Experience of adjunctive cannabis use for chronic non-cancer pain: Findings from the Pain and Opioids IN Treatment (POINT) study

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1. Introduction

Chronic non-cancer pain (CNCP) is a common disorder that makes a major contribution to disease burden. The recent Global Burden of Disease 2010 study estimated that in 2010, low back pain, neck pain and migraines were the 1st, 4th and 8th largest contributors respectively to global non-fatal health burden (years lived with disability; Vos et al., 2012). CNCP also affects other domains, and can have a major adverse impact on social and financial well-being, as well as health care costs (Beubler et al., 2006). With the ageing of the population in many high income countries, the burden of chronic pain is likely to increase in the future.

Management of CNCP has been considered best through effective physical and psychological programmes, aided by non-opioid pharmacotherapy (Savage, 1999). Even when a combination of interventions is used, many people continue to experience pain that impairs daily functioning. Short-term controlled trials have evaluated pharmaceutical opioids in the treatment of a range of CNCP conditions and have demonstrated modest attenuation of pain (Bloodworth, 2005); one systematic review concluded that there is only weak evidence of long-term analgesic benefit (as defined by improved physical function and quality of life) (Noble et al., 2010).

There has been considerable debate about the role and efficacy of cannabinoids for medicinal use in a range of CNCP conditions (Bostwick, 2014; Farrell et al., 2014; Robson, 2014). A recent review concluded that there is poor quality evidence of cannabinoid analgesic efficacy from controlled trials of neuropathic pain associated with multiple sclerosis, spinal cord injury or HIV neuropathy (Farrell et al., 2014). Despite the limited data, there is strong advocacy by users for the symptomatic benefit of adjunctive cannabis, and increasing general interest in its use. Although in most jurisdictions, doctors cannot prescribe cannabis despite requests from patients to do so, in countries where cannabis use may be legally obtained via either prescription or authorised by a medical practitioner, chronic pain is the most common indication for use [e.g., the Netherlands (Hazekamp and Heerdink, 2013) and Canada (Ware et al., 2003)]. Although increasing numbers of US States are allowing the
medical use of cannabis, most recently including New York, in many places cannabis remains illegal for any purpose. Many CNCP patients have resorted to obtaining cannabis from the illicit market, risking the consequences of arrest and legal penalties (Lucas, 2009), and exposure to contaminants potentially worsening the medical condition.

To date there have been few reports of patterns of use of cannabis for symptom control in chronic pain, whether initiated for this purpose or adapted for this use by recreational users (Ogborne et al., 2000; Ware et al., 2003). There is also little information about the role of cannabis use as an adjunct to the use of opioids for pain control. Clearly, there is a need for studies of efficacy of cannabis in the management of CNCP, both in its own right and as an adjunct to opioid use. In this paper, we use data from a national, community-based sample of people who have been prescribed opioids for their pain (Campbell et al., 2014b), to examine the extent to which cannabis is in fact used by this group. In Australia, as in many countries, there is no regulatory framework for medicinal cannabis or cannabinoid use, and cannabis possession and use are not legal. We specifically examined:

1. The prevalence of non-medicinal use of cannabis and of cannabis use disorder;
2. The prevalence and correlates of use of cannabis for pain;
3. The association between cannabis use for pain, opioid dose and degree of interference from pain.

2. Methods

The Pain and Opioids IN Treatment (POINT) study includes 1514 people in Australia who have been prescribed opioids for chronic non-cancer pain; full details of the cohort and study design have been reported elsewhere (Campbell et al., 2014a,b). The study was approved by the Human Research Ethics Committee of the University of New South Wales (HREC reference: #HC12149). The study also received A1 Australian National Pharmacy Guild Approval to approach pharmacists to assist with recruitment of participants (Approval no. 815).

POINT participants were 18 years or older; competent in English; and mentally and physically able to complete telephone and self-complete interviews; without serious cognitive impairments; living with chronic non-cancer pain; prescribed a Schedule 8 opioid (an Australian classification that includes morphine, oxycodone, methadone, buprenorphine and fentanyl; Therapeutic Goods Administration, 2013); and had been taking such opioids for CNCP for more than 6 weeks. A history of injecting drug use (IDU) was not an exclusion criterion, but those currently prescribed pharmaceutical opioids as opioid substitution therapy (OST) for heroin dependence were not eligible for inclusion. Persons taking opioids for cancer pain were excluded. A database of pharmacies and chemists across Australia (n = 5745) and their contact details was obtained. Pharmacies were allocated into a wave and successive waves contacted each week via fax to ascertain interest in assisting with study recruitment. Those who indicated they were interested in more information, or who did not respond to the fax were called and the study was explained to a pharmacist.

