International Journal of Pharmacy Practice, 2023, **31**, 70–79
https://doi.org/10.1093/ijpp/riac073
Advance access publication 29 November 2022
Research Paper

IJPP International Journal of Pharmacy Practice

OXFORD

Medicinal cannabis for patients with chronic non-cancer pain: analysis of safety and concomitant medications

Elise A. Schubert[1], Johannes C. Alffenaar[1,2], Masego T. Johnstone[3], John W. Barlow[4] and Nial J. Wheate[1,*]

[1]School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, NSW, 2006, Australia,
[2]Westmead Hospital, Westmead, NSW, 2145, Australia,
[3]George Clinical, Newtown, NSW, 2042, Australia,
[4]Applied Cannabis Research, Sydney, 2000, Australia

[*]Correspondence: Nial Wheate, School of Pharmacy, Faculty of Medicine and Health, The University of Sydney, NSW, 2006, Australia.
Email: nial.wheate@sydney.edu.au

Abstract

Objectives This study aimed to explore the incidence of adverse events (AEs) reported by patients when initiating medicinal cannabis treatment for chronic pain, and the association of cannabis constituents, dose and concomitant medicines with AE incidence.

Methods Patient demographics, cannabis products and AE data were collected as part of the Cannabis Access Clinics Observational Study, and concomitant medicines were obtained from patient health summaries provided by referring doctors. Cannabis products were grouped by their constituents as either cannabidiol-only or containing both cannabidiol and Δ-9-tetrahydrocannabinol.

Key findings From a total of 275 patients, each had a median of six concomitant medicines, with opioids (n = 179; 65%) the most common. A total of 35.6% patients took 10 or more other medicines, and they were associated with a 3.6 times higher likelihood to report the AE of fatigue (P = 0.048). Patients who received concomitant gabapentinoids were 2.4 times more likely to report dizziness (P = 0.036), patients on tricyclic antidepressants were 1.8 times more likely to report somnolence (P = 0.034) and 3.4 times more likely to report anxiety (P = 0.04), when compared with patients who were not prescribed those classes of medications. Those patients who were prescribed products containing both cannabidiol and Δ-9-tetrahydrocannabinol were 1.5 times more likely (P = 0.004) to have experienced an AE when compared with those prescribed only cannabidiol.

Conclusions These findings show that certain concomitant medications and cannabis constituents may be associated with AE incidence when initiating medicinal cannabis. These potential pharmacokinetic and pharmacodynamic interactions require further study to develop guidance for prescribers and pharmacists.

Keywords: medicinal cannabis; concomitant medicines; drug interactions

Introduction

Chronic non-cancer pain is common and complex and can have physical, financial, social and psychological effects on patients, as well as significant costs to the economy and healthcare systems.[1] Chronic pain originates and extends beyond an initial injury or disease and is recognised as an independent condition of its own accord.[2, 3] The management of chronic pain is multidisciplinary, with many people requiring analgesia; however, the adverse effects can outweigh the benefits, particularly when used long-term.[4, 5] Medicines commonly used include paracetamol, non-steroidal anti-inflammatory drugs, opioids, antidepressants, gabapentinoids and benzodiazepines.[4] Unfortunately, many of these are associated with high-risk adverse events (AEs) including sedation, respiratory depression and dizziness; all of which can be aggravated if multiple medications are used together.[6]

Medicinal cannabis has been proposed as an alternative for the management of chronic pain, and it is currently being prescribed by medical practitioners and investigated in clinical trials.[7, 8] Derived from the *Cannabis sativa* plant, cannabis products contain many different active compounds, including phytocannabinoids, terpenes and flavonoids.[9, 10] The two most well-known constituents of medicinal cannabis are the phytocannabinoids cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), both of which are being examined for their effectiveness in treating pain.[10,11] Cannabis exerts its action both through the endocannabinoid system, and other targets. The endocannabinoid system includes the cannabinoid receptors type 1 (CB_1) and 2 (CB_2), their endogenous ligands called endocannabinoids, and the enzymes that target their synthesis and breakdown.[12] THC is an agonist at both CB_1 and CB_2 where it produces its antinociceptive and intoxicating effects.[13,14] CBD has a low affinity for CB_1 and CB_2 receptors, but may indirectly interact with them by enhancing the levels of endocannabinoids.[15, 16] Overall, CBD is likely to be effective in chronic pain conditions by reducing levels of circulating pro-inflammatory cytokines.[17, 18] Cannabis is generally regarded as well tolerated, with CBD having fewer safety issues when compared with THC.[9] Both have been implicated in pharmacokinetic and pharmacodynamic

Received: 27 January 2022 Accepted: 13 September 2022

interactions; however, the clinical consequences of such are not well established.[19, 20]

There is a possible synergistic effect between cannabis and opioids,[21, 22] and when administered together patients have been shown to reduce their opioid use.[23–25] There have been multiple mechanisms proposed for the synergism[26] including that the antinociceptive effects of the opioids may be enhanced by THC activation of kappa and delta opioid receptors. Synergism could also occur at the intracellular signal transduction level, or by the increased synthesis/release of endogenous opioids by cannabinoids.[26–28] However; the safety of prescribing cannabis with opioids and other analgesics is not well known,[9] or whether there may be any additive incidence of AEs consistent with what is observed with concomitant prescribing of conventional analgesics such as benzodiazepines, opioids and gabapentinoids.[29] The aim of this study was to explore the incidence of AEs reported by patients initiating medicinal cannabis treatment for chronic pain, and if cannabis constituents, dose and concomitant medicines were associated with AE incidence.

