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Drug Interactions in People on Cannabidiol: Is There Cause for Concern?

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Abstract

Introduction: Cannabidiol (CBD) exhibits multiple therapeutic properties, but its use in advanced cancer patients raises concerns about potential drug–drug interactions (DDIs) due to polypharmacy. This study aims to look for evidence of DDIs between concomitant medications and CBD oil in a randomized placebo-controlled trial of CBD oil for symptom control (MedCan-1 parent study).

Materials and Methods: Surrogate measures were used to identify possible drug interactions: (1) the maximum mL of oil self-selected by patients in CBD or placebo groups in relation to opioids, specific drug groups, or individual agents; (2) the occurrence of any new or worse adverse effect in relation to the study arm and the concomitant medication classes/medications of interest.

Results: The dose of CBD self-selected by participants was not related to opioid use or medications, including benzodiazepines and antipsychotics. The likelihood of developing an adverse effect while on study or when taking specific medications was not increased by CBD. Participants on paracetamol tolerated a higher dose of CBD.

Discussion: Concerns regarding the development of clinically significant drug interactions when taking CBD in the context of anti-cancer and other concomitant medications at least in the short term may be unfounded.

Keywords: cannabidiol; concomitant medications; drug interactions; medicinal cannabis; palliative care; supportive care

Introduction

Cannabidiol (CBD) is reported to have a range of anxiolytic, antipsychotic, anti-inflammatory, anti-oxidative, anticonvulsant, and neuroprotective effects.[1] Despite limited evidence of efficacy,[2] cannabinoids have been approved in Australia for medical use in a number of conditions, including palliative care.[3]

Patients with advanced cancer are commonly prescribed multiple medications to alleviate symptom burden, along with medications for common diseases in the elderly. Polypharmacy increases the likelihood of drug–drug interactions (DDIs) that may lead to an increased incidence of side effects. It is important to consider this when prescribing medicinal cannabis.

CBD is one of almost 500 bioactive compounds found in cannabis.[4] Cytochrome P450 enzymes (subfamilies 2C, 1A, 3A, and 2D) have a predominant role in CBD hydroxylation. Further, CBD inhibits hepatic drug metabolism by CYP3A4 and CYP3A5, and to a lesser extent, CYP3A7 and CYP2C19.[5,6] The human CYP3A subfamily is involved in the metabolism of more than half of all currently prescribed medications, while CYP2C enzymes metabolize at least 20%,[7] creating potential for a wide array of CBD DDIs. For example, as a potent CYP3AA inhibitor, CBD will potentially increase the levels of ribociclib, a targeted agent used for the treatment of cancer, which may result in an increased risk of ribociclib adverse effects (AEs).[8]

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Other potential sources of DDIs include the effect of CBD on UDP-glucuronosyltransferase (UGT) enzymes and various membrane proteins (e.g., *p*-glycoprotein,[9] breast cancer resistance proteins, and multi-drug resistance proteins).[10] Interactions are also possible when CBD is co-administered with a drug that has shared side effects. For example, high-dose (150–600 mg/day) CBD has a sedative effect,[11,12] that could be amplified when co-administered with opioids or benzodiazepines. Similarly, an increased incidence of nausea and diarrhea is also possible as an additive effect in those patients on chemotherapy.[13]

Potential DDIs with CBD have been described,[14,15] and it is recommended that CBD be prescribed with a "start low and go slow" approach. Most existing clinical interaction data describe alterations in serum levels of anticonvulsant medications upon coadministration with CBD.[16,17] In a study of resistant epilepsy, increases in serum levels of topiramate and rufinamide and a decrease in clobazam occurred when CBD doses were increased.[17]

In a placebo-controlled randomized controlled trial (RCT) designed to determine the effect of CBD on total symptom burden,[18] participants self-titrated CBD/placebo oil over the range 50–600 mg CBD/day according to side-effects and/or perceived benefit. In this sub-study, the possibility of drug interactions was investigated through a detailed analysis of the concomitant medications taken during the study by trial participants.