Ninety-three percent of all pharmacies (n = 5332) were contacted, and 35% agreed to assist with recruitment (Campbell et al., 2014a,b).
Interested pharmacists were enrolled in the study for a six-week period. Pharmacists were asked to approach customers that were prescribed a Schedule 8 opioid for CNCP for a period of greater than 6 weeks. Interested customers were given a flyer about the study by the pharmacist, and either contacted the POINT team directly, or gave their name and phone number to the pharmacist, who sent details to researchers. Pharmacists were reimbursed $20 for each eligible participant they referred into the study (regardless of the person’s entry into the study). POINT staff determined the eligibility of those who were referred to the study, or who contacted the POINT team. Eligible participants who provided informed consent completed a baseline phone interview, which took 1–1.5 h.

2.1. Measures

The domains assessed in the interview were based on recommendations made under the auspices of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT; Dworkin et al., 2005; Turk et al., 2003) to ensure we covered all areas recommended by this expert group. Full details of the specific measures used in the POINT baseline interview are described elsewhere (Campbell et al., 2014b).

Questions on cannabis use for recreational purposes and for pain were included in the interview. Cannabis use disorders (ICD-10 harmful use and dependence) were assessed using the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI) version 3.0 (Kessler and Ustun, 2004).

Pain ratings and participant reports of pain relief were obtained using the Brief Pain Inventory (BPI; Tan et al., 2004). This was assessed as a continuous score out of 10 (with higher scores indicating greater pain severity/interference). The Pain Self Efficacy Questionnaire was also used (Nicholas, 2007; Nicholas et al., 2008); with lower score indicating poorer coping with pain. Participants were also asked if they suffered from incident pain (also termed “breakthrough pain”).

Participants reported whether they were living with a range of chronic pain and physical health conditions. In order to facilitate ascertainment of pain conditions, a glossary of conditions that may lead to chronic pain was developed (see glossaries in Campbell et al. (2014b)). Questions were taken from the Chronic Conditions section of the CIDI 3.0 (Kessler and Ustun, 2004). Lifetime drug and alcohol use disorders (ICD-10 harmful use and dependence) were also assessed via the CIDI 3.0.

Past two week depression and generalised anxiety disorder were measured by the PHQ-9 and GAD-7 modules of the Pfizer Health Questionnaire (Kroenke et al., 2010). Previously validated cut-offs were used for screening tools as follows: symptoms indicating moderate to severe depression were defined as a score of ≥10 on the PHQ-9 (Kroenke et al., 2001), symptoms of moderate to severe anxiety were defined as a score of ≥10 on the GAD-7 (Spitzer et al., 2006).

Participants were asked about current prescribed medications, with examples being given for each class of medications examined. Detailed data on pharmaceutical opioid use was also obtained from a medication diary completed over a one-week period as part of the self-complete questionnaire.
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mailed to participants. Oral morphine equivalent (OME) daily doses (in mg) were estimated following consultation and synthesis of guidelines for conversion ratios from multiple international clinical expert groups (Nielsen et al., 2014).

The Opioid Related Behaviours in Treatment (ORBIT) scale (Larance et al., 2014; Mattick et al., 2012) was designed to assist in the identification of behaviours relating to pharmaceutical opioids that may reflect problems with treatment, including diversion and non-adherence. Those who reported endorsing any of the items in the past 3 months were defined as having engaged in at least some form of nonadherence in that period.

2.2. Statistical analyses

Proportions and 95% confidence intervals (95%CI) were estimated for the cannabis use variables. Odds ratios and their 95%CI from logistic regressions were calculated to compare those using cannabis for pain compared to the rest of the POINT cohort; and among cannabis users, to compare those who used only for recreational purposes, with those using for pain. For linear variables, Mann–Whitney U or t-tests were completed. Multivariable regressions were run to examine independent correlates of cannabis use for pain. All analyses were conducted using STATA version 12.0.

3. Results

One in six of the cohort (16%) had used cannabis for pain relief, and 6% had done so in the previous month. A quarter (24%) reported that they would use it for pain relief if they had access to it (Table 1).

Among those using cannabis for pain, the average pain relief they reported they obtained from using cannabis was 70% (where 100% meant complete pain relief). In contrast, the average reported pain relief they reported receiving from their medications was 50%. Of those who had used cannabis for pain relief, n = 34 felt that cannabis provided 100% pain relief; only four of these reported that their medications gave them 100% pain relief (and among all those using cannabis for pain relief, n = 10 reported 100% pain relief from their medications).