Methods

Study design

This analysis was a retrospective, observational, cohort study performed using data collected as part of the Cannabis Access (CA) Clinics Observational Study (CACOS).

Setting

The CACOS was conducted Australia-wide across multiple sites through CA Clinics' network of doctors who prescribe medicinal cannabis to patients with diverse health conditions. In this setting medicinal cannabis was prescribed when conventional treatments were either inappropriate or ineffective. Prescriptions for these unregistered treatments were either obtained through the Special Access Scheme-B pathway, or through an Authorised Prescriber.[30] Surveys (Supplementary Figure S1) were provided to each patient enrolled to collect their reported outcomes before each routine clinic visit. The study was approved by the Bellberry Human Research Ethics Committee (Ref: 2019-04-338). Patient written informed consent was obtained prior to any study related activities.

Participants

Patients were approached, informed, consented and enrolled into CACOS during their initial consultations by a medical practitioner at CA Clinics. Eligible patients for this analysis were those seeking medicinal cannabis treatment through CA Clinics for chronic pain, who had returned more than one survey after their initial consultation. The observational period was from when each patient first commenced to the date they completed the first survey after commencing medicinal cannabis. Data were collected between December 2018 and May 2020 and stored in the Research Electronic Data Capture (REDCap) clinical database.

Variables and data sources/measurement

Medicinal cannabis products

Cannabis products were selected by the prescriber and included all pharmaceutical grade cannabinoid containing products, including CBD, Δ-9-THC, a combination of CBD/THC and other cannabinoid minors.[31] Only oral formulations were included in this analysis. Non-oral formulations (vapourized whole/granulated flower) were excluded due to their differing pharmacokinetics which could not be accounted for when analysing the effect of the dose on outcomes. The dose and frequency of the medicinal cannabis products used by patients was reported in their surveys and validated with clinic records, from which the dose of CBD and/or THC (mg/day) was calculated. All products in this study were derived from the plant and were not synthetic. Ratios of CBD and THC varied in each product and the median doses of each were stated.

Concomitant medication usage

Medications that were concurrently used with cannabis were collated using patient health summaries that were provided by referring medical practitioners at CA Clinics. These medications were deemed by the medical practitioner to be currently prescribed and taken by the patients at the time of referral. Concomitant medications were coded in accordance with the fifth level chemical subgroup of the World Health Organization Anatomical Therapeutic classification system.[32] The 20 most prescribed concomitant medicines were reported. Other concomitant medicines of potential clinical significance were those reported to have CYP450 interactions with cannabis.[33]

AE reporting

AEs were self-reported via surveys provided through REDCap. The questionnaire was sent to patients before their second clinic visit after commencing cannabis treatment. Patients were asked *'Have you been experiencing any side effects from your medicinal cannabis prescribed by CA Clinics?'*. They were given a predefined list of adverse effects to select from and options of 'Other' or 'None'. The severity of the AEs was not surveyed and were therefore not included in this report. The AEs were categorised according to their MedDRA System Organ Class (SOC).

Bias

Eligibility for inclusion into this analysis was predetermined to attempt to minimise selection bias. The risk of recall bias in CACOS design was addressed by providing surveys to patients online periodically during treatment. Multivariate analyses of key AEs were performed to account for all variables and some demographic data to reduce confounding bias.

Study size

The study size was determined by convenience sampling of all eligible patients from the entire CACOS cohort who had returned surveys at the time of analysis in May 2020.

Statistical methods

The data were analysed using SPSS Statistics 1.0.0.1327. Mean and standard deviations were calculated for continuous variables, and frequency as a proportion of the group was calculated for categorical variables. Binary logistic regression was used to determine if the number of concomitant medications could predict AE reporting. Chi-squared and relative risk analyses were used to compare the incidence of AEs at the first survey time point for patients who were on a product containing THC compared to a CBD-only product, and also for patients on concomitant CNS active drugs: opioids, benzodiazepines, gabapentinoids,

tricyclic antidepressants and serotonin-noradrenaline re-uptake inhibitors (SNRIs). A binary logistic regression was performed to determine if the dose of CBD and THC could predict whether or not a patient reported an AE at the MedDRA SOC level. Further sub-analyses on the MedDRA SOC that were significant were conducted to examine if any individual AEs were statistically significant. Where there was statistical significance ($P \leq 0.05$), but if the odds ratios (OR) was close to one, it was classified as not clinically relevant. The five most common adverse effects and any others found to be significant in the univariate analyses were included in multivariate analyses with age, sex and any variables found with a significance level of $P < 0.2$. The priori level of significance in this analysis was $P \leq 0.05$.

Results

Demographics

In total 275 patients were eligible for this analysis from 1597 enrolled in CACOS. Arthritis was the most common indication, followed by general musculoskeletal and neuropathic pain. The average age of patients receiving medicinal cannabis treatment for chronic pain in this cohort was 54 years, and most patients were women (Table 1).

Concomitant medication use

Of the chronic pain cohort, 269/275 (97.8%) patients received at least one other medication, 178 (65.7%) were taking five or more and 98 (35.6%) were taking 10 or more other medications. The median (min–max) number of concomitant medications was 6 (0–33). The 20 most prescribed concomitant medications were opioids, paracetamol and proton pump inhibitors (Table 2). Binary logistic regression showed patients who were taking 10 or more concomitant medicines were associated with a higher number of total AEs ($P = 0.045$; OR = 1.187, CI: 1.004–1.403) when compared with those taking fewer than 10 concomitant medications. Chi-square analysis shows that those who were taking 10 or more other medications were 3.6 times more likely to report fatigue ($P = 0.048$; RR = 3.612, CI: 0.924–14.127) when compared with those who were on fewer medications.

