03–1·13)	0·0004	1·12 (1·07–1·17)	<0·0001
4-year	4·3 (4·9)	6·4 (5·1)	7·3 (6·1)	1·07 (1·03–1·12)	0·0005	1·10 (1·06–1·15)	<0·0001
Oral morphine equivalent‡							
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)	0·0001
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
Percentage that 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

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.

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**

	Current level of pain severity			
	Adjusted mean (SE)	β	95% CI	p value
Cannabis use at previous study wave				
No cannabis use (ref)	5·0 (0·05)	..	..	..
Less frequent use	5·1 (0·12)	0·16	−0·07 to 0·39	0·18
Near-daily or daily use	5·5 (0·13)	0·53	0·27 to 0·80	0·0001
Adjusted for pain severity at previous study wave				
No cannabis use (ref)	5·0 (0·02)	..	..	..
Less frequent use	5·0 (0·10)	0·06	−0·12 to 0·26	0·51
Near-daily or daily use	5·2 (0·10)	0·21	0·01 to 0·40	0·037
Adjusted for previous pain severity and clinical covariates*				
No cannabis use (ref)	4·9 (0·03)	..	..	..
Less frequent use	5·0 (0·13)	0·35	−0·01 to 0·71	0·061
Near-daily or daily use	5·1 (0·14)	0·45	−0·21 to 1·11	0·18
Adjusted for previous pain severity and clinical covariates* and Pain Self-Efficacy Questionnaire				
No cannabis use (ref)	4·9 (0·03)	..	..	..
Less frequent use	5·1 (0·13)	0·37	−0·01 to 0·75	0·056
Near-daily or daily use	5·2 (0·14)	0·43	−0·23 to 1·10	0·201

*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.

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

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 female (*vs* 842 [55%] in the POINT cohort) and 58 (7%) were aged 18–34 years (*vs* 73 [5%]), 438 (55%) were aged 35–64 years (*vs* 952 [62%]), and 304 (38%) were aged 65 years or older (*vs* 489 [33%]). 500 (63%) people were prescribed oxycodone (*vs* 938 [62%] in the POINT cohort), 138 (17%) were prescribed morphine (*vs* 225 [15%]), and 190 (24%) were prescribed buprenorphine patches (*vs* 332 [21%]).

At baseline, two-fifths of the cohort reported ever using cannabis, 195 (13%) reported use in the past 12 months, and 126 (9%) reported use in the past month. Both past 12-month and past-month use increased from baseline to the 4-year timepoint (table 1).

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 118 [68%] of 174 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 175 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 134 participants), and ineffectiveness in relieving pain (3-year follow-up 37 [22%] of 166 participants; 4-year follow-up 16 [12%] of 134 participants; appendix).

	Current amount of pain interference			
	Adjusted mean (SE)	β	95% CI	p value
Cannabis use in previous study wave				
No cannabis use (ref)	5·4 (0·06)	..	..	..
Less frequent use	5·8 (0·14)	0·38	0·11 to 0·66	0·0065
Near-daily or daily use	5·9 (0·15)	0·46	0·15 to 0·77	0·0034
Adjusted for pain interference in previous study wave				
No cannabis use (ref)	5·4 (0·03)	..	..	..
Less frequent use	5·8 (0·12)	0·32	0·08 to 0·55	0·0087
Near-daily or daily use	5·6 (0·11)	0·15	−0·08 to 0·37	0·20
Adjusted for previous oral morphine equivalent and clinical covariates*				
No cannabis use (ref)	5·3 (0·03)	..	..	..
Less frequent use	5·6 (0·14)	0·33	−0·23 to 0·89	0·25
Near-daily or daily use	5·2 (0·15)	−0·56	−1·41 to 0·28	0·19
Adjusted for previous oral morphine equivalent and clinical covariates* and Pain Self-Efficacy Questionnaire				
No cannabis use (ref)	5·4 (0·04)	..	..	..
Less frequent use	5·7 (0·16)	0·35	−0·22 to 0·92	0·23
Near-daily or daily use	5·2 (0·19)	−0·63	−1·46 to 0·19	0·13

*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)**

	Current oral morphine equivalent use mg/day			
	Adjusted mean (SE)	β	95% CI	p value
Cannabis use in previous study wave				
No cannabis use (ref)	97·5 (2·77)	..	..	..
Less frequent use	100·7 (7·46)	3·31	−11·74 to 18·36	0·67
Near-daily or daily use	105·3 (13·44)	7·84	−18·75 to 34·44	0·56
Adjusted for oral morphine equivalent in previous study wave				
No cannabis use (ref)	96·3 (1·32)	..	..	..
Less frequent use	91·7 (5·15)	−4·56	−15·13 to 6·01	0·40
Near-daily or daily use	100·3 (7·43)	4·08	−10·79 to 18·95	0·59
Adjusted for previous oral morphine equivalent and clinical covariates*				
No cannabis use (ref)	91·2 (1·45)	..	..	..
Less frequent use	88·2 (6·78)	1·05	−31·25 to 33·35	0·95
Near-daily or daily use	91·5 (8·88)	27·64	−28·87 to 84·15	0·34
Adjusted for previous oral morphine equivalent and clinical covariates* and Pain Self-Efficacy Questionnaire				
No cannabis use (ref)	85·5 (1·74)	..	..	..
Less frequent use	95·1 (8·85)	7·00	26·97 to 40·96	0·69
Near-daily or daily use	97·1 (12·66)	32·76	−25·04 to 90·57	0·27

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

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)**

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 levels of generalised anxiety disorder 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 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 who 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 4-year follow-up (table 2).