On the basis that co-administration of other drugs might limit the dose of oil tolerated in the CBD group, the association between the final dose of oil and daily opioid use (oral morphine equivalent [OME]), the final dose of CBD selected by participants, was compared as a surrogate measure of potential drug interactions.

We also hypothesized that the association between the final dose of oil and daily opioid use (OME) would differ between treatment arms and that the number of potentially drug-related new AEs would be greater in the CBD group than in the placebo group.

Methods

The methodology for this paper was modified from the work of Schubert et al.[19]

Study aims

To determine whether:

1. The maximum mL of oil self-selected by patients on CBD or placebo was associated with opioid use.
2. The maximum mL of oil self-selected by patients on CBD or placebo is associated with specific drug groups or individual agents.
3. The occurrence of any new or worse adverse effect is associated with the study arm and the concomitant medication classes or medications of interest.

Study participants

Participants were those recruited from five tertiary medical sites in Queensland to a RCT of CBD vs placebo (MedCan-1, ACTRN 12618001220257). Full details have been published previously.[18] The aim of the parent study was to determine whether CBD oil resulted in better symptom control than palliative care alone. Participants were >18 years old with advanced cancer who had a total symptom distress score (TSDS) as measured by an Edmonton Symptom Assessment Scale (ESAS) of ≥10/90 (with at least one score ≥3). Patients were excluded if they had severe organ dysfunction or co-morbidities that would impede their ability to fulfill all trial requirements.

Approval was provided by Mater Misericordiae Limited Human Research Ethics Committee.

Study procedure

CBD/placebo dose. Participants were assigned to receive synthetic (–) cannabidiol oil 100 mg/mL or matched placebo. Patients self-administered the study medication as per dosing schedule instructions (Table 1). A 2-week titration phase to a maximum of 6 mL/day (equivalent to 600 mg/day CBD for those on the active arm) or that dose that provided symptom relief with tolerable side effects at day 14 (the primary outcome point) was followed by a further 2-week assessment period on the selected dose to 28 days. Doses could be decreased at any stage according to perceived AEs.

Drug groups and individual agents. All participants provided a list of concomitant medications and were advised to continue them all, including opioids, but alteration in drug doses was allowed.

Daily OME doses of all opioids, including breakthrough doses, were calculated according to GP Pain Help.[20]

Other drugs were categorized into groups according to the Australian Medical Handbook.[21] The drug classes chosen as being most likely to interact with

Table 1. Dosing Schedule for CBD or Placebo Oil

Days	CBD (100 mg/mL)	Placebo	mL/dose	mL/day	Cumulative/week
0, 1	50 mg		0.5 mL	0.5 mL	End day 7–10 mL
2, 3	100 mg		1 mL	1 mL	
4, 5	200 mg		1 mL BD	2 mL	
6, 7	300 mg		1 mL TDS	3 mL	
8, 9	400 mg		1 mL	4 mL	Day 14 end—33 mL
			1 mL		
			2 mL		
10, 11	500 mg		2 mL	5 mL	
			1 mL		
			2 mL		
12, 13	600 mg		2 mL TDS	6 mL	W3—42 mL
14–28		Continue final dose if perceived to be of benefit and tolerated			W4—42 mL

CBD, cannabidiol.

cannabinoids were antipsychotics, antidepressants, tricyclic antidepressants (TCAs), benzodiazepines, opioids, corticosteroids, gabapentanoids, and anti-cancer therapies. The individual drugs of interest were those used most commonly by participants.

Adverse effects. AEs worse than baseline, or new, were analyzed in those participants who remained in the study on or after day 7 and documented at days 7, 14, and 28 according to the National Cancer Institute Common Toxicity Criteria (v4.0).[22] AEs of special interest were those reported in the literature at the time and from our pilot study[23]—to be most often associated with CBD (dry mouth, somnolence, dizziness, nausea, vomiting, and abdominal pain). Additionally, all "other" AEs were recorded.

Statistics

Dose of oil (mL) vs drug groups or individual agent analysis. Continuous outcome data [mL of oil, OME (mg/day)] were assessed for normality using graphical and summary methods. For each concomitant drug group or individual agent of interest, the maximum dose of oil at each time point in both arms were compared using the Wilcoxon Rank Sum Test.

