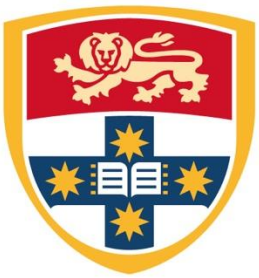

THE UNIVERSITY OF SYDNEY

Medicinal cannabis as a potential treatment for chronic pain and anxiety

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A thesis submitted in fulfilment of the requirements of the degree of

Doctor of Philosophy

DECLARATION

I hereby declare that this submission is my own work and to the best of my knowledge it contains no material previously published or written by another person, nor material which to a substantial extent has been accepted for the award of any degree or diploma at The University of Sydney or any other educational institution. Any contribution made to the research by colleagues, with whom I have worked at The University of Sydney or elsewhere, during my candidature, is fully acknowledged.

I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.

Conflict of interest statement: The CA Clinics Observation Study (CACOS) reported on in this thesis was designed and funded by Applied Cannabis Research, and the data was collected by CA Clinics. Applied Cannabis Research gave permission for researchers at The University of Sydney to analyse the data and publish the studies used in this thesis.

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ABBREVIATIONS

The following abbreviations are used in this work:

11-OH-THC	11-hydroxy-Δ^9-THC
2-AG	2-arachidonoyl glycerol
5-HT	5-hydroxytryptamine
7-OH-CBD	7-hydroxy-cannabidiol
AE	Adverse event
AEA	Arachidonoyl ethanolamide
AI	Aromatase inhibitor
AIMSS	Aromatase-inhibitor associated musculoskeletal symptoms
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
ARTG	Australian Register of Therapeutic Goods
AUC	Area under the curve
BBB	Blood brain barrier
BCE	Before the current era
BPI-SF	Brief Pain Inventory Short Form
CACOS	CA Clinics Observational Study
CAIMSS	Cannabis for aromatase-inhibitor associated musculoskeletal symptoms
Cannabis	Cannabis sativa
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2

CBD	Cannabidiol
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum concentration
CNC	Clinical trial nurse coordinator
CNS	Central nervous system
CRP	C-reactive protein
CYP	Cytochrome P450
DSMB	Data safety and monitoring board
ECS	Endocannabinoid system
EQ-5D-5L	European Quality of Life 5-Dimension 5-Levels
FAAH	Fatty acid amide hydrolase
FARB	Fatty acid binding protein
GABA	Gamma-aminobutyric acid
GAD	Generalised anxiety disorder
GMP	Good manufacturing practice
GPR	G protein-coupled receptor
GRCS	Global rating of change scale
HED	Human equivalent dose
HREC	Human Research Ethics Committee
HRQoL	Health-related quality of life
IL	Interleukin
IMP	Investigational medicinal product
IP	Intraperitoneal

IQR	Interquartile range
K_{el}	Elimination rate constant
MCID	Minimal Clinically Important Difference
MCP	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MENQOL	Menopause-Specific Quality of Life
MOA	Mechanism of action
MQS III	Medication Quantification Scale version III
NAPE	*N*-arachidonoyl phosphatidylethanolamine
NK	Natural killer
NOAC	Non-vitamin K antagonist oral anticoagulant
NOAEL	No-observed-adverse event level
NSAID	Non-steroidal anti-inflammatory
OA	Osteoarthritis
OAT	Organic anion transporting
OR	Odds ratio
PBMC	Peripheral blood mononuclear cell
PCIF	Patient Information and Consent Form
PEA	Palmitoylethanolamide
PFC	Prefrontal cortex
P-gp	P-glycoprotein
PPAR	Peroxisome proliferator activated receptors
PROMIS	Patient Reported Outcomes Measurement Information System
PTSD	Post-traumatic stress disorder

REDCap	Research Electronic Data Capture
RR	Relative risk
SAE	Serious adverse events
SAS	Special Access Scheme
SAS-B	Special Access Scheme Category B
SD	Standard deviation
SNRIs	Serotonin-noradrenaline re-uptake inhibitors
SOC	System organ class
SSRI	Selective serotonin reuptake inhibitors
SUSARs	Suspected unexpected serious adverse reactions
TGA	Therapeutic Goods Administration
TGO93	Australian Therapeutic Goods Order 93
Th1	Type 1 T helper
Th2	Type 2 T helper
T_{max}	Time until maximum concentration
TNF	Tumour Necrosis Factor
TRP	Transient receptor potential
TRPV	Transient receptor potential vanilloid
UGT	Glucuronosyltransferase
VAS	Visual analogue scale
VDBP	Vitamin D binding protein
WOMAC	Western Ontario and McMaster Universities Arthritis Index
Δ^9THC	Delta-9-tetrahydrocannabinol

ABSTRACT

Cannabis has been used for thousands of years for many different purposes. Since 2016, Australian patients can access medicinal cannabis with a prescription from an authorised prescriber or through approval from the Therapeutic Goods Administration's Special Access Scheme. Medicinal cannabis contains over 100 phytocannabinoids; however, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant and researched. The most common indications for which medicinal cannabis is prescribed are chronic pain conditions and anxiety; however, evidence surrounding its efficacy remains conflicting. This thesis aimed to explore the real-world use of cannabis for these indications, and the potential of translating this evidence into a clinical trial setting.

