Article

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Medicinal cannabis for Australian patients with chronic refractory pain including arthritis

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Abstract

Objectives: To examine the tolerability and effectiveness of medicinal cannabis prescribed to patients for chronic, refractory pain, with a subset analysis on arthritis.

Methods: This was an interim analysis of the CA Clinics Observational Study investigating self-reported adverse events (AEs) and changes in health-related quality of life (HRQoL) outcomes over time after commencing medicinal cannabis. Patients were prescribed medicinal cannabis by a medical practitioner, containing various ratios of Δ^9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD).

Results: The overall chronic pain cohort, and specifically the balanced CBD:THC products, were associated with significantly reduced pain intensity scores ($p = 0.003$, $p = 0.025$), with 22% of patients reporting a clinically meaningful reduction in pain intensity. Patients in the arthritis subset ($n = 199$) reported significantly reduced pain intensity scores ($p = 0.005$) overall, and specifically for those taking CBD-only ($p = 0.018$) and balanced products ($p = 0.005$). Other HRQoL outcomes, including pain interference and pain impact scores were significantly improved depending on the CBD:THC ratio. Products that contained a balanced ratio of CBD:THC were associated with improvements in the most number of PROMIS-29 domains. Approximately half ($n = 364$; 51%) of the chronic pain cohort experienced at least one AE, the most common being dry mouth (24%), somnolence (19%) or fatigue (12%). These findings were similar in the arthritis subset.

Discussion: Medicinal cannabis was observed to improve pain intensity scores and HRQoL outcomes in patients with chronic, refractory pain, providing real-world insights into medicinal cannabis' therapeutic potential.

Keywords
Medicinal cannabis, cannabidiol, Δ^9-tetrahydrocannabinol, chronic pain, arthritis, observational study

Introduction

Chronic pain is that which persists for longer than three months, either due to an ongoing condition, or from an originating injury that is not resolved within the normal healing time.[1] One common cause of chronic pain is arthritis, where the most prevalent type, osteoarthritis, affects more than 240 million people worldwide.[2] Overall, approximately one in five people experience chronic pain, where they face long lasting physical, psychological, social and financial issues. Chronic pain

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also puts a financial burden onto the wider economy due to factors such as the high cost of disease management and increased absenteeism.[3–5]

An imperative part of managing chronic pain is pharmacological therapy, which comprises analgesics such as paracetamol and non-steroidal anti-inflammatories, opioids and adjuncts, including anxiolytics, muscle relaxants, antiepileptics, antidepressants and disease modifying agents.[6] Despite these treatment options, the long-term safe and effective relief of chronic non-cancer pain remains difficult as the often limited efficacy of analgesics needs to be weighed against their adverse events (AEs).[6] In particular, the AEs of opioid medications, including respiratory depression, tolerance and dependence limit their long-term use.[7] Despite this, opioid use remains problematic, and the current opioid epidemic necessitates the search for better and safer alternatives.[8] There is some emerging evidence of the effectiveness of medicinal cannabis, particularly in the management of chronic pain that is refractory to conventional treatment.[9–11]

Cannabinoids exert their actions both through the endocannabinoid system and other targets, resulting in diverse pharmacological potential not only for pain conditions, but also for other clinical indications. The main components of the endocannabinoid system are the cannabinoid receptor type 1 (CB_1), cannabinoid receptor type 2 (CB_2), and their endogenous ligands anandamide and 2-arachindonoylglycerol.[12] The CB_1 receptors, which are predominantly found on central and peripheral neurons, affect cognition, memory, motor function, analgesia, and can cause psychoactive effects.[13] The CB_2 receptors are mainly found on immune cells both within and outside the brain, where they modulate immune cell migration and cytokine release, thus having an integral role in chronic, inflammatory pain mechanistic pathways.[11,13,14] Well-known for producing the 'high' effect, Δ^9-tetrahydrocannabinol (THC) is an agonist of both CB_1 and CB_2 where it is believed to exert its antinociception action against both acute and chronic pain.[11,15] Cannabidiol (CBD) on the other hand has a low affinity for CB_1 and CB_2 and does not produce intoxicating effects. Evidence is building for CBD in the management of chronic, pathological pain, with little evidence for acute pain.[11,16,17] While the mechanism through which CBD provides antinociception is not completely understood, it is likely to involve reducing levels of circulating pro-inflammatory cytokines.[18,19]

Although legalised in Australia in 2016,[20] most medicinal cannabis products are not yet approved by the Therapeutic Goods Administration (TGA). Therefore, in order to prescribe these unregistered products, medical practitioners must apply for patient-specific approval through the Special Access Scheme (SAS-B). Other pathways through which patients can obtain medicinal cannabis is from an 'Authorised Prescriber'; a medical practitioner who is authorised by the TGA to prescribe certain unregistered medicines for specific conditions, or through participation in clinical trials.[21] With an increase in the range of unregistered medicinal cannabis products currently available in Australia, it is important to have more information on their safety and therapeutic efficacy. Thus, our analysis of the CA Clinics Observational Study (CACOS) data aimed to examine the safety and self-reported effectiveness of various medicinal cannabis products from using patient-reported AEs and health-related quality of life (HRQoL) outcomes for patients with chronic refractory pain, with a subset analysis on our largest pain cohort; arthritis.