Adverse effects subgroup analysis. The sum of the six AEs of special interest was calculated for each participant. The association between the total number of AEs for each participant (0–6) and treatment arm, mL of oil, and drug groups or individual agents was assessed using negative binomial regression to account for time exposure (length of time on study). Results are reported as incidence rate ratios (IRRs).

The occurrence of at least one of the six AEs of special interest, compared with no effect occurring, according to treatment arm and drug group or individual agent of interest was assessed using logistic regression, disregarding the individual participant's time in the study.

The effect of exposure to each drug group or individual agent of interest on the likelihood of a specific adverse effect, adjusted for treatment arm, was assessed using multivariable logistic regression and reported as an odds ratio (OR).

Non-normally distributed data are summarized as median (range) or median (interquartile range [IQR]). Estimates such as IRR and OR are reported with the corresponding 95% confidence interval. Significance was set at $p \leq 0.05$. No adjustment was made for multiple comparisons.

Results

Patient characteristics and flow

As previously reported,[18] of the 142 eligible patients randomized to MedCan-1, 121 (58 on CBD and 63 on placebo), reached the primary analysis point at day 14. Forty-two (CBD) and 44 (placebo) reached day 28.

The mean (standard deviation [SD]) age of all participants was 64.6 (12.8) years, and 75% were male. The most common cancer diagnoses were prostate, breast, colorectal, and gynecological. Participants in both arms were well matched for performance status [median 70/100 (range 30–90)], ability to conduct activities of daily living, baseline cognition, quality of life, and depression ratings.[18]

The symptom burden of all participants at baseline was moderate, with a mean (SD) score of 33.9/90 (13.5). There was a statistical difference in baseline ESAS (TSDS) scores (mean [SD] ESAS score 30.7/90 [13.5] vs 36.4/90 [13.4]) between arms at baseline of doubtful clinical significance (with no difference at any other timepoint).[18]

Attrition throughout the study was similar in both arms.

Concomitant medications

The median number of concomitant medications [regular plus "as required" (prn) medications] per participant in the CBD and placebo groups were 13 (range 4–25) and 14 (range 4–30), $p = 0.12$.

Maximum dose of oil taken

Of the 142 participants who commenced the study (including those who exited before day 14), the median (range, IQR) final volume of trial medication to day 14 was 4.0 (0.5–6.0, 3.0–6.0) mL for CBD and 6.0 (0.5–6.0, 3.0–6.0) mL for placebo ($p = 0.046$). This equates to a median of CBD of 400 mg/day (range [50–600 mg] for those in the active arm.)

When the analysis was restricted to the 121 participants who remained in the study at day 14, the median (range) final volume of trial medication and placebo at day 14 was 6.0 mL (0.5–6) in both arms but with a marked difference in IQR (3.0–6.0 for CBD and 5.0–6.0 for placebo), $p = 0.047$. This equates to a median of CBD of 600 mg/day (range [50–600 mg] for those in the active arm.

Effect of medications on maximum mL of study oil taken

Corticosteroids were the most frequent concomitant medication. The five most frequently used individual medications were paracetamol, metoclopramide, pantoprazole, dexamethasone, and pregabalin (Table 2).

Opioids. At baseline, 103/142 (72.5%) of all participants were taking opioids (71.4% of those on CBD and 73.6% on placebo). Most participants (85%) were on opioids at some time during the study. Eight participants were on methadone (3 CBD and 5 placebo). There was no difference in the number taking oxycodone and non-oxycodone opioids in each arm (Supplementary Table S1).

The OME dose was calculated for all participants at baseline, days 7, 14, 21, and 28.[18] There was no difference in OME dose between arms at any timepoint. This applied to all participants, including those not on opioids (Supplementary Table S1), and when those participants not on opioids were excluded (Table 3).

Medications (Table 4). At day 14, when all 142 participants were considered, those in the placebo arm on dexamethasone and/or opioids excluding oxycodone had a lower maximum dose of oil than those not on dexamethasone or non-oxycodone opioids. In the CBD group, those on paracetamol had a higher maximum dose of oil than those not on paracetamol. For the 121 participants who remained in the study at day 14, there was no statistically significant association between the maximum mL of oil achieved by day 14 and any medication class or medication of interest in either the CBD or placebo groups (Supplementary Table S2).