Almost half (43%) of the sample had used cannabis for recreational purposes at some time. One in eight (12%) of the entire cohort had met criteria for an ICD-10 cannabis use disorder in their lifetime (Table 1).

Those using cannabis for pain were younger and more likely to be male than those who did not (Table 2). Those using cannabis for pain were significantly more likely to have met criteria for a range of other licit and illicit substance use disorders and to meet criteria for moderate or severe depression and generalised anxiety (Table 2). People who had used cannabis for pain were more likely to have back or neck problems, less likely to have arthritis, and had been living with pain for a significantly longer period (156 months vs. 120 months) compared with those not using cannabis for pain. Those who had used cannabis for pain reported higher pain severity, greater interference from
and poorer coping with pain, and more days out of role in the past year, compared to those who had not used (Table 2). People who had used cannabis for pain had been prescribed opioids for longer, were on higher opioid doses, were more likely to also have been prescribed benzodiazepines, and were more likely to be non-adherent with their prescribed opioids (Table 2).

We also examined potential differences between those who used cannabis for pain, and those who had also used it only for recreational purposes (Table 3). By and large, the same correlates were found as for the overall comparisons. Those who used cannabis for pain were more likely than those who had only used it recreationally to report greater pain severity, greater pain interference, and poorer coping with pain. They also reported more days out of role in the past year and had higher levels of substance use disorders and mental health problems. However, there were no differences between the two groups in the median prescribed opioid dose, nor in non-adherent use of prescribed opioids.

We additionally examined whether the association between cannabis use for pain, interference from pain, perceived pain relief reported from their medications and daily opioid dose, reflected greater pain severity (Table 4). The use of cannabis for pain remained significantly associated with greater interference from pain after controlling for reported pain severity (adjusted coefficient 0.68; 95%CI 0.43–0.94). The use of cannabis for pain was not associated with self-reported levels of pain relief from opioids or with opioid dose (Table 4).

4. Discussion

There is increasing debate about the use of cannabinoids for medicinal purposes, with jurisdictions in many countries increasingly choosing to decriminalise or legalise cannabis use, or to schedule synthetic cannabinoids for this purpose. In many countries, however, no cannabinoids are legally available for the treatment of any condition, including chronic non-cancer pain.

Despite this, we found a high prevalence of cannabis use in a cohort of community-based people living with CNCP across Australia. In the general population, only 4.7% of those aged over 40 years had used cannabis in the past year (Australian Institute of Health and Welfare, 2011), compared with 13% of our sample, which had a median age of 58 years. In this cohort, which had been prescribed opioids for CNCP, one in six had used cannabis for pain relief, and one in four would do so if they had access to the drug. Among those using cannabis for pain, subjective ratings of the relief achieved from cannabis compared very favourably with the same ratings of pain relief from opioids.

The group using cannabis for pain was significantly younger (median 48 years vs. 59 years), and had a more complex history, including greater reported pain and interference, and a higher likelihood of licit and illicit substance use problems, mental health problems and use of psychiatric medications. They were taking significantly higher doses of opioids and had done so for longer.

The greater degree of pain severity and interference from pain among those using cannabis for pain have a number of possible explanations. Those using cannabis for pain were clearly a group who had greater problems across a number of domains including psychological distress and substance use problems, so the use of cannabis for pain may reflect those characteristics. Alternatively, the adjunctive use of cannabis for pain could reflect attempts to manage distress, given the experience...
of greater interference from pain reported. It is impossible to decide between these possibilities in a cross-sectional study. Data from subsequent follow-ups of this cohort will provide an opportunity to explore whether there is an association between cannabis use for pain and a range of outcomes over time.

Although the literature on cannabis and its impact on pain remains equivocal, findings here suggest that from a service user perspective, there is a significant sub-population of people living with CNCP who see cannabis as a helpful adjunct to pain relief. This parallels the uncertainty about the value of long term opioid medication in chronic pain populations. Although few controlled studies have demonstrated effectiveness of opioids in CNCP, some patients strongly attest to the benefits of opioids for pain relief and are resistant to opioid cessation. This resistance and testimony are likely to be powerful drivers of the continued prescription of opioids by doctors treating patients with CNCP, particularly where other treatment strategies are difficult to access or only have moderate benefit.