Methods

Setting and informed consent

This was an interim analysis of data collected as part of the CACOS, a prospective, open-label, observational study. This was conducted across multiple sites through CA Clinics, an Australian-wide network of clinicians who prescribe medicinal cannabis to patients with diverse health conditions. Prescriptions for these unregistered treatments were either obtained through the SAS-B pathway, or through an Authorised Prescriber, as part of the standard practice at CA Clinics. Using these prescriptions, patients purchased their cannabis product from a local pharmacist where they were provided any relevant information and directions for use. The study was approved by the Bellberry Human Research Ethics Committee (Ref: 2019-04-338). All participants signed the Patient Information and Consent Form prior to any study related activities.

Medicinal cannabis product

Medicinal cannabis included prescribed cannabinoid containing products (CBD-only, mixed, THC-only and other cannabinoid minors). Prescribed products were either oral liquids, capsules, flos, or granulate, and were grouped as CBD-only, CBD-dominant, balanced and THC-dominant. Dominant products were defined as containing at least a two-fold ratio increase in the main cannabinoid, for example, a CBD-dominant product could comprise CBD 10 mg/mL and THC 5 mg/mL. The THC-dominant group includes participants that were prescribed THC-only products due to a small cohort. The dose and frequency of the medicinal cannabis products used by patients was

reported in their surveys and crossed-checked with their clinic records, from which the dose of CBD and/or THC (mg/day) was calculated.

Study population

The study population were patients seeking medicinal cannabis treatment through CA Clinics who were enrolled in CACOS. Thus, participants in this study included those using medicinal cannabis for chronic pain purposes, as well as a subset analysis for patients using medicinal cannabis for arthritis management. Data used in this analysis was collected between December 2018 and May 2020 and stored using Research Electronic Data Capture. Figure 1 details the analysis cohort selection process.

AE reporting

Adverse events were reported via an online AE questionnaire. This was routinely administered to patients during their treatment where they were asked the following question: *'Have you been experiencing any side effects from your medicinal cannabis prescribed by CA Clinics?'*. They were given a pre-selected list of AEs to select from, as well as the option of 'Other' or 'None'. The questionnaire was sent to participants before each clinic visit. The patient-reported AEs were categorised according to MedDRA System Organ Classes (SOC) for analysis.[22]

Patient-reported outcomes measurement information system analysis

The patient-reported outcomes measurement information system (PROMIS)-29 (v2.0) is a validated, generic HRQoL tool that comprises seven domains of patient-reported outcome measures used to evaluate self-reported physical, mental and social health and wellbeing in people with chronic illness.[23,24] It has been used as a primary measure of change in HRQoL.[24]

Patients were included in the analysis if they had completed a minimum of two PROMIS-29 questionnaires during the observational period at the time of cross-sectional sampling. The PROMIS-29 data for patients who had not completed two surveys at the time of analysis were excluded from this analysis.

The observational period for each patient for this analysis was defined as the time between the first and

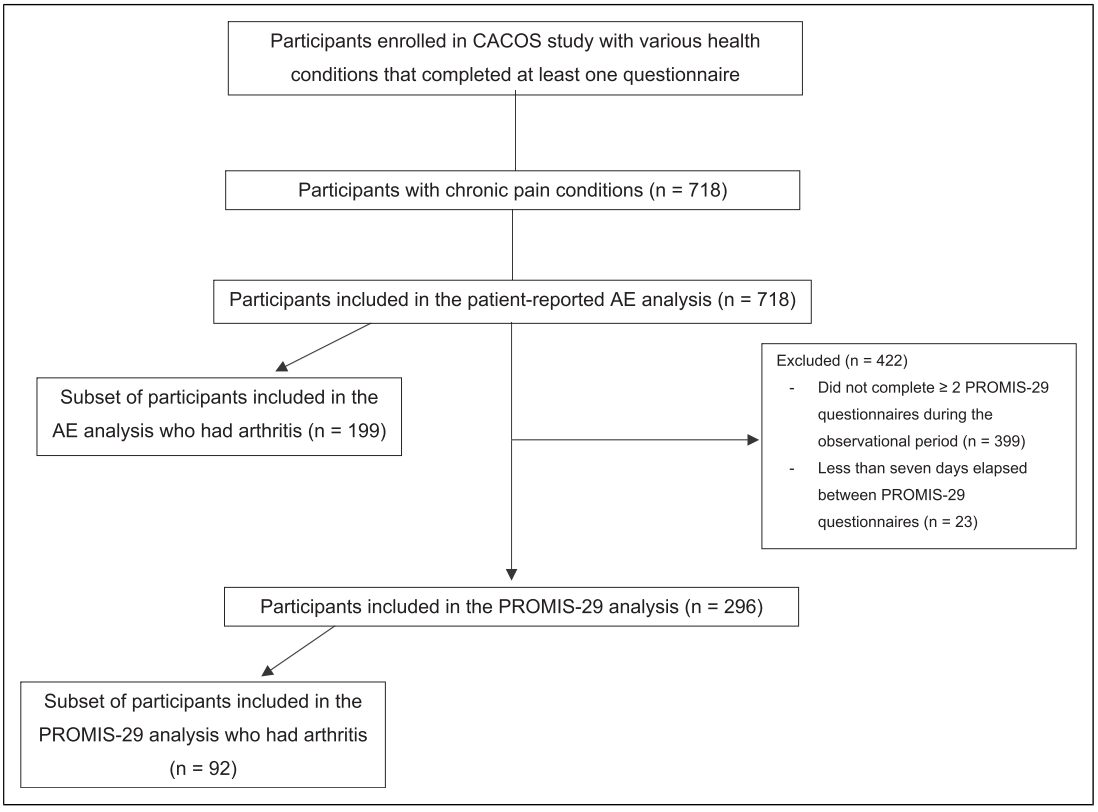

Figure 1. Cohort inclusion flow chart for the adverse events and PROMIS-29 analyses from the CA clinics observational study participants with chronic pain.