Association of adverse effects with concomitant medications

At day 7, 134 participants (66 out of 70 CBD and 68 out of 72 placebo) remained in the study and could be evaluated for new or worse AEs.

Table 2. Number (%) of Participants on Medications/Medication Categories of Interest at Some Time During the Study ($n = 142$)

Medication class and medications of interest	CBD $n = 70$ number, %	Placebo $n = 72$ number, %	p-value
Antipsychotics	14 (20.0%)	16 (22.2%)	0.75
Antidepressants	21 (30.0%)	25 (34.7%)	0.55
Tricyclic antidepressants	5 (7.1%)	6 (8.3%)	0.79
Benzodiazepines prescribed[a]	21 (30.0%)	28 (38.9%)	0.26
Chemotherapy	23 (32.9%)	25 (34.7%)	0.81
Immunomodulators	12 (17.1%)	10 (13.9%)	0.59
Hormone therapy	13 (18.6%)	11 (15.3%	0.60
Corticosteroids (including dexamethasone)	39 (55.7%)	45 (62.5%)	0.41
Dexamethasone	26 (37.1%)	38 (52.8%)	0.06
Pregabalin	16 (22.9%)	24 (33.3%)	0.17
Paracetamol	32 (45.7%)	42 (58.3%)	0.13
Metoclopramide	32 (45.7%)	41 (56.9%)	0.18
Pantoprazole	28 (40.0%)	23 (31.9%)	0.32

CBD, cannabidiol.

[a]Many benzodiazepines were prescribed as PRN, so actual exposure is unknown.

Table 3. Median (Range) Dose of Opioids (OME) by Treatment Group at Baseline, Day 14 and Day 28

	CBD	Placebo	All participants	*p*-value for CBD vs placebo
Baseline	80 (1.27–590), *n* = 50	70 (10.0–555), *n* = 53	80 (1.27–590), *n* = 103	0.40
Day 14	110 (5–640), *n* = 40	73 (10–520), *n* = 49	90 (5–640), *n* = 89	0.09
Day 28	120 (4–590), *n* = 29	75 (10 = 520), *n* = 34	80 (4–590), *n* = 63	0.58

All participants excluding those not on opioids at each time point.
CBD, cannabidiol; OME, oral morphine equivalent.

Total number of adverse effects according to treatment group and number of concomitant medications. The total number of new or worse AEs of special interest from baseline to day 28 for individual participants ranged from 0 to 6, with a median (range) of 1 (0–5) and 1 (0–6) in the placebo group (Fig. 1). Adjusted for length of time in the study, there was no difference detected in the total number of AEs between treatment groups (IRR, 95% CI: 1.11 [0.79–1.56]), $p = 0.56$. Adjusted for both treatment arm and time in study, there was no effect on the number of AEs of special interest according to the number of concomitant medications taken (IRR, 95% CI: 0.99 [0.97–1.03]), $p = 0.82$. In this model, treatment arm remained nonsignificant (IRR, 95% CI: 1.10 [0.78–1.56], $p = 0.58$).

Adjusted for time in the study, neither treatment arm, or drug group, or individual agent had a detectable effect on the number of AEs experienced by individual participants, except for those on hormone therapy, who experienced fewer AEs than those not on hormone therapy (Table 5).

Similar results were obtained when the effects of treatment arm and drug group or individual agent, unadjusted for time in the study, on the occurrence of ANY adverse effect of special interest were assessed using logistic regression. The one exception was for those on antidepressants (excluding TCAs), who were less likely to experience any of the AEs of special interest. Of the 44 participants on antidepressants with evaluable AEs, 25/44 (56.8%) of those on antidepressants experienced at least one of the six AEs compared with 71/90 (77.8%) of those not on antidepressants, $p = 0.01$ (Supplementary Table S3).