Other medication classes with potential pharmacokinetic interactions of clinical significance observed to be prescribed with medicinal cannabis were statins ($n = 44$), non-vitamin K antagonist oral anticoagulants (NOACs) ($n = 8$), antiplatelets ($n = 23$), warfarin ($n = 4$), anti-infectives including azole antifungals ($n = 11$) and antiretrovirals ($n = 1$).

Association of medicinal cannabis AEs with concomitant central nervous system (CNS) active drugs

Overall, 43.3% ($n = 119$) of patients reported at least one AE when initiating cannabis treatment; the most common being dry mouth ($n = 62$; 23%), somnolence ($n = 49$; 18%) and fatigue ($n = 27$; 9.8%). Those concomitantly prescribed opioids, benzodiazepines and SNRIs had no increased incidence of any AEs (Supplementary Table S1). Patients who were concomitantly prescribed a gabapentinoid were 2.4-times more likely to report dizziness ($P = 0.036$; RR = 2.37, CI: 1.04–5.43), those who were on tricyclic antidepressants were 1.8 times more likely to report somnolence ($P = 0.034$; RR = 1.85, CI: 1.07–3.19), and 3.4 times more likely to report anxiety ($P = 0.04$; RR = 3.41, CI: 1.00–11.59) when compared with patients who were not concomitantly taking these medications (Table 3). Patients also took combinations of CNS active drugs which were associated with an increased incidence of AEs such as somnolence, depression and nausea (Table 4).

A comparison was undertaken of the incidence of AEs in patients who were prescribed a product containing both CBD and THC versus CBD-only.

The median (Q1–Q3) daily doses in the combined products was CBD 15 mg (7.5–22.5 mg) per day and THC 12.5 mg (10–20 mg) per day. The median dose of the CBD-only products was 50 mg (30–100 mg) per day. Patients taking a product containing both CBD and THC ($n = 123$)

Table 1. Cohort demographic data for patients included in this analysis

Demographic		Number of patients ($N = 275$)
Age, years, mean (SD)		54 (16)
Sex, *n* (%)	Women	175 (63.6)
	Men	100 (36.4)
Pain Indication, *n* (%)	Arthritis	85 (31)
	Musculoskeletal pain	54 (20)
	Neuropathic pain	80 (29)
	Fibromyalgia	32 (12)
	Migraine	8 (2.9)
	Cancer-related pain	1 (0.4)
	Chronic regional pain syndrome	4 (1.5)
	Gastrointestinal	3 (1.1)
	Trigeminal neuralgia	4 (1.5)
	Endometriosis	3 (1.1)
	Spasmodic/spasticity	1 (0.4)
Observation period, days, Median (Q1–Q3)*		25 (16.0–41.9)

*Period between when patients returned their first survey, and when they reported to have started medicinal cannabis treatment.

Table 2. The 20 most commonly prescribed concomitant medications in this cohort of chronic pain patients (*N* = 275)

	Concomitant medications	*N* (%)
1	Opioids	179 (65)
2	Paracetamol	110 (40)
3	Proton pump inhibitors	102 (37)
4	Gabapentinoids	99 (36)
5	Benzodiazepines	84 (31)
6	Non-steroidal anti-inflammatories AND corticosteroids	78 (28)
7	Vitamins, minerals and electrolytes	65 (24)
8	Beta$_2$ agonists	55 (20)
9	Serotonin-noradrenaline re-uptake inhibitors	52 (19)
10	Anti-emetics	48 (18)
11	Tricyclic antidepressants	45 (16)
12	Statins	44 (16)
13	Selective serotonin re-uptake inhibitors	42 (15)
14	Inhaled corticosteroids	39 (14)
15	Antibacterials	37 (14)
16	Laxatives	36 (13)
17	Angiotensin II receptor blockers	32 (12)
18	Monoclonal antibodies	29 (11)
19	Beta-blockers	28 (10)
20	Hormone replacement therapy	27 (10)

were 1.5 times more likely to report AEs than those who were prescribed a CBD-only product (*n* = 152) (*P* = 0.004; RR = 1.47, CI: 1.13–1.91). Patients who were on a product containing THC were significantly more likely to report somnolence, confusion, fatigue and balance problems (Table 5).

Dose of CBD, THC and reporting of AEs

The median dose of CBD and THC when a patient reported an AE is shown in Table 6. Higher doses of CBD were statistically associated with fewer patients reporting the MedDRA SOC's psychiatric disorders (*P* = 0.020, OR = 0.99, CI: 0.98–1.00), and general disorders and administration site conditions (*P* = 0.004; OR = 0.97, CI: 0.96–0.99). However; these findings are unlikely to be clinically relevant due to the OR being close to 1 (Table 6).

Multivariate analyses of key AEs

Somnolence was associated with using cannabis containing THC (*P* = 0.033; OR = 0.38, 95% CI: 0.16–0.93), and using tricyclic antidepressants (*P* = 0.039; OR = 2.26, 95% CI: 1.04–4.92). Reporting dizziness was associated with age (*P* = 0.015; OR = 1.04, CI 95% CI: 1.01–1.08); however, clinical relevance is not likely. There were no significant outcomes in multivariate analyses for dry mouth, fatigue and nausea (Supplementary Table S2).

Discussion

The findings show that gabapentinoids and tricyclic antidepressants may be associated with AE incidence when initiating medicinal cannabis. In addition, patients who were prescribed products containing both CBD and THC were more likely to experience an AE when compared with those prescribed only CBD. The dose of CBD and THC prescribed were not associated with a clinically relevant change in AE incidence.