Using lagged-effects models, we examined the effect of past cannabis use on current pain severity (table 3), current pain interference (table 4), and current oral morphine equivalent consumption (table 5) in people using cannabis compared with those not using cannabis (complete case analysis; for multiple imputation analysis see appendix).

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.

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 (table 4). In adjusted models, after controlling for age, sex, previous pain interference, pain factors (eg, duration of pain, pain severity, and pain self-efficacy), and oral morphine equivalent, previous cannabis use was not independently associated with current pain interference.

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

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[27] 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;[13] perceptions of efficacy and safety of cannabis for medical use might therefore increase in Australia, as they have done in other jurisdictions.[28] 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.[14–16]

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.[29,30] 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.[31] Although previous reviews have found moderate support for cannabis use in reducing chronic non-cancer pain,[5–7,8] they have mainly relied on randomised controlled trials, in which people with complex comorbidities have been excluded. Considering recent findings[31] 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,[32,33] although a systematic review found a lack of high-quality clinical studies testing potential opioid-sparing effects.[11] 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,[34] particularly when there are no disincentives for being honest.[35] 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 consumption have also depended on self-reported cannabis and opioid use.[32,33,36,37] Additionally, we recorded frequency of cannabis use, rather than quantity and type of cannabis, but there are major complexities in reliably measuring total cannabis consumption given variations in tetrahydrocannabinol content and amounts consumed in a session of use.[38,39] Finally, although we found no 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.

Contributors

GCa conceived the paper with LD, NL, WDH, and RB. GCa and GCh analysed the data. GCh, TD, and RB provided oversight for all statistical analyses. All authors made substantial contributions to critical review, editing, and revision of the manuscript, and all authors approved the final version.

Declaration of interests

GCa reports grants from Reckitt Benckiser outside the submitted work. WDH reports grants from Australian Therapeutic Goods Administration and personal fees as a Member of the Australian Advisory Council on Medical Uses of Cannabis, both outside the submitted work. AP reports grants from Mundipharma and an untied educational grant from Sequirus for studies of tapentadol, both outside the submitted work. NL has received research grant funding from Indivior, Braeburn, and NSW Health, and consultancies or advisory board participation from Indivior and Mundipharma, all outside the submitted work. RB reports grants from Indivior for the development of an opioid-related behaviour scale and a study of opioid substitution therapy uptake among patients with chronic non-cancer pain, all outside the submitted work. BL reports grants from Reckitt Benckiser for studies of the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among patients with chronic non-cancer pain; and Indivior for studies of buprenorphine-naloxone and buprenorphine depot; an untied educational grant from Seqirus for studies of tapentadol; and grants from Mundipharma, all outside the submitted work. SN reports grants from the National Drug and Alcohol Research Centre during the conduct of the study, and grants from Indivior outside the submitted work. MC reports personal fees from Mundipharma outside the submitted work. RPM reports National Health and Medical Research Council project grants during the conduct of the study. MF received investigator-initiated untied educational grants from Indivior for studies of buprenorphine depot and naloxone; and an untied educational grant from Seqirus for studies of tapentadol, all outside the submitted work. LD received grants from Indivior for studies of buprenorphine-naloxone, buprenorphine depot, and naloxone; and from Reckitt Benckiser for the development of an opioid-related behaviour scale, and a study of opioid substitution therapy uptake among patients with chronic non-cancer pain; an untied educational grant from Seqirus for studies of tapentadol; and a grant from the Australian Therapeutic Goods Administration, all outside the submitted work. GCh, FB, MS, and TD declare no competing interests.

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References

1 Chou R, Turner JA, Devine EB, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015; **162:** 276–86.

2 Krebs EE, Gravely A, Nugent S, et al. Effect of opioid *vs* nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain: the space randomized clinical trial. *JAMA* 2018; **319:** 872–82.

3 Fischer B, Argento E. Prescription opioid related misuse, harms, diversion and interventions in Canada: a review. *Pain Physician* 2012; **15** (3 suppl): ES191–203.

4 Fischer B, Rehm J. Revisiting the 'paradigm shift' in opioid use: developments and implications 10 years later. *Drug Alcohol Rev* 2017; **37:** S199–202.

5 Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. *Ann Intern Med* 2017; **167:** 319–31.

6 Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015; **313:** 2456–73.