Individual adverse effects. As previously reported, there was no statistical difference in the number of individual AEs of special interest between those on placebo and those on CBD.[18]

Table 4. Maximum mL of Oil (Median, Range) Achieved by Day 14 in All 142 Participants Who Entered the Study, According to Whether They Were on the Medication of Interest during the Study

Drug class or medication of interest	CBD mL oil—NOT on med of interest	CBD mL oil—on med of interest	*p*-value	Placebo mL oil—NOT on med of interest	Placebo mL oil—on med of interest	*p*-value*
Antipsychotics	4.5 (0.5–6.0), *n* = 56	3.0 (2.0–6.0), *n* = 14	0.31	6.0 (0.5–6.0), *n* = 56	6.0 (0.5–6.0), *n* = 16	0.43
Antidepressants excluding tricyclics	4.0 (0.5–6.0), *n* = 49	5.0 (1.5–6.0), *n* = 21	0.31	6.0 (0.5–6.0), *n* = 47	6.0 (1.0–6.0), *n* = 25	0.15
Tricyclic antidepressants	4.0 (0.5–6.0), *n* = 65	3.0 (2.0–6.0), *n* = 5	0.23	6.0 (0.5–6.0), *n* = 66	6.0 (4.0–6.0), *n* = 6	0.20
Benzodiazepines	4 (0.5–6.0), *n* = 49	4 (0.5–6.0), *n* = 21	0.72	6.0 (0.5–6.0), *n* = 44	6.0 (0.5–6.0), *n* = 28	0.42
Chemotherapy	5.0 (0.5–6.0), *n* = 47	4.0 (0.5–6.0), *n* = 23	0.43	6.0 (0.5–6.0), *n* = 47	6.0 (0.5–6.0), *n* = 25	0.72
Immunomodulators	4.0 (0.5–6.0), *n* = 58	3.5 (0.5–6.0), *n* = 12	0.58	6.0 (0.5–6.0), *n* = 62	6.0 (3.0–6.0), *n* = 10	0.42
Hormone therapy	4.0 (0.5–6.0), *n* = 57	6.0 (0.5–6.0), *n* = 13	0.54	6.0 (0.5–6.0), *n* = 61	6.0 (0.5–6.0), *n* = 11	0.07
Corticosteroids	4.0 (0.5–6.0), *n* = 31[a]	5.0 (0.5–6.0), *n* = 39	0.81	6.0 (0.6–6.0), *n* = 27[b]	6.0 (0.5–6.0), *n* = 45	0.32
Opioids excluding oxycodone	4.0 (0.5–6.0), *n* = 28	4.0 (0.5–6.0), *n* = 42	0.77	6.0 (0.5–6.0), *n* = 29	6.0 (0.5–6.0), *n* = 43	0.02 †
Dexamethasone	4.0 (0.5–6.0), *n* = 44[c]	4.5 (0.5–6.0), *n* = 26	0.71	6.0 (0.5–6.0), *n* = 34[d]	5.5 (0.5–6.0), *n* = 38	0.03
Paracetamol	3.0 (0.5–6.0), *n* = 38	5.5 (0.5–6.0), *n* = 32	0.03	6.0 (0.5–6.0), *n* = 30	6.0 (0.5–6.0), *n* = 42	0.20
Oxycodone	4.5 (0.5–6.0), *n* = 34	4.0 (0.5–6.0), *n* = 36	0.73	6.0 (0.5–6.0), *n* = 32	6.0 (0.5–6.0), *n* = 40	0.95
Metoclopramide	4.0 (0.5–6.0), *n* = 38	3.5 (0.5–6.0), *n* = 32	0.62	6.0 (0.5–6.0), *n* = 31	6.0 (0.5–6.0), *n* = 41	0.79
Pantoprazole	4.0 (0.5–6.0), *n* = 42	4.5 (0.5–6.0), *n* = 28	0.68	6.0 (0.5–6.0), *n* = 49	6.0 (0.5–6.0), *n* = 23	0.59
Pregabalin	4.5 (0.5–6.0), *n* = 54	3.5 (0.5–6.0), *n* = 16	0.44	6.0 (0.5–6.0), *n* = 48	6.0 (1.0–6.0), *n* = 24	0.68

CBD, cannabidiol; IQR, interquartile range.
*Wilcoxon Rank Sum test.
†Median (IQR) for those in the placebo group not on opioids was 6 (6–6) compared with 6 (3–6) mL for those on opioids, hence the *p*-value of 0.02.
[a]31/70 on no corticosteroid (including dexamethasone).
[b]27/72 on no corticosteroid (including dexamethasone).
[c]13/44 not on dexamethasone but on another corticosteroid.
[d]7/34 not on dexamethasone but on another corticosteroid.