The AE data collected in this study is limited as it is patient reported and subject to recall and confirmation bias and may be confounded by concomitant medicines. Previous recreational cannabis use may affect patients' response to medicinal cannabis; however, this is unable to be accounted for. The survey response rate and characteristics of non-responders could not be determined, which could affect the generalizability of this study. Medication histories obtained from referring medical practitioners may not be comprehensive, excluded dosing information, over the counter medications and does not distinguish between regular and 'when required' regimens. The study was exploratory in nature, multiplicity has not been accounted for, so the risk of erroneously rejecting the null hypothesis (type I error rate) may be increased.[34]

The prescribing of cannabis is increasing, and in many cases, it is used alongside conventional treatments. Regulatory agencies have warned that cannabis may be implicated in pharmacokinetic and pharmacodynamic interactions[35]; however, clinical relevance and clear guidance for prescribers and pharmacists is lacking. Medicinal cannabis prescribed on its own is generally regarded as relatively safe and not associated with fatal overdoses or respiratory depression; unlike opioids.[9, 36]

The results of this study show that polypharmacy was common with 65% (*n* = 178) of patients taking 5 or more concomitant medicines, and 35.1% (*n* = 104) taking 10 or more concomitant medicines all likely to be indicated for various comorbidities such as cardiovascular disease and asthma (Table 2). Ueberall *et al.* found in their open-label study of participants taking nabiximols, that 51.0% (*n* = 408) of patients were taking 10 or more other medications,[37] demonstrating a trend of polypharmacy in chronic pain cohorts seeking cannabis. Although in many instances

Table 3 Comparison of incidence of AEs that occurred before the second clinic visit^ depending if (yes/no) patients are co-prescribed gabapentinoids and tricyclic antidepressants

MedDRA system organ class		Total	Gabapentinoids (n = 99)				Tricyclic antidepressants (n=45)			
		N = 275	Yes (n = 99)	No (n = 176)	P^^	Relative risk (95% confidence interval)^^^	Yes (n = 45)	No (n = 230)	P^^	Relative risk (95% confidence interval)^
Psychiatric disorders n (%)	Somnolence	49 (17.8)	22 (22.2)	27 (15.3)	0.152	1.45 (0.87–2.40)	13 (28.9)	32 (13.9)	0.034*	1.85 (1.07–3.19)
	Anxiety	10 (3.6)	4 (4.0)	6 (3.4)	0.788	1.19 (0.34–4.01)	4 (8.9)	6 (2.6)	0.040*	3.41 (1.00–11.59)
	Confusion	8 (2.9)	4 (4.0)	4 (2.3)	0.402	1.78 (0.46–6.95)	1 (2.2)	7 (3.0)	0.764	0.73 (0.09–5.79)
	Disorientation	5 (1.8)	2 (2.0)	3 (1.7)	0.851	1.19 (0.20–6.97)	1 (2.2)	4 (1.7)	0.824	1.28 (0.15–11.17)
	Depression	6 (2.2)	4 (4.0)	2 (1.1)	0.114	3.55 (0.66–19.07)	2 (4.4)	4 (1.7)	0.256	2.56 (0.48–12.54)
	Paranoia	1 (0.4)	0	1 (0.6)	0.452	—	1 (2.2)	0	0.024*	—
	Euphoria	4 (1.5)	1 (1.0)	3 (1.7)	0.644	0.59 (0.06–5.62)	0	4 (1.7)	0.373	—
	Hallucinations	2 (0.7)	0	2 (1.1)	0.287	—	1 (2.2)	1 (0.4)	0.197	5.11 (0.33–80.22)
Gastrointestinal disorders n (%)	Dry mouth	62 (22.5)	24 (24.2)	38 (21.6)	0.614	1.12 (0.72–1.76)	11 (24.4)	51 (22.2)	0.739	1.10 (0.63–1.95)
	Nausea	20 (7.3)	5 (5.1)	15 (8.5)	0.287	0.59 (0.22–1.58)	3 (6.7)	17 (7.4)	0.864	0.90 (0.28–2.95)
	Diarrhoea	4 (1.5)	2 (2.0)	2 (1.1)	0.557	1.78 (0.25–12.43)	0	4 (1.7)	0.373	—
	Vomiting	1 (0.4)	0	1 (0.6)	0.452	—	0	1 (0.4)	0.658	—
General disorders and administration site conditions n (%)	Fatigue	27 (9.8)	13 (13.1)	14 (8.0)	0.166	1.65 (0.81–3.37)	5 (11.1)	22 (9.6)	0.750	1.16 (0.46–2.91)
	Balance problems	9 (3.3)	5 (5.1)	4 (2.3)	0.214	2.22 (0.61–8.09)	1 (2.2)	8 (3.5)	0.665	0.64 (0.83–4.98)
Nervous system disorders n (%)	Dizziness	21 (7.6)	12 (12.1)	9 (5.1)	0.036*	2.37 (1.04–5.43)	5 (11.1)	16 (7.0)	0.337	1.60 (0.62–4.14)
Other (undefined)* n (%)	Other	19 (6.9)	5 (5.1)	4 (2.3)	0.285	1.60 (0.67–3.81)	3 (6.7)	16 (7.0)	0.944	0.96 (0.29–3.15)
None	None	156 (56.7)	53 (53.5)	103	0.423	0.92 (0.73–1.14)	20 (44.4)	136(59.1)	0.069	0.75 (0.53–1.06)

^Median (Q1–Q3) observational period from commencement of cannabis until second clinic visit is 25 days (16.0–41.9)
^^Statistical significance determined using Chi-square test.
^^^Relative risk not applicable if $n \leq 1$.