7 Stockings E, Campbell G, Hall W, et al. Cannabis and cannabinoids for the treatment of people with chronic non-cancer pain conditions: a systematic review and meta-analysis of controlled and observational studies. *Pain* 2018; published online May 25. DOI:10.1097/j.pain.0000000000001293.

8 National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press, 2017.

9 Walsh Z, Callaway R, Belle-Isle L, et al. Cannabis for therapeutic purposes: patient characteristics, access, and reasons for use. *Int J Drug Policy* 2013; **24:** 511–16.

10 Hazekamp A, Heerdink ER. The prevalence and incidence of medicinal cannabis on prescription in the Netherlands. *Eur J Clin Pharmacol* 2013; **69:** 1575–80.

11 Nielsen S, Sabioni P, Trigo JM, et al. Opioid-sparing effect of cannabinoids: a systematic review and meta-analysis. *Neuropsychopharmacology* 2017; **42:** 1752–65.

12 Campbell G, Nielsen S, Bruno R, et al. The Pain and Opioids IN Treatment study: characteristics of a cohort using opioids to manage chronic non-cancer pain. *Pain* 2015; **156:** 231–42.

13 Australian Government Department of Health Therapeutics Goods Administration. Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia. Version 1, December, 2017. Canberra: Commonwealth of Australia, 2017.

14 Haroutounian S, Ratz Y, Ginosar Y, et al. The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. *Clin J Pain* 2016; **32:** 1036–43.

15 Hoggart B, Ratcliffe S, Ehler E, et al. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. *J Neurol* 2015; **262:** 27–40.

16 Ware MA, Wang T, Shapiro S, Collet JP. Cannabis for the management of pain: assessment of safety study (COMPASS). *J Pain* 2015; **16:** 1233–42.

17 Campbell G, Mattick R, Bruno R, et al. Cohort protocol paper: the Pain and Opioids In Treatment (POINT) study. *BMC Pharmacol Toxicol* 2014; **15:** 17.

18 Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2005; **113:** 9–19.

19 Turk DC, Dworkin RH, Allen RR, et al. Core outcome domains for chronic pain clinical trials: IMMPACT recommendations. *Pain* 2003; **106:** 337–45.

20 Cleeland CS. The Brief Pain Inventory (BPI). 1991. https://www.mdanderson.org/research/departments-labs-institutes/departments-divisions/symptom-research/symptom-assessment-tools/brief-pain-inventory.html (accessed June 19, 2018).

21 Nicholas MK. The pain self-efficacy questionnaire: taking pain into account. *Eur J Pain* 2007; **11:** 153–63.

22 Nielsen S, Degenhardt L, Hoban B, Gisev N. A synthesis of oral morphine equivalents (OME) for opioid utilisation studies. *Pharmacoepidemiol Drug Saf* 2016; **25:** 733–37.

23 Kroenke K, Spitzer R, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16:** 606–13.

24 Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166:** 1092–97.

25 WHO. Composite International Diagnostic Interview, version 3.0. Geneva: World Health Organization, 2001.

26 Degenhardt L, Lintzeris N, Campbell G, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. *Drug Alcohol Depend* 2015; **147:** 144–50.

27 Australian Government Australian Institute of Health and Welfare. National Drug Strategy Household Survey 2016. Detailed findings. Canberra: Australian Institute of Health and Welfare, 2017.

28 Troutt WD, DiDonato MD. Medical cannabis in Arizona: patient characteristics, perceptions, and impressions of medical cannabis legalization. *J Psychoactive Drugs* 2015; **47:** 259–66.

29 Swift W, Gates P, Dillon P. Survey of Australians using cannabis for medical purposes. *Harm Reduct J* 2005; **2:** 18.

30 Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: results of a prospective survey. *Pain* 2003; **102:** 211–16.

31 Wilson M, Gogulski HY, Cuttler C, et al. Cannabis use moderates the relationship between pain and negative affect in adults with opioid use disorder. *Addict Behav* 2018; **77:** 225–31.

32 Corroon JM Jr, Mischley LK, Sexton M. Cannabis as a substitute for prescription drugs—a cross-sectional study. *J Pain Res* 2017; **10:** 989–98.

33 Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. *Cannabis Cannabinoid Res* 2017; **2:** 160–66.

34 Darke S. Self-report among injecting drug users: a review. *Drug Alcohol Depend* 1998; **51:** 10.

35 Lance CE, Vandenberg RJ. Statistical and methodological myths and urban legends: doctrine, verity and fable in the organizational and social sciences. New York: Taylor & Francis Group, 2009.

36 Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. *Eur J Intern Med* 2018; **49:** 44–50.

37 Boehnke KF, Litinas E, Clauw 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.

38 Norberg MM, Mackenzie J, Copeland J. Quantifying cannabis use with the timeline followback approach: a psychometric evaluation. *Drug Alcohol Depend* 2012; **121:** 247–52.

39 van der Pol P, Liebregts N, de Graaf R, Korf DJ, van den Brink W, van Laar M. Validation of self-reported cannabis dose and potency: an ecological study. *Addiction* 2013; **108:** 1801–18.