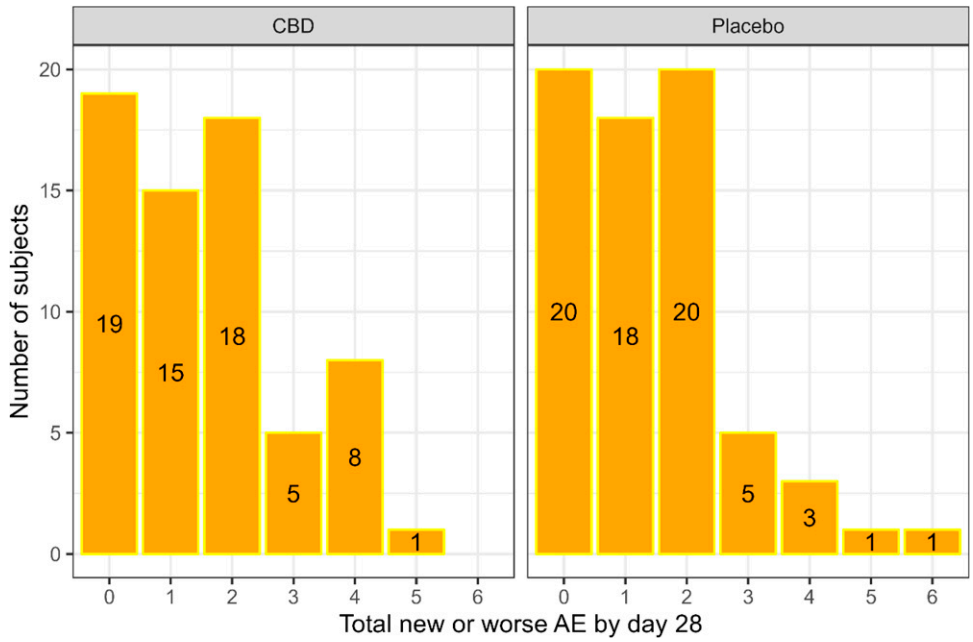

FIG. 1. Number of new or worse adverse effects of interest experienced by participants in the CBD or placebo groups from baseline to day 28.

The most frequently reported "other" AEs that were new or worse than baseline were pain, constipation, fatigue, anxiety, diarrhea, and dyspnoea, with no difference between arms except for dyspnoea (8 CBD, 2 placebo, $p = 0.04$).

The effect of drug groups or individual agents on both the six AEs of special interest was explored (Supplementary Table S4) and the four most frequently reported "other" AEs using multivariable logistic regression to estimate risk (data available on request). Broken down by adverse effect, treatment group, and drug group or individual agent, numbers were small, thus any inferences or clinical import should be treated with caution, but there was no suggestion of any interaction of concern.

Discussion

CBD has the potential to interact with multiple medications.[24] In our RCT of CBD vs placebo for the management of symptoms related to advanced cancer,[18] trial participants were taking many concomitant medications, including opioids, and the majority were on anti-cancer therapy. Despite concern about the possibility of drug interactions with cannabis and other medications, we have been unable to demonstrate any significant clinical interactions based on the surrogate measures of patient-chosen dose of CBD and frequency of AEs.

The few significant interactions found may be related to small numbers rather than being clinically meaningful. Why hormonal therapy or antidepressants should be protective against CBD-induced AEs is hard to explain. There was a suggestion that paracetamol could be protective against the side effects of CBD (Table 4), but this was not supported by other analyses.