last data points collected. The minimum observational period for inclusion in this analysis was defined as 7 days, given that the PROMIS-29 is validated from a 7-day period. Analysis of the PROMIS-29 domains was conducted using T-score reference tables from the PROMIS-29 v2.0 conversion tables, and pain intensity was reported as a numerical scale from 1–10.[24] Pain impact scores were calculated according to the National Institutes of Health Task Force recommendations.[25] Clinically significant changes in PROMIS-29 scores between the patient's first and last surveys were also determined using the published Minimal Clinically Important Difference (MCID), and patients were categorised as either 'improved', 'not changed' or 'worsened'. The MCID used for pain intensity and pain interference was 2.0,[25] physical function was 1.9,[25,26] anxiety was 2.3,[27] depression was 3.0,[27] fatigue was 2.5[28] and pain impact score was 3.0.[25] Sleep disturbance and social functioning had no published MCID, so a default score of 2.0 was used.[26–28]

Statistical Analysis

The data were analysed using SPSS Statistics 1.0.0.1327 (IBM, New York). Data for continuous variables was assessed for normality using the Shapiro–Wilk test and summarised as mean and standard deviation. Where normality was not observed, the median and interquartile range was calculated. Categorical data were described by frequencies and proportions and compared by χ^2 tests. Paired two-tailed t-tests were used for comparison of PROMIS-29 T-score means over the observational period. χ^2 tests were used to compare categorical (medicinal cannabis product and 'improved', 'not changed' or 'worsened' outcomes) variables. One-way ANOVAs were performed to test for differences in the T-score change between medicinal cannabis products within the chronic pain cohort and the arthritis subset. A two-way ANOVA was performed to test for differences in the T-score change between medicinal cannabis products and pain groups.

Results

Participant demographics

There were 718 participants who had a chronic pain condition included in the AE analysis, and of these, 199 patients reported they had an arthritis condition. A total of 296 participants were eligible to be included in the PROMIS-29 analysis, and 92 of these participants had an arthritis condition (Tables 1 and 2). Across each cohort analysed, the most commonly reported chronic pain indications were arthritis, musculoskeletal pain, neuropathic pain and fibromyalgia. Further participant demographics including age, sex, pain indication and the length of the observational period are given in Tables 1 and 2. Participants were prescribed various dosage products of medicinal cannabis, including oral oils and capsules, vapourised flos (whole flowers), and granulate (granulated whole flower). The median (Q1–Q3) reported doses of both THC and CBD in the AE and PROMIS-29 analyses are described in Tables 3–6.

Changes in pain and other HRQoL outcomes

From the PROMIS-29 analyses there were clinically meaningful and statistically significant improvements reported in several HRQoL domains for the chronic pain patients ($n = 296$), and the arthritis subset ($n = 92$) (Tables 3 and 4, Supplemental Tables 1 and 2). The median (Q1–Q3) dose of each cannabis product is listed in Tables 3 and 4. Overall, for the chronic pain cohort, there were significant reductions in pain interference ($p = 0007$), pain intensity ($p = 0.003$) and pain impact scores ($p = 0.02$).

Participants taking a CBD-only product in the overall chronic pain cohort did not report significant improvements in any PROMIS-29 domains; however, in the arthritis subset, there was significantly improved pain intensity ($p = 0.018$), and pain impact scores ($p = 0.023$), with 26% ($n = 15$) and 52% ($n = 30$) of the cohort reporting a clinically meaningful improvement, respectively.

Participants taking a balanced product also saw significant improvements in multiple PROMIS-29 categories. Overall, for the chronic pain participants, those taking a balanced product had significantly improved pain interference ($p = 0.007$), pain intensity ($p = 0.025$) and pain impact scores ($p = 0.023$), corresponding with clinical meaningful improvements in 43% ($n = 49$), 24% ($n = 27$) and 42% ($n = 47$) of participants, respectively. In the arthritis subset, participants reported clinically meaningful and statistically significant improvements in pain interference (46%; $n = 13$; $p = 0.014$), pain intensity (43%; $n = 12$; $p = 0.005$), sleep disturbance (57%; $n = 16$; $p = 0.036$), social functioning (43%; $n = 12$, $p = 0.013$) and pain impact scores (50%; $n = 14$; $p = 0.035$).

Participants taking a CBD-dominant or THC-dominant product did not report any statistically significant improvements in any PROMIS-29 domain in both the chronic pain cohort and arthritis subset. Statistical significance was not reached by any medicinal cannabis product in the remaining PROMIS-29 domains (physical functioning, anxiety, depression and fatigue).

Table 1. Cohort demographic data for participants included in the AE and PROMIS-29 analyses.