Medicine has had to address (and aims to minimise) the potential risks and harms of long term opioid use by chronic pain patients. A similar logic would suggest that doctors should aim to minimise potential harms from persistent cannabis use in a small but significant population of chronic pain sufferers who continue to use cannabis adjunctively for pain relief. Although evidence from controlled clinical trials of cannabinoids for pain is lacking, the experience of individual patients suggests that there may be benefits of cannabinoids for some.

4.1. Strengths and limitations

Some limitations of the study need to be considered. A clear strength of the study is the scope of our recruitment: 93% of Australian community pharmacies were approached, and a third assisted with recruitment; the geographic spread of participants was also similar to the spread of the Australian population (Campbell et al., 2014a).

One issue, however, is the potential that we did not recruit a representative sample of people prescribed opioids for their chronic pain. In order to investigate this possibility, during recruitment we gathered additional data from a random sample of recruiting pharmacies (n = 71) on the characteristics of their opioid customers during the six week recruitment window of their involvement, and on the number of flyers distributed to their customers. Of the total flyers recorded as “distributed” by these pharmacies, 17% resulted in a contact with the study team from a customer. It is difficult to know what proportion of the “distributed” flyers were distributed to potentially eligible customers (and therefore what proportion of the flyers were given to people who would not have contacted us as they would not be eligible) i.e. what proportion of potentially eligible customers decided not to contact us to be involved in the study.

We additionally asked these pharmacists to collect data on the number and characteristics of customers purchasing opioids during the six-week recruitment window when they were recruiting for us. We found that of the total number of customers recorded as purchasing opioids in these pharmacies, 52% were female (the POINT cohort was 55% female); and 7% were 18–34 years, 55% 35–64 years
and 38% 65+ years (vs. 5%, 62% and 33% respectively, in the POINT cohort). Of these customers, 63% were prescribed oxycodone (vs. 62% in the POINT cohort), 16.5% prescribed morphine (vs. 15% in the POINT cohort), 21% prescribed fentanyl patches (vs. 15% in the POINT cohort) and 24% prescribed buprenorphine patches (vs. 21% in the POINT cohort). Although we cannot be sure that all the opioid customers recorded by these pharmacists had been taking these opioids for chronic pain, and for six weeks or more, the striking similarity in these demographic and opioid prescription characteristics is very reassuring.

Another limitation is the potential biases that may be introduced by the reliance on self-report data. However, self-report is generally reliable when there are no disincentives for being honest (Chan, 2009) and particularly enhances the validity of self-reported substance use (Darke, 1998). In this study all participants were assured that their responses would be de-identified and confidential; further, any non-disclosure of cannabis use would serve to make any observed associations more conservative. Information on chronic medical illnesses or other health problems were not verified through patient records. Nonetheless, the rates of pain conditions and findings were similar to those in previous research with people living with chronic pain.

Finally, we did not assess the amount of cannabis consumed, only frequency. Assessing the amount of cannabis consumed is a very challenging task for consumers of the drug. Attempts to quantify the amount of cannabis consumed in a “joint” or a “cone” have suggested that there is substantial variation across consumers in the amount of cannabis consumed in these measures, and additionally that consumers are not very accurate in estimating how much they are consuming in these measures (Norberg et al., 2012). There is increasing recognition, particularly in the US, that with the expansion of medicinal cannabis use for chronic pain, doctors need better understanding of the long-term effects of cannabis use, and of strategies to minimise its harms. This ultimately extends to considering the role of prescription pharmaceutical cannabinoids that can better regulate cannabinoid dose, composition, and routes of administration to avoid smoking (and its related harmful consequences) and also avoid dealing with illicit drug subcultures and markets to secure supply.

In Australia, as in many countries, there is no regulatory framework for medicinal cannabinoid use. This means that cannabis use is effectively marginalised from any discussion or consideration of treatment strategies, despite being used by perhaps one in eight people living with CNCP. Health practitioners need a better understanding the potential harms and benefits of cannabis use among patients they may be treating for CNCP.

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Contributors

LD, MF and WH conceived of the study. LD led the writing of the paper, with NL making a contribution to writing of sections of the first draft. GC undertook the analyses. All authors contributed to the analytic plan, contributed to writing and review of the manuscript. LD is guarantor.

Conflict of interest

LD and NL have received untied educational grants from Reckitt Benckiser for post-marketing surveillance of new OST medications in Australia. LD, NL, RB and MF have received untied educational grants from Mundipharma for post-marketing surveillance of a new oxycodone formulation in Australia. MC has received payments from Mundipharma Pty Limited for preparation and presentation of educational material. Neither had any knowledge of this manuscript.

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