The median dose of CBD self-selected by participants in the study (400 mg/day) would generally be considered a "moderate" dose, which may be associated with drowsiness.[25] This is supported by a trend towards an increased incidence of somnolence in the treatment arm in the parent study. It is acknowledged that higher doses are used in other settings, for example, in childhood epilepsy, and that there is evidence of potential additional drug interactions at this dose level.[26]

Opioids are metabolized by CYP3A4, 3A5, 2C19, and 2B6, all of which are inhibited by CBD, which presents potential for interaction. The concomitant use of CBD and oxycodone can theoretically increase

Table 5. Incidence Rate Ratio (IRR) for Effect of Concomitant Medications or Medication Classes on the Incidence of New or Worse Adverse Effects over the 28 Day Study Period

Medication or medication class of interest and treatment arm (CBD)	Incidence rate ratio for a new or worse AE with 95% CI for medication or medication class of interest and treatment arm	*p*-value
Antipsychotics	0.94 (0.60–1.43)	0.76
Treatment arm	1.10 (0.78–1.55)	0.57
Antidepressants excluding tricyclics	0.74 (0.50–1.07)	0.11
Treatment arm	1.11 (0.77–1.52)	0.64
Tricyclic antidepressants	0.86 (0.61–1.20)	0.39
Treatment arm	1.14 (0.95–1.36)	0.15
Benzodiazepines prescribed	0.88 (0.61–1.28)	0.51
Treatment arm	1.09 (0.77–1.34)	0.61
On chemotherapy	1.35 (0.95–1.90)	0.09
Treatment arm	1.12 (0.80–1.56)	0.52
On Immunomodulators	0.87 (0.52–1.40)	0.56
Treatment arm	1.11 (0.78–1.56)	0.54
On hormone therapy	0.59 (0.35–0.95)	0.04
Treatment arm	1.12 (0.80–1.57)	0.51
Corticosteroids excluding dexamethasone	0.91 (0.61–1.36)	0.66
Treatment arm	1.11 (0.78–1.56)	0.54
Dexamethasone	1.32 (0.84–1.87)	0.10
Treatment arm	1.15 (0.82–1.62)	0.42
Corticosteroids, including dexamethasone	1.27 (0.90–1.80)	0.18
Treatment arm	1.11 (0.79–1.57)	0.53
Paracetamol	0.91 (0.65–1.29)	0.61
Treatment arm	1.09 (0.77–1.55)	0.60
Opioids excluding oxycodone	1.06 (0.75–1.50)	0.74
Treatment arm	1.11 (0.79–1.56)	0.55
Oxycodone	1.14 (0.81–1.62)	0.44
Treatment arm	1.12 (0.79–1.58)	0.51
Metoclopramide	1.30 (0.92–1.84)	0.12
Treatment arm	1.19 (0.98–1.42)	0.40
Pantoprazole	0.83 (0.58–1.20)	0.33
Treatment arm	1.12 (0.80–1.59)	0.50
Pregabalin	0.97 (0.66–1.41)	0.86
Treatment arm	1.11 (0.78–1.56)	0.57

The IRRs are adjusted for the length of time the participant was in the study. An IRR of less than one is interpreted that the risk for the exposed group is a fraction of the risk for the unexposed group. For example, those on hormone therapy (IRR 0.59) experienced on average 59% fewer adverse events than those not on hormone therapy. Those on chemotherapy (IRR 1.35) experienced on average 35% more adverse events than those not on chemotherapy.

CBD, cannabidiol.

oxycodone levels by 75%, increasing the risk of adverse effects, including somnolence.[27] CBD inhibits *P*-glycoprotein-mediated transport,[9] which is responsible for morphine, oxycodone, and methadone efflux from within the blood–brain barrier. There is a paucity of findings related to CBD–opioid interactions, but individual case reports have shown CBD to increase methadone levels in children with cancer.[28]

We found no evidence of any clinically significant interaction between opioids and CBD—there was no significant change in opioid dose over time in either the CBD or placebo arm, specifically no dose reduction. Neither oxycodone nor opioids in general increased the likelihood of a CBD-related adverse effect.