Table 4 Comparison of AEs incidences that occurred before the second clinic visit depending on whether patients were co-prescribed combinations of CNS active drugs.

Central nervous system active drug combinations	Adverse events with significant association	*P* value^^	RR (95% confidence interval)^^^
Opioid and benzodiazepine (*n* = 18)	Nil	N/A	—
Opioid and gabapentinoid (*n* = 25)	Nil	N/A	—
Opioid and TCA (*n* = 8)	Somnolence (*n* = 4)	0.016	2.97 (1.41–6.23)
	Disorientation (*n* = 1)	0.022	8.34 (1.05–66.48)
	Paranoia(*n* = 1)	0.001	—
	Hallucination (*n* = 1)	0.001	33.38 (2.29–487.32)
Opioid and SNRI (*n* = 7)	Nausea (*n* = 2)	0.028	4.25 (1.22–14.90)
Benzodiazepine and gabapentinoid (*n* = 3)	Nil	N/A	—
Benzodiazepine and TCA (*n* = 5)	Anxiety (*n* = 1)	0.049	6.00 (0.93–38.81)
	Depression (*n* = 1)	0.006	10.80 (1.53–76.39)
Benzodiazepine and SNRI (*n* = 2)	Nil	N/A	—
Gabapentinoid and TCA (*n* = 4)	Nil	N/A	—
Gabapentinoid and SNRI (*n* = 5)	Somnolence(*n* = 3)	0.013	3.52 (1.64–7.55)
	Depression(*n* = 1)	0.006	10.80 (1.53–76.39)
TCA and SNRI (*n* = 0)	—	N/A	—
Opioid, benzodiazepine and gabapentinoid (*n* = 17)	Confusion (*n* = 2)	0.025	5.06 (1.10–23.20)
	Balance(*n* = 2)	0.042	4.34 (0.97–19.30)
Opioid, benzodiazepine and TCA (*n* = 2)	Anxiety (*n* = 1)	0.001	15.17 (3.29–69.87)
	Nausea (*n* = 1)	0.020	7.18 (1.68–30.69)
Opioid, benzodiazepine and SNRI (*n* = 6)	Nil	N/A	—
Opioid, gabapentinoid and TCA (*n* = 4)	Dry mouth (*n* = 3)	0.011	3.45 (1.87–6.35)
	Dizziness (*n* = 2)	0.001	7.13 (2.44–20.83)
	None (*n* = 0)	0.021	—
Opioid, gabapentinoid and SNRI (*n* = 10)	Nil	N/A	—
Opioid, TCA and SNRI (*n* = 3)	Nil	N/A	—
Benzodiazepine, gabapentinoid and SNRI (*n* = 2)	Nil	N/A	—
Benzodiazepine, gabapentinoid and TCA (*n* = 1)	Somnolence (*n* = 1)	0.031	—
	Anxiety (*n* = 1)	<0.001	—
	Depression (*n* = 1)	<0.001	—
	Dizziness (*n* = 1)	<0.001	—
Gabapentinoid, TCA and SRNI (*n* = 1)	Fatigue (*n* = 1)	0.002	—
	Balance (*n* = 1)	<0.001	—
Opioid, benzodiazepine, gabapentinoid and TCA (*n* = 8)	Nil	N/A	—
Opioid, benzodiazepine, gabapentinoid and SNRI (*n* = 5)	Somnolence (*n* = 3)	0.013	3.52 (1.64–7.55)
Opioid, benzodiazepine, TCA, SNRI (*n* = 2)	Nausea (*n* = 1)	0.020	7.17 (1.68–30.69)
Opioid, gabapentinoid, TCA and SNRI (*n* = 1)	Nil	N/A	—

AE, adverse event; CNS, central nervous system; TCA, tricyclic antidepressant; SNRI, serotonin-noradrenaline re-uptake inhibitor.
^Median (Q1–Q3) observational period from commencement of cannabis until second clinic visit was 25 days (16.0–41.9).
^^Statistical significance determined using Chi-square test and only statistically significant variables are reported.
^^^Relative risk not applicable if $n \leq 1$.

polypharmacy is clinically necessary to treat patients with comorbidities, the increased risk of drug–drug and drug–disease interactions can result in negative outcomes such as: falls, reduced functional capacity and adverse drug reactions.[38] We found that patients who were taking 10 or more concomitant medicines were 3.6 times more likely to report the AE of fatigue, maintaining concerns that concomitant medicines may contribute to AEs when commencing medicinal cannabis.[9, 36]

It is established that the concomitant use of CNS depressants such as opioids, gabapentinoids, antipsychotics, benzodiazepines, tricyclic antidepressants, cannabis and alcohol may result in profound sedation, respiratory depression, coma and death.[29, 39] With cannabis often prescribed as an adjunct to conventional treatment as shown in our study, the additive risk of AEs from pharmacodynamic interactions is an important consideration.[33, 40] Cannabis produces intoxicating effects such as sedation and psychomotor impairment which may potentiate, or be potentiated by, other CNS depressants.[40] Our study showed no increased incidence of AEs with concomitant opioids, benzodiazepines or SNRIs. Opioids were the most common concomitant medication,

Table 5 Comparison of the incidence of AEs depending on whether patients were prescribed either a THC containing product or a CBD-only product.