Chronic pain			
Demographic		AE analysis (*n* = 718)	PROMIS-29 (*n* = 296)
Age, years, mean (SD.)		53.6 (16.6)	53.7 (15.8)
Sex, *n* (%)	Female	182 (61.5)	182 (61.5)
	Male	114 (38.5)	114 (38.5)
Pain indication, *n* (%)	Arthritis	199 (27.7)	92 (31.1)
	Musculoskeletal pain	186 (25.9)	59 (19.9)
	Neuropathic pain	180 (25.1)	82 (27.7)
	Fibromyalgia	84 (11.7)	35 (11.8)
	Migraine	21 (2.9)	9 (3.0)
	Cancer-related pain	11 (1.5)	2 (0.7)
	Chronic regional pain syndrome	9 (1.3)	5 (1.7)
	Gastrointestinal	8 (1.1)	3 (1.0)
	Trigeminal neuralgia	8 (1.1)	4 (1.4)
	Endometriosis	6 (0.8)	3 (1.0)
	Spasmodic/Spasticity	4 (0.6)	1 (0.3)
	Dysmenorrhea	1 (0.1)	-
	Glaucoma	1 (0.1)	1 (0.3)
Observation period, days, Median (Q1–Q3)[a]		81.2 (42.3–225.6)	91.1 (42.8–231.4)

[a]Period between reporting of AEs by the patient if they returned more than one survey (318 patients only returned one survey), or period elapsed between the first and last PROMIS-29 completion.

Table 2. Arthritis subset demographic data for participants included in the AE and PROMIS-29 analyses.

Arthritis subset			
Demographic		AE analysis (*n* = 199)	PROMIS-29 (*n* = 92)
Age, years, mean (SD.)		59.3 (15.5)	60.0 (13.7)
Sex, *n* (%)	Female	123 (61.8)	63 (68.5)
	Male	76 (38.2)	29 (31.5)
Observation period, days, Median (Q1–Q3)[a]		110.2 (177.7)	113.1 (55.4–232.1)

[a]Period between reporting of AEs by the patient if they returned more than one survey (318 patients only returned one survey), or period elapsed between the first and last PROMIS-29 completion.

There were no differences in the proportion of those categorised as improved, not changed or worsened. In addition, analysis of a two-way ANOVA did not show any significant effect between the change in T-scores of the PROMIS-29 domain, the medicinal cannabis product and the chronic pain group. A one-way ANOVA (including post-hoc Tukey and Bonferroni analysis) did not show statistical significance in the change in T-scores of the various PROMIS-29 domains between medicinal cannabis categories within the overall chronic pain group. However, within the arthritis subset, there were several PROMIS-29 domains that had statistically significant differences between medicinal cannabis products. Participants taking a CBD-only product reported significantly better physical function ($p = 0.005$), social ability ($p = 0.004$) and pain impact ($p = 0.024$) scores than those taking a THC-dominant product. CBD-dominant products were also significantly better than THC-dominant products at improving social ability scores ($p = 0.025$). Lastly, participants taking a balanced product also reported significantly better outcomes than the THC-dominant products in pain interference ($p = 0.017$), physical function ($p = 0.005$), social functioning ($p = 0.002$) and pain impact scores ($p = 0.005$)

Patient-reported AEs

A total of 1232 AEs were reported across all the medicinal cannabis product categories from a total of 718 participants included in the chronic pain cohort (Table 5). At least one AE was reported by 51% of participants ($n = 364$). In the arthritis subgroup, 48% ($n = 96$) of the participants reported at least one AE. The median

Table 3. The PROMIS-29 domains that patients reported statistically significant improvements over the observational period with different medicinal cannabis products, and the cannabinoid dose at the final survey timepoint.

			Chronic pain				
PROMIS-29 domain			All products (*n* = 296)	CBD-only (*n* = 174)	CBD-dominant (*n* = 37)	Balanced (*n* = 113)	THC-dominant (*n* = 37)
Pain interference			✓			✓	
Pain intensity			✓			✓	
Pain impact			✓			✓	
Physical function							
Sleep disturbance							
Anxiety							
Depression							
Social functioning							
Fatigue							
Dose (mg/day), median (Q1–Q3)	Oral	*n*	287	173	36	112	29
		CBD	50 (15–100)	85 (45–125)	20 (11–30.2)	25 (12.5–50)	0 (0–2)
		THC	0 (0–20)	0 (0–0)	7.8 (5.5–16.4)	20 (7.5–30.6)	42 (33–66)
	Inhaled	*n*	9	1	1	1	8
		CBD	0 (0–0)	90 (90–90)	90 (90–90)	16 (16–16)	0 (0–0)
		THC	198 (44–330)	10 (10–10)	10 (10–10)	12.6 (12.6–12.6)	236.5 (55–495)

Table 4. The PROMIS-29 domains that patients with arthritis reported statistically significant improvements over the observational period with different medicinal cannabis products, and the cannabinoid dose at the final survey timepoint.

			Arthritis subset				
PROMIS-29 domain			All products (*n* = 92)	CBD-only (*n* = 58)	CBD-dominant (*n* = 16)	Balanced (*n* = 28)	THC-dominant (*n* = 9)
Pain interference			✓			✓	
Pain intensity			✓	✓		✓	
Pain impact				✓		✓	
Physical function							
Sleep disturbance						✓	
Anxiety							
Depression							
Social functioning						✓	
Fatigue							
Dose (mg/day), median, (Q1–Q3)	Oral	*n*	88	58	16	28	5
		CBD	75 (18.1–110)	100 (60–150)	22.5 (15–35.2)	21.9 (13.8–34.4)	0.8 (0–2.1)
		THC	0 (0–14)	0 (0–0)	6.8 (5.3–12.5)	15 (8–20.5)	42 (15–50)
	Inhaled	*n*	4	0	0	0	4
		CBD	0 (0–0)	—	—	—	0 (0–0)
		THC	495 (302.5–660)	—	—	—	495 (302.5–660)

(Q1–Q3) reported number of AEs over the entire observational period by each participant was 1 (0–2), and in the arthritis subset the median was 0 (0–2).