The tolerability and effectiveness of medicinal cannabis for chronic, refractory pain, with a subset analysis on arthritis, was explored using data from the CA Clinics Observational Study (CACOS). Self-reported adverse events (AEs) were reported and changes in health-related quality of life (HRQoL) outcomes were measured using the Patient-Reported Outcomes Measurement Information System Version 29 (PROMIS-29). The overall cohort of patients with chronic pain (n = 296) reported significantly reduced pain intensity scores ($p = 0.003$), in particular those taking a balanced CBD:THC product ($p = 0.025$). Similarly, those in the arthritis subset (n = 92) reported significantly reduced pain intensity ($p = 0.005$); specifically, the groups taking a CBD-only ($p = 0.018$) or balanced product ($p = 0.005$). Other HRQoL outcomes were also improved depending on the CBD:THC ratio prescribed. In total, 51% of patients reported an AE, with the most common being dry mouth (24%), somnolence (19%), or fatigue (12%).

Given the uptake of medicinal cannabis prescribing for chronic pain conditions, this thesis explored the incidence of patient-reported AEs, and the association these may have with cannabis constituents, dose, and concomitant medicines. Data was collected as part of the CACOS, and concomitant medicines were obtained using patient health summaries provided by referring practitioners. From a total of 275 patients, each patient had a median of six concomitant medications, where opioids (65%) were the most common. Those who were taking 10 or more concomitant medicines were associated with a 3.6 times higher likelihood to report the AE fatigue ($p= 0.048$), those taking a gabapentinoid were 2.4 times more likely to report dizziness ($p= 0.036$), and patients taking a tricyclic antidepressant were 1.8 times more likely to report somnolence ($p =0.034$), and 3.4 times more likely to report anxiety ($p = 0.04$). In addition, those who were taking a product that contains THC were 1.5 times more likely to report an AE when compared to those on CBD-only. These findings demonstrate that AE incidence may be associated with concomitant medicines and cannabis constituents, warranting further research into these interactions.

Next in this thesis, clinical trial protocols were developed to facilitate the crucial translation of these real-world results into rigorous trial data. First, transdermal delivery of CBD for osteoarthritis was considered to overcome the limited bioavailability and significant first pass metabolism of CBD. This protocol aims to determine the pharmacokinetics, safety, optimal dose, and efficacy of transdermal creams containing CBD and PEA, a cannabimimetic. The first stage of this study was designed as part of this thesis as an open label, single ascending dose trial to determine the dose required to achieve the target plasma concentration. The second stage was designed as a randomised, double-blind, placebo-controlled, three-arm cross-over study to examine the efficacy and tolerability of CBD and PEA in osteoarthritis pain.

The second clinical trial protocol was developed as part of this thesis after a thorough review was undertaken summarising the current pre-clinical, clinical, and safety evidence into the use of CBD in patients experiencing aromatase inhibitor associated arthralgia. Overall, this protocol aims to improve outcomes in patients with hormone receptor positive breast cancer who are experiencing arthralgia and other AEs from ongoing aromatase inhibitor therapy. This pilot clinical trial was designed as a randomised, double-blind, placebo-controlled, two-arm cross-over study comparing a CBD extract against placebo in improving joint pain and other HRQoL symptoms.

Finally, the use of cannabis for anxiety was reviewed revealing encouraging pharmacological actions, yet inconclusive clinical data. Paradoxically, it is reported that cannabis may either produce an anxiolytic, or anxiogenic response, theorised to be due to dose or patient factors, such as tolerance. The CACOS data of those using medicinal cannabis for an anxiety condition, and a subset analysis on patients with post-traumatic stress disorder, was reported to determine the effectiveness and tolerability. Overall, patients with anxiety ($n = 198$) reported significantly reduced anxiety ($p < 0.001$), and this was observed in those taking a CBD-only ($p < 0.001$), balanced ($p < 0.001$), and THC dominant ($p = 0.011$) product. Those with PTSD ($n = 57$) also reported significantly reduced anxiety symptoms ($p < 0.001$), observed only in the CBD-only group ($p < 0.001$). Similar to the results seen for the chronic pain studies, other HRQoL domains outcomes were improved depending on the CBD:THC ratio, and the most common AEs reported were dry mouth (32.6%), somnolence (31.3%), and fatigue (18.5%).

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Chapter two of this thesis is published as *[Schubert EA, Johnstone MT, Benson MJ, Alffenaar JC, Wheate NJ. Medicinal cannabis for Australian patients with chronic refractory pain including arthritis. Br J Pain. 2023; 17(2), 206–217].* I co-designed the study with the co-authors, analysed the data, and wrote the drafts of the manuscript.

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In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material in has been granted by the corresponding author.

Elise Schubert, March 2023

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Nial Wheate, March 2023

CHAPTER ONE

Introduction

CHAPTER 1: INTRODUCTION

1.1. History of medicinal cannabis

Medicinal cannabis is derived from *cannabis sativa* (cannabis), a plant which has been cultivated by humans over thousands of years for many different purposes. With evidence dating back to 4,000 BCE in China, cannabis was originally used in textiles, as a food source, and in ancient medical practices. The world's oldest pharmacopoeia, the *Pen-ts'ao Ching,* first documented the medical uses of cannabis for ailments such as rheumatic pain, constipation, and also made reference to its psychoactive properties. Once the cannabis plant reached India, it became extensively used both recreationally and in Eastern medical practices (1, 2).

Cannabis was first introduced to Western medicine in the mid-19th century, where both its psychoactive and therapeutic purposes were studied and used for a vast number of conditions. At this time, it was medically indicated for symptoms such as sedation, hypnotism, analgesia, and appetite stimulation (3-5). The early 20th century saw a decline in the use of cannabis, attributed to a lack of consistency and efficacy between preparations, and because the active constituents were not yet isolated (3). Additionally, governments began to enforce legal restrictions on the recreational use of cannabis, with punishments including both heavy fines and imprisonment (6). The criminalisation of cannabis began with the 1925 Geneva Convention, a transnational drug control treaty which also imposed prohibitions on opium and coca. This prevented modern research on the use of cannabis in pharmacotherapy, whilst other options