MedDRA system organ class		Cannabinoid product			
		THC containing (n = 123)	CBD-only (n = 152)	P^	Relative risk (95% confidence interval)
Dose, mg, median (Q1–Q3)	**CBD**	15 (7.5–22.5)	50 (30–100)	—	—
	THC	12.5 (10–20)	0	—	—
Psychiatric disorders n (%)	Somnolence	32 (26.0)	17 (11.2)	0.001*	2.33 (1.36–3.98)
	Anxiety	5 (4.1)	5 (3.3)	0.733	1.24 (0.37–4.17)
	Confusion	7 (5.7)	1 (0.7)	0.01*	8.65 (1.08–69.36)
	Disorientation	4 (3.3)	1 (0.7)	0.109	4.94 (0.56–43.66)
	Depression	2 (1.6)	4 (2.6)	0.570	0.62 (0.12–3.32)
	Paranoia	1 (0.8)	0	0.265	—
	Euphoria	3 (2.4)	1 (0.7)	0.220	3.71 (0.39–35.20)
	Hallucinations	2 (1.6)	0	0.115	
Gastrointestinal disorders n (%)	Dry mouth	34 (27.6)	28 (18.4)	0.069	1.50 (9.66–2.33)
	Nausea	9 (7.3)	11 (7.2)	0.980	1.01 (0.43–2.36)
	Diarrhoea	3 (2.4)	1 (0.7)	0.220	3.71 (0.39–35.20)
	Vomiting	0	1 (0.7)	0.367	—
General disorders and administration site conditions n (%)	Fatigue	19 (15.4)	8 (5.3)	0.005*	2.94 (1.33–6.47)
	Balance problems	8 (6.5)	1 (0.7)	0.007*	9.89 (1.25–77.97)
Nervous system disorders n (%)	Dizziness	12 (9.7)	9 (5.9)	0.234	1.65 (0.72–3.78)
Other (undefined)* n (%)	Other	9 (7.3)	10 (6.6)	0.810	1.11 (0.47–2.65)
Total AE reporters		65 (52.8)	54 (35.2)	0.004*	1.47 (1.13–1.91)

AE, Adverse event; THC, tetrahydrocannabinol; CBD, cannabidiol.
^Statistical significance determined using Chi-square test.

Table 6 Summary of logistic regression analyses for whether CBD and THC dose predict whether or not an AE is reported

MedDRA system organ class		*n* (%)	CBD (*N* = 152)			THC (*N* = 123)		
			Dose median (IQR)	OR (95 % confidence interval)	*P* ^	Dose median (IQR)	OR (95 % confidence interval)	*P*
Psychiatric disorders	Yes	60 (21.8)	21 (9–50)	0.99 (0.98–1.00)	0.020*	7 (0–15)	1.00 (0.99–1.01)	0.889
	No	215 (78.2)	30 (15–60)			0 (0–10)		
Somnolence	Yes	49 (17.8)	20 (9–50)	0.99 (0.98–1.00)	0.032*	8 (0–15)	1.00 (0.99–1.01)	0.909
	No	226 (82.2)	30 (15–60)			0 (0–10)		
Gastrointestinal disorders	Yes	74 (26.9)	25 (10–60)	1.00 (0.99–1.00)	0.466	4 (0–12)	1.01 (1.00–1.02)	0.219
	No	201 (73.1)	28 (15–60)			0 (0–10)		
General disorders and administration site conditions	Yes	32 (11.6)	16 (10–26)	0.97 (0.96–0.99)	0.004*	10 (1–15)	1.00 (0.99–1.01)	0.919
	No	243 (88.4)	30 (15–60)			0 (0–10)		
Fatigue	Yes	27 (9.8)	19 (10–28)	0.98 (0.96–1.00)	0.013*	8 (0–15)	1.00 (0.98–1.01)	0.659
	No	248 (90.2)	30 (15–60)			0 (0–10)		
Balance	Yes	9 (3.3)	13 (10–15)	0.94 (0.88–1.00)	0.038*	10 (10–12)	1.00 (0.98–1.02)	0.938
	No	266 (96.7)	28 (15–60)			0 (0–11)		
Nervous system disorders	Yes	21 (7.6)	19 (8–50)	0.99 (1.00–1.01)	0.764	5 (0 –10)	1.00 (0.98–1.02)	0.787
	No	254 (92.4)	28 (14–60)			0 (0–11)		
Other (undefined)	Yes	19 (6.9)	25 (8–60)	1.00 (0.99–1.01)	0.869	0 (0–13)	1.01 (0.99–1.02)	0.359
	No	256 (93.1)	26 (13–60)			0 (0–11)		
None	Yes	156 (56.7)	30 (18–75)	1.00 (1.00–1.01)	0.130	0 (0–10)	0.99 (0.98–1.00)	0.092
	No	119 (43.3)	25 (10–58)			4 (0–13)		

^Statistical significance determined using binary logistic regression.

and as they appear to have no association with increased AE incidence with cannabis, this is an encouraging finding for patients who often have these prescribed simultaneously. On the other hand, patients prescribed a gabapentinoid reported an increased incidence of dizziness, and tricyclic antidepressants were associated with an increased incidence of somnolence and anxiety. These findings may be demonstrating a potentiation of AEs by the initiation of cannabis, as dizziness is listed as a common AE of gabapentinoids,[41, 42] and sedation and anxiety are reported with tricyclic antidepressants.[43]

Patients taking a product containing both CBD and THC were 1.5 times more likely to report an AE when compared to those taking CBD-only, and we found that somnolence, confusion, fatigue and balance problems were significantly more likely in the CBD and THC group. These findings highlight the possibility for high-risk AEs when THC is commenced, and reinforces the need for slow titration.[9] Cannabis exerts psychoactive and intoxicating effects through activation of the CB_1 receptors by THC in the CNS.[13] An intoxicating dose of THC has been reported to be 10–20 mg,[9] and the median (IQR) dose of THC reported in our study was 12.5 mg (10–20 mg) per day. This is potentially high enough to be intoxicating to some patients, likely contributing to the higher incidence of AEs in those taking a product containing THC. CBD's lower affinity for the CB_1 receptors means it is less likely to produce intoxicating effects, as seen in our findings.[44] This demonstrates the lower risk of CBD-only products.