There have been few studies on the effect of CBD on serum antidepressant levels due to CYP inhibition.[29] CBD may affect the metabolic profiles of duloxetine (as CBD inhibits CYP1A2 and CYP2D6) and venlafaxine (as CBD inhibits 2C19, 2C9, and 3A4). CBD can theoretically increase the sedation and drowsiness commonly seen with TCAs.[30] Approximately one-third of the participants in this study were taking anti-depressants (Table 2), but less than 10% were on TCAs, the levels of which can theoretically be increased by up to 75% when used in conjunction with CBD.[27] Increased levels of drowsiness were not detected in those patients taking both medications in this study. Antidepressants as a drug class comprises several different drugs with different metabolic pathways and side-effect profiles, however.

Cannabidiol use has been associated with reduced need for benzodiazepines.[31] Clobazam is the benzodiazepine at the focus of most research[17]; its metabolism by CYP3A4 is potently inhibited by CBD. The concomitant use of benzodiazepines did not increase the

incidence of AEs in our study, although our recording of concomitant medications did not differentiate those taken on a regular basis or as required ("prn"), and no patient was taking clobazam.

In a study assessing the incidence of AEs reported by patients initiating cannabis for chronic pain,[19] those patients taking 10 or more other medications were 3.6 times more likely to report fatigue. Those taking gabapentin were more likely to report dizziness and those on TCAs somnolence or anxiety. We could not demonstrate any association between the number of concomitant medications and AEs. Similarly, the addition of CBD did not appear to increase the incidence of AEs that might be associated with individual drugs or drug classes.

This study is limited by the relatively small number of patients taking individual medications but strengthened by the fact that the number of concomitant medications was high (median >10 per patient). Similarly, we cannot determine whether CBD resulted in reduced efficacy of drugs (such as theophylline or olanzapine). The trial participants were all closely monitored such that any deleterious pharmacodynamic effects (e.g., on anticoagulation with warfarin) would have been identified and addressed early. All patients in the study had symptoms related to their cancer, and the majority were receiving anticancer treatment with associated side effects. Therefore, DDIs may have been "buried" and less likely attributed to cannabis. Further, the study over 14–28 days was of relatively short duration. Of interest, however, a subsequent study by our group using the same methodology to test a THC/CBD combination product,[32] did identify a greater incidence of adverse effects in the treatment arm within the same period, suggesting that this duration of treatment is sufficient to recognize treatment-related AEs.

This study examined pure synthetic CBD, whereas most cannabis products contain tetrahydracannabidiol (THC). Future work should examine whether the addition of this cannabinoid contributes more to drug interactions.

In conclusion, this substudy would suggest that concerns regarding clinically significant drug interactions with CBD, at least in the short term, may be unfounded.

Authors' Contributions

Conception and design of the study—G.D., G.M., J.H., and P.G. Acquisition of data—G.D., J.H., and R.G. Analysis and interpretation of data—G.D., R.G., P.G., and J.H. Statistical support—R.G. Drafting of the article—G.D., R.G., T.G., G.M., P.G., and J.H. Article revision—G.D., R.G., T.G., G.M., P.G., and J.H. Approval of the final article—G.D., R.G., G.M., T.G., P.G., and J.H. J.H. is the guarantor of this project.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Research ethics approval was obtained from all participating sites (Mater Misericordiae Ltd. Human Research Ethics Committee, EC00332, HREC/18/MHS/43, and St Vincent's Health and Aged Care Human Research and Ethics Committee, EC00324, HREC 18/16).

Consent to Participate

Written informed consent was obtained from all individual participants included in the study.

Author Disclosure Statement

The authors have no relevant financial or nonfinancial interests to disclose.

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Supplementary Material

Supplementary Table S1
Supplementary Table S2
Supplementary Table S3
Supplementary Table S4

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Abbreviations Used

AE = Adverse Effect
CBD = Cannabidiol
CYP = Cytochrome P450
DDIs = Drug-drug Interactions
ESAS (TSDS) = Edmonton Symptom Assessment Scale (total symptom distress score)
IQR = Interquartile Range
IRRs = Incidence Rate Ratios
OME = Oral Morphine Equivalent
OR = Odds Ratio
RCT = Randomized controlled trial
SD = Standard Deviation
TCAs = Tricyclic Antidepressants
THC = Tetrahydrocannabidiol
UGT = UDP-glucuronosyltransferase