Across all chronic pain patients, the most common AEs reported for each medicinal cannabis product were dry mouth, somnolence and fatigue (Table 5, Supplemental Table 3). This was the same in the overall arthritis subset, and in participants taking a CBD-dominant or balanced product. Participants with arthritis taking CBD-only commonly reported dry mouth (*n* = 28, 23.7%), fatigue (*n* = 16, 13.6%) and nausea (*n* = 14, 11.9%), whereas those taking a THC-dominant product reported dry mouth (*n* = 11, 29.7%), fatigue (*n* = 5, 13.5%) and somnolence (*n* = 3, 8.1%) (Table 6, Supplemental Table 4). The median (Q1–Q3) dose of CBD and THC of each cannabis product is listed in Tables 5 and 6.

Table 5. The five highest incidence patient-reported adverse events by medicinal cannabis products during the observational period.

Chronic pain: common AEs							
Medicinal cannabis product			All products (n = 718)	CBD-only (n = 369)	CBD-dominant (n = 64)	Balanced (n = 211)	THC-dominant (n = 74)
First most common AE			Dry mouth (n = 297; 24.1%)	Dry mouth (n = 118; 25.1%)	Dry mouth (n = 30; 22.9%)	Dry mouth (n = 95; 20.7%)	Dry mouth (n = 54, 31.6%)
Second most common AE			Somnolence (n = 228; 18.5%)	Somnolence (n = 74; 15.7%)	Somnolence (n = 27; 20.6%)	Somnolence (n = 92; 20%)	Somnolence (n = 35, 20.5%)
Third most common AE			Fatigue (n = 144; 11.7%)	Fatigue (n = 54; 11.5%)	Fatigue (n = 15; 11.5%)	Fatigue (n = 61; 13.3%)	Other (n = 17, 9.9%)
Fourth most common AE			Dizziness (n = 95; 7.7%)	Nausea (n = 42; 8.9%)	Dizziness (n = 12; 9.2%)	Dizziness (n = 39, 8.5%)	Fatigue (n = 14, 8.2%)
Fifth most common AE			Other (n = 89, 7.2%)	Other (n = 42; 8.9%)	Other (n = 11; 8.4%)	Nausea (n = 30, 6.5%)	Anxiety, euphoria and balance problems (n = 7, 4.1%)
Dose (mg/day), median (Q1–Q3)	Oral	n	Oral	n	62	208	59
		CBD	40 (15–100)	CBD	22.5 (10.5–37.8)	20 (12.5–37.5)	0 (0–3)
		THC	0 (0–15)	THC	8.3 (4.6–77.2)	17.5 (10–30)	44 (22–80)
	Inhaled	n	Inhaled	n	2	3	15
		CBD	0 (0–16)	CBD	108 (99–117)	12 (12–98)	0 (0–6)
		THC	99 (44–275)	THC	12 (11–13)	12.6 (9.5–77.2)	198 (65–330)

Table 6. The five highest incidence patient-reported adverse events by medicinal cannabis products during the observational period in the arthritis subset.

Arthritis subset: common AEs							
Medicinal cannabis product			All products (*n* = 199)	CBD-only (*n* = 108)	CBD-dominant (*n* = 20)	Balanced (*n* = 57)	THC-dominant (*n* = 14)
First most common AE			Dry mouth (*n* = 94; 26.9%)	Dry mouth (*n* = 28; 23.7%)	Dry mouth (*n* = 15; 31.3%)	Dry mouth (*n* = 40; 27.4%)	Dry mouth (*n* = 11; 29.7%)
Second most common AE			Somnolence (*n* = 53; 15.2%)	Fatigue (*n* = 16; 13.6%)	Somnolence (*n* = 8; 16.7%)	Somnolence (*n* = 29; 19.9%)	Other (*n* = 7; 18.9%)
Third most common AE			Fatigue (*n* = 40; 11.5%)	Other, nausea (*n* = 14; 11.9%)	Anxiety, fatigue (*n* = 5; 10.4%)	Fatigue (*n* = 14; 9.6%)	Fatigue (*n* = 5; 13.5%)
Fourth most common AE			Nausea, dizziness and other (*n* = 28; 8%)	Somnolence, dizziness (*n* = 13; 11%)	Euphoria (*n* = 4; 8.3%)	Dizziness (*n* = 12; 8.2%)	Somnolence (*n* = 3; 8.1%)
Fifth most common AE			Balance problems (*n* = 19; 5.4%)	Balance problems (*n* = 7; 5.9%)	Depression, nausea and dizziness (*n* = 3; 6.3%)	Nausea (*n* = 11; 7.5%)	Anxiety, confusion, disorientation and balance problems (*n* = 2; 5.4%)
Dose (mg/day), median (Q1–Q3)	Oral	*n*	193	108	20	57	8
		CBD	40 (17.5–100)	100 (40–150)	25 (16.5–37)	18.8 (12.5–30)	1.6 (0.4–2.75)
		THC	0 (0–13)	0 (0–0)	8.6 (6–15.9)	15 (10–21)	46 (17.5–60)
	Inhaled	*n*	6	0	0	0	6
		CBD	0 (0–4.5)	—	—	—	0 (0–6)
		THC	302.5 (149.8–577.5)	—	—	—	302.5 (108–660)

Discussion

This analysis of the existing CACOS participant data provides important insight into the tolerability and effectiveness of pharmaceutical grade medicinal cannabis prescribed by a medical practitioner in Australia for the treatment of chronic pain, including pain caused by arthritis (based on patient-self reports).

Self-reported AEs of medicinal cannabis are consistent with existing studies

Across all the medicinal cannabis categories approximately half (51%) of our analysed cohort experienced at least one self-reported AE during the observation period, the highest incidence being dry mouth, somnolence and fatigue. A systematic review and meta-analysis of cannabinoids for medical use which examined 6462 patients across 79 trials found that 58% of participants reported at least one AE. The most commonly reported in that analysis were dizziness (n = 4243), dry mouth (n = 4181), nausea (n = 3579), fatigue (n = 2717) and somnolence (n = 3168),[29] showing consistency with our findings and adding to real-world insights.

To compare medicinal cannabis to other conventional treatments for chronic pain, a systematic review has shown that for patients taking opioids, 80% of the population experienced at least one AE, with the most common being constipation (41%), nausea (32%) and somnolence (29%).[30] As such, there is merit to the investigation of the comparative efficacy and tolerability of medicinal cannabis to conventional opioid treatment, and whether it could be useful in patients who experience opioid induced AEs, such as severe constipation.

Reduction in pain outcomes are consistent with existing trials of medicinal cannabis

In this analysis, medicinal cannabis, depending on the ratio of CBD to THC, appeared to be associated with significant improvements in pain intensity, pain interference, social functioning and pain impact scores.

Although the CBD-only products did not reach statistical significance in the overall chronic pain cohort, participants with arthritis did report significant improvements in pain intensity and pain impact scores. With arthritis being an inflammatory condition, the anti-inflammatory actions of CBD may be resulting in improved outcomes in these patients.[31] There is preliminary human clinical trial data demonstrating CBD to reduce pro-inflammatory cytokines during a lipopolysaccharide challenge.[32] Additionally, a prospective cohort study examined the use of CBD (mean dose = 30 mg/day) in chronic pain patients found that 54% of patients reduced their opioid use, and 94% of patients reported improved quality of life.[33] Overall, further clinical trial data is needed to show analgesic effects for CBD-only products in chronic pain conditions, and our findings are encouraging for the potential use of CBD in arthritis patients, particularly as it is regarded as well-tolerated and non-intoxicating.[34]

Participants taking a balanced product reported significant changes across the most of the PROMIS-29 domains in both the overall chronic pain group and the arthritis subset. The cannabinoid profile of nabiximols, a pharmaceutical grade oral spray that contains 2.5 mg CBD and 2.7 mg THC per spray,[35] is relatively consistent with the balanced products in this study. Studies examining the use of nabiximols in pain conditions have produced mixed results.[36,37] An open-label study looking at nabiximols as an add-on treatment to pre-existing analgesics in severe chronic pain at a dose of 19.2 mg THC and 17.8 mg CBD per day found that patients experienced significant pain intensity relief.[38] Johnson et al. found that nabiximols (23 mg THC and 22 mg CBD) was effective in reducing intractable cancer-related pain, where 43% of patients had a reduction in pain by ≥ 30%.[39] Other trials for pain associated with conditions such as spinal cord injury and diabetes have produced negative outcomes.[37]

We did not find statistically significant changes in any PROMIS-29 domain reported in participants using THC-dominant or CBD-dominant products. The results need to be interpreted carefully given the small sample sizes included in the analysis (n = 37). A study by van de Donk et al.[40] on patients with fibromyalgia found that their CBD-dominant product (Bedrollite) at a dose of 18 mg CBD and <1 mg THC per day, reduced spontaneous pain scores by at least 30% for approximately 40% of the population; however, overall, this was not statistically significant.[40] Berman et al. reported statistically significant improvements in pain intensity and sleep scores from patients prescribed a THC-dominant product; however, this did not reach their clinically important threshold of a reduction in pain by ≥ 2.[41] Johnson et al. also compared the efficacy of a THC product to nabiximols and found that THC did not produce statistically significant results in reduction of pain intensity, and was found to be similar to placebo.[39] These findings are consistent with our analysis.

The potential superiority of balanced and CBD-only products is further reflected where our statistical analysis revealed that the THC-dominant products were significantly less effective than the CBD-only, CBD-dominant and balanced products in the arthritis

cohort in certain PROMIS-29 HRQoL domains, including pain impact, pain interference, physical function and social functioning scores. This may be due to the inflammatory and immune-related nature of arthritic conditions, for which it is believed that CBD targets.[42,43]