The use of concomitant analgesics and medications prone to pharmacokinetic and pharmacodynamic interactions alongside medicinal cannabis demonstrated in this study raise safety concerns. Both CBD and THC affect the metabolism of other medications through induction and inhibition of CYP450 enzymes and drug transporters such as P-glycoprotein.[19, 20] Both *in vitro* and human pharmacokinetic studies suggest that CBD is a potent inhibitor of CYP2C19 and CYP3A4, and case studies have reported increased exposure of tacrolimus, methadone and warfarin with CBD use.[9, 45–49] THC is less associated with drug interactions compared with CBD; however, it is still metabolised by, and can inhibit, CYP450 enzymes.[50, 51] There were many concomitant medications reported in our cohort that could theoretically have their drug serum concentrations increased as a result of these interactions. These include high risk medications such as anticoagulants, opioids and benzodiazepines which could lead to a greater risk of AEs such as sedation, falls and bleeding. With emerging clinically important drug–drug interactions, particularly involving CBD,[52] and polypharmacy in a majority of our chronic pain cohort, clinical pharmacokinetic studies are needed to guide prescribers on important drug–drug interactions.

Future directions

Controlled, confirmatory studies are needed to establish the consequences of prescribing medicinal cannabis with concomitant medicines to inform clear guidelines for prescribers. Additionally, the potential for medicinal cannabis to reduce the requirement of conventional analgesics should be studied with accurate medication histories with dosing information taken prior to, and during, medicinal cannabis treatment.

Conclusion

Polypharmacy is common for a majority of chronic pain patients who have sought medicinal cannabis treatment, and our findings suggest that the incidence of AEs such as dizziness, fatigue and somnolence may be associated with concomitant medicines, particularly gabapentinoids and tricyclic antidepressants. Future research is needed to better understand the impact of pharmacokinetic and pharmacodynamic interactions with medicinal cannabis in clinical care to ensure its safe and effective provision and use.

Supplementary Material

Supplementary data are available at *Journal of Pharmacy and Pharmacology* online.

Supplementary Figure S1 Supplementary Figure 1 is a copy of the CA Clinics Observational Study survey provided to participants that were collected and analysed as part of this study. The surveys ask for patient details, medicinal cannabis product details, underlying medical conditions and symptoms, adverse events, PROMIS 29 (Version 2.0) and global impression of change.

References

1. Phillips CJ. The cost and burden of chronic pain. *Rev Pain* 2009; 3: 2–5. https://doi.org/10.1177/204946370900300102
2. Merskey HaB N. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. *Pain Suppl* 1986; 3: S1–226.
3. Raffaeli W, Tenti M, Corraro A et al. Chronic pain: what does it mean? A review on the use of the term chronic pain in clinical practice. *J Pain Res* 2021; 14: 827–35. https://doi.org/10.2147/JPR.S303186
4. Hylands-White N, Duarte RV, Raphael JH. An overview of treatment approaches for chronic pain management. *Rheumatol Int* 2017; 37: 29–42. https://doi.org/10.1007/s00296-016-3481-8
5. Lembke A, Humphreys K, Newmark J. Weighing the risks and benefits of chronic opioid therapy. *Am Fam Physician* 2016; 93: 982–90.
6. 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. https://doi.org/10.1001/jama.2018.0899
7. Arnold JC, Nation T, McGregor IS. Prescribing medicinal cannabis. *Aust Prescr* 2020; 43: 152–9. https://doi.org/10.18773/austprescr.2020.052
8. Pertwee RG. Cannabis and cannabinoids: pharmacology and rationale for clinical use. *Pharmacol Commun* 1999; 3: 539–45.
9. Arnold JA. primer on medicinal cannabis safety and potential adverse effects. *Aust J Gen Pract* 2021; 50: 345–50.
10. Pertwee R. *Handbook of Cannabis*. Oxford, UK: Oxford Academic Press; 2014.
11. Vučković S, Srebro D, Vujović KS et al. Cannabinoids and pain: new insights from old molecules. *Front Pharmacol* 2018; 9: 1259.
12. Di Marzo V, Melck D, Bisogno T et al. Endocannabinoids: endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends Neurosci* 1998; 21: 521–8.
13. Pertwee RG. Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacol Ther* 1997; 74: 129–80.
14. Costa B. Pain. In: Pertwee R (ed.). *Handbook of Cannabis*. Oxford, UK: Oxford Academic Press; 2014.
15. Smita K, Sushil Kumar V, Premendran JS. Anandamide: an update. *Fundam Clin Pharmacol* 2007; 21: 1–8.
16. Elmes MW, Kaczocha M, Berger WT et al. Fatty acid-binding proteins (FABPs) are intracellular carriers for Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). *J Biol Chem* 2015; 290: 8711–21.
17. Nichols JM, Kaplan BLF. Immune responses regulated by cannabidiol. *Cannabis Cannabinoid Res* 2020; 5: 12–31.