Limitations

The main limitation of this study was that it relied upon data collected from a patient-reported survey-based observational study where potential confounders and patient bias were not able to be controlled for; however, clinical evidence of this kind is an increasingly recognised source of data,[44] particularly in the field of medicinal cannabis where patients are accessing prescribed products prior to conclusive evidence from randomised controlled trials. Other limitations of our analysis are related to the uncontrolled nature of an observational study and the snapshot approach taken to data analysis inclusion. These include unknown prior use of cannabis, varying observational periods, no differentiation between isolate or broad or full spectrum products, and differing dose administration routes and THC/CBD doses. The different drug exposures between inhaled and oral administration may affect AE and effectiveness outcomes. The severity, persistence and incidence of AEs were not tracked over time and instead were reported as a total number, regardless of the number of surveys completed. Effectiveness was only measured between the first and last survey, so an increase or decrease in effectiveness over time was not measured. Considerably varied group sizes and CBD and THC doses between groups were observed which may affect the validity of the results which should be accounted for in future controlled studies. The time of day that patients took their medicinal cannabis, and the subsequent affect this may have on AEs, sleep and other HRQoL outcomes was not considered in this analysis. Lastly, given the exploratory nature of the study, data was not corrected for multiplicity. Despite these limitations, the real-life cohort provides important information which is useful for designing a prospective controlled trial.

Conclusion

Overall, our analysis of the data showed that approximately half of people who took medicinal cannabis for refractory chronic pain and arthritis experienced at least one AE, with the most common being dry mouth, somnolence and fatigue. Differences in HRQoL domains analysed were largely dependent on the CBD and THC ratios in the prescribed product, with the balanced and CBD-only products associated with the highest HRQoL improvements. Most notable are the observed differences in self-reported pain intensity scores which appear to be significantly reduced over time in parallel to the use of medicinal cannabis in both the chronic pain cohort and the arthritis subset. In addition, this analysis provides insights into other HRQoL outcomes that various products of medicinal cannabis may be useful for and warrants further exploration through clinical trials, such as pain interference, pain impact, sleep disturbances and social functioning.

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Ethical approval

Ethical approval for this study was obtained from the Bellberry Human Research Ethics Committee (Ref: 2019-04-338).

Informed consent

Written informed consent was obtained from all subjects before the study.

Trial Registration

N/A (observational study)

Guarantor

NJW.

Contributorship

EAS was responsible for the study conception and design, analyses, interpretation and drafting the manuscript. MTJ was responsible for design, data acquisition, interpretation and revision of manuscript. MB was responsible for study conception and design, data acquisition, interpretation and revision of manuscript. JWA was responsible for design, interpretation of data, and revision of manuscript. NJW was responsible for study conception and design, interpretation of data, and revision of manuscript. All authors have approved the manuscript for publication and agree to be accountable for all aspects of the work.

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Supplemental Material

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References

1. Treede R-D, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain* 2015; 156: 1003–1007. DOI: 10.1097/j.pain.0000000000000160.
2. Katz JN, Arant KR and Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: A review. *JAMA* 2021; 325: 568–578. DOI: 10.1001/jama.2020.22171.
3. Hogg MN, Kavanagh A, Farrell MJ, et al. Waiting in pain II: an updated review of the provision of persistent pain services in Australia. *Pain Med* 2020; 22: 1367–1375. DOI: 10.1093/pm/pnaa374.
4. Blyth FM, March LM, Brnabic AJ, et al. Chronic pain in Australia: a prevalence study. *Pain* 2001; 89: 127–134. DOI: 10.1016/s0304-3959(00)00355-9.
5. Phillips CJ. The cost and burden of chronic pain. *Rev Pain* 2009; 3: 2–5. DOI: 10.1177/204946370900300102.
6. Hylands-White N, Duarte RV and Raphael JH. An overview of treatment approaches for chronic pain management. *Rheumatol Int* 2017; 37: 29–42. DOI: 10.1007/s00296-016-3481-8.
7. 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: 872–882. DOI: 10.1001/jama.2018.0899.
8. Dowell D, Haegerich TM and Chou R. CDC guideline for prescribing ppioids for chronic pain - United States, 2016. *Morb Mortal Wkly Rep* 2016; 65: 1–49. DOI: 10.15585/mmwr.rr6501e1.
9. Johal H, Devji T, Chang Y, et al. Cannabinoids in chronic non-cancer Pain: a systematic review and meta-analysis. *Clin Med Insights Arthritis Musculoskelet Disord* 2020; 13: 117954412090646. DOI: 10.1177/1179544120906461.
10. Aviram J, Pud D, Gershoni T, et al. Medical cannabis treatment for chronic pain: outcomes and prediction of response. *Eur J Pain* 2020: 25: 1532–2149. DOI: 10.1002/ejp.1675.
11. Costa B. Pain. In: Pertwee R (ed) *Handbook of Cannabis*. Oxford: Oxford University Press, 2014.
12. Di Marzo V, Melck D, Bisogno T, et al. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci* 1998; 21: 521–528. DOI: 10.1016/S0166-2236(98)01283-1.
13. Howlett AC, Barth F, Bonner TI, et al. International union of pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* 2002; 54: 161–202. DOI: 10.1124/pr.54.2.161.
14. Cabral GA and Staab A. Effects on the immune system. *Handbook Exp Pharmacol* 2005; 168: 385–423. DOI: 10.1007/3-540-26573-2_13.
15. Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther* 1997; 74: 129–180. DOI: 10.1016/s0163-7258(97)82001-3.
16. DeLong GT, Wolf CE, Poklis A, et al. Pharmacological evaluation of the natural constituent of Cannabis sativa, cannabichromene and its modulation by Δ(9)-tetrahydrocannabinol. *Drug and Alcohol Dependence* 2010; 112: 126–133. DOI: 10.1016/j.drugalcdep.2010.05.019.
17. Izzo AA, Borrelli F, Capasso R, et al. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends Pharmacol Sci* 2009; 30: 515–527. DOI: 10.1016/j.tips.2009.07.006.
18. Mechoulam R, Peters M, Murillo-Rodriguez E, et al. Cannabidiol – recent advances. *Chem Biodivers* 2007; 4: 1678–1692. DOI: 10.1002/cbdv.200790147.
19. Nichols JM and Kaplan BLF. Immune responses regulated by cannabidiol. *Cannabis Cannabinoid Res* 2020; 5: 12–31. DOI: 10.1089/can.2018.0073.
20. Freckelton I. Medicinal cannabis law reform in Australia. *J L Med* 2016; 23: 497–515
21. (TGA) TGA. Access to medicinal cannabis products, 2020, https://www.tga.gov.au/node/769199 (accessed 10 08 2020).
22. Brown EG, Wood L and Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Safety* 1999; 20: 109–117. DOI: 10.2165/00002018-199920020-00002.
23. Hays RD, Spritzer KL, Schalet BD, et al. PROMIS®-29 v2. 0 profile physical and mental health summary scores. *Qual Life Res* 2018; 27: 1885–1891.
24. Rose AJ, Bayliss E, Huang W, et al. Evaluating the PROMIS-29 v2.0 for use among older adults with

multiple chronic conditions. *Qual Life Res Int J Qual Life Aspects Treat Care Rehabil* 2018; 27: 2935–2944. DOI: 10.1007/s11136-018-1958-5.
25. Deyo RA, Ramsey K, Buckley DI, et al. Performance of a patient reported outcomes measurement information system (PROMIS) short form in older adults with chronic musculoskeletal pain. *Pain Med* 2016; 17: 314–324.
26. Hays RD, Spritzer KL, Fries JF, et al. Responsiveness and minimally important difference for the patient-reported outcomes measurement information system (PROMIS) 20-item physical functioning short form in a prospective observational study of rheumatoid arthritis. *Ann Rheum Dis* 2015; 74: 104–107. DOI: 10.1136/annrheumdis-2013-204053.
27. Kroenke K, Yu Z, Wu J, et al. Operating characteristics of PROMIS four-item depression and anxiety scales in primary care patients with chronic pain. *Pain Med* 2014; 15: 1892–1901. DOI: 10.1111/pme.12537.
28. Yost KJ, Eton DT, Garcia SF, et al. Minimally important differences were estimated for six patient-reported outcomes measurement information system-cancer scales in advanced-stage cancer patients. *J Clin Epidemiol* 2011; 64: 507–516. DOI: 10.1016/j.jclinepi.2010.11.018.
29. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015; 313: 2456–2473. DOI: 10.1001/jama.2015.6358.
30. Kalso E, Edwards JE, Moore AR, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain* 2004; 112: 372–380. DOI: 10.1016/j.pain.2004.09.019.
31. Malfait AM, Gallily R, Sumariwalla PF, et al. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA* 2000; 97: 9561–9566. DOI: 10.1073/pnas.160105897.
32. Hobbs JM, Vazquez AR, Remijan ND, et al. Evaluation of pharmacokinetics and acute anti-inflammatory potential of two oral cannabidiol preparations in healthy adults. *Phytother Res* 2020; 34: 1696–1703. DOI: 10.1002/ptr.6651.
33. Capano A, Weaver R and Burkman E. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgrad Med J* 2020; 132: 56–61. DOI: 10.1080/00325481.2019.1685298.
34. Arnold J. A primer on medicinal cannabis safety and potential adverse effects. *Aust J Gen Pract* 2021; 50: 345–350. DOI: 10.31128/AJGP-02-21-5845.
35. Überall MA. A review of scientific evidence for THC:CBD oromucosal spray (Nabiximols) in the management of chronic pain. *J Pain Res* 2020; 13: 399–410. DOI: 10.2147/jpr.S240011.
36. Fisher E, Moore RA, Fogarty AE, et al. Cannabinoids, cannabis, and cannabis-based medicine for pain management: a systematic review of randomised controlled trials. *Pain* 2021; 162: S45–s66. DOI: 10.1097/j.pain.0000000000001929.
37. Henderson L, Kotsirilos V, Cairns E, et al. Medicinal cannabis in the treatment of chronic pain. *Aust J Gen Pract* 2021; 50: 724–732.
38. Ueberall MA, Essner U and Mueller-Schwefe GH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-registry. *J Pain Res* 2019; 12: 1577–1604. DOI: 10.2147/JPR.S192174.
39. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010; 39: 167–179. DOI: 10.1016/j.jpainsymman.2009.06.008.
40. van de Donk T, Niesters M, Kowal MA, et al. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain* 2019; 160: 860–869. DOI: 10.1097/j.pain.0000000000001464.
41. Berman JS, Symonds C and Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004; 112: 299–306. DOI: 10.1016/j.pain.2004.09.013.
42. Sokolove J and Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. *Ther Adv Musculoskelet Dis* 2013; 5: 77–94. DOI: 10.1177/1759720X12467868.
43. Pisetsky DS and Ward MM. Advances in the treatment of inflammatory arthritis. *Best Pract Res Clin Rheumatol* 2012; 26: 251–261. DOI: 10.1016/j.berh.2012.03.001.
44. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med* 2016; 375: 2293–2297. DOI: 10.1056/NEJMsb1609216.