18. Mechoulam R, Peters M, Murillo-Rodriguez E et al. Cannabidiol – recent advances. *Chem Biodivers* 2007; 4: 1678–92.
19. Rong C, Carmona NE, Lee YL et al. Drug-drug interactions as a result of co-administering Δ9-THC and CBD with other psychotropic agents. *Expert Opin Drug Saf* 2018; 17: 51–4.
20. Morrison G, Crockett J, Blakey G et al. A phase 1, open-label, pharmacokinetic trial to investigate possible drug-drug interactions between clobazam, stiripentol, or valproate and cannabidiol in healthy subjects. *Clin Pharmacol Drug Dev* 2019; 8: 1009–31.
21. Desroches J, Beaulieu P. Opioids and cannabinoids interactions: involvement in pain management. *Curr Drug Targets* 2010; 11: 462–73.
22. The Therapeutic Goods Administration. *Guidance for the Use of Medicinal Cannabis in the Treatment of Chronic Non-cancer Pain in Australia* 2017. https://www.tga.gov.au/sites/default/files/guidance-use-medicinal-cannabis-treatment-chronic-non-cancer-pain-australia.pdf (26 January 2022, date last accessed).
23. Bulbul A, Mino EA, Khorsand-Sahbaie M, Lentkowski L. Opioid dose reduction and pain control with medical cannabis. *J Clin Oncol* 2018;36:189.
24. Sohler NL, Starrels JL, Khalid L et al. Cannabis use is associated with lower odds of prescription opioid analgesic use among HIV-infected individuals with chronic pain. *Subst Use Misuse* 2018; 53: 1602–7.
25. Capano A, Weaver R, 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.
26. Abrams DI, Guzman M. Cannabis in cancer care. *Clin Pharmacol Ther* 2015; 97: 575–86.
27. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. *Life Sci* 2004; 74: 1317–24.
28. Chahl LA. Experimental and clinical pharmacology: opioids - mechanisms of action. *Aust Prescr* 1996; 19: 63–5.
29. Savelloni J, Gunter H, Lee KC et al. Risk of respiratory depression with opioids and concomitant gabapentinoids. *J Pain Res* 2017; 10: 2635–41.
30. Australian Government. *Special Access Scheme: Therapeutic Goods Administration*; 2021 https://www.tga.gov.au/form/special-access-scheme (26 January 2022, date last accessed).
31. Australian Government. *Medicinal Cannabis Products by Active Ingredients: Therapeutic Goods Administration* 2021 https://www.tga.gov.au/medicinal-cannabis-products-active-ingredients (26 January 2022, date last accessed).
32. World Health Organisation. *Anatomical Therapeutic Chemical (ATC) Classification* 2021 https://www.who.int/tools/atc-ddd-toolkit/atc-classification (26 January 2022, date last accessed).
33. Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. *Br J Clin Pharmacol* 2018; 84: 2477–82.
34. Li G, Taljaard M, Van den Heuvel ER et al. An introduction to multiplicity issues in clinical trials: the what, why, when and how. *Int J Epidemiol* 2016; 46: 746–55.
35. Australian Government. *Opioids: Boxed Warning and Class Statements: Therapeutic Goods Administration* 2019 https://www.tga.gov.au/opioids-boxed-warning-and-class-statements (26 January 2022, date last accessed).
36. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med* 2018; 49: 12–9.
37. Ueberall MA, Essner U, 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: 1577–604.
38. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf* 2014; 13: 57–65.
39. Sutherland AM, Nicholls J, Bao J et al. Overlaps in pharmacology for the treatment of chronic pain and mental health disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; 87: 290–7.
40. Arellano AL, Papaseit E, Romaguera A et al. Neuropsychiatric and general interactions of natural and synthetic cannabinoids with drugs of abuse and medicines. *CNS Neurol Disord Drug Targets* 2017; 16: 554–66.
41. Parsons B, Tive L, Huang S. Gabapentin: a pooled analysis of adverse events from three clinical trials in patients with postherpetic neuralgia. *Am J Geriatr Pharmacother* 2004; 2: 157–62.
42. Çağlar Okur S, Vural M, Pekin Doğan Y et al. The effect of pregabalin treatment on balance and gait in patients with chronic low back pain: a retrospective observational study. *J Drug Assess* 2019; 8: 32–5.
43. Australian Medicines Handbook. *Tricyclic Antidepressants*. *Adelaide*: Australian Medicines Handbook Pty Ltd. 2021 https://amhonline.amh.net.au/ (26 January 2022, date last accessed).
44. Maria Grazia Cascio RGP. Known pharmacological actions of nine nonpsychotropic phytocannabinoids. 2014. In: *Handbook of Cannabis* [Internet]. Oxford Scholarship Online: Oxford University Press.
45. Damkier P, Lassen D, Christensen MMH et al. Interaction between warfarin and cannabis. *Basic Clin Pharmacol Toxicol* 2019; 124: 28–31.
46. Leino AD, Emoto C, Fukuda T et al. Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus. *Am J Transplant* 2019; 19: 2944–8.
47. Madden K, Tanco K, Bruera E. Clinically significant drug-drug interaction between methadone and cannabidiol. *Pediatrics*. 2020; 145: e20193256.
48. Jiang R, Yamaori S, Okamoto Y et al. Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19. *Drug Metab Pharmacokinet* 2013; 28: 332–8.
49. Yamaori S, Ebisawa J, Okushima Y et al. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: role of phenolic hydroxyl groups in the resorcinol moiety. *Life Sci* 2011; 88: 730–6.
50. Brown JD. Potential adverse drug events with tetrahydrocannabinol (THC) due to drug-drug interactions. *J Clin Med* 2020; 9: 919.
51. Food and Drug Administration. *SYNDROS (Dronabinol) Oral Solution* 2017 https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205525s003lbl.pdf (26 January 2022, date last accessed).
52. Nasrin S, Watson CJW, Perez-Paramo YX et al. Cannabinoid metabolites as inhibitors of major hepatic CYP450 enzymes, with implications for cannabis-drug interactions. *Drug Metab Dispos* 2021; 49: 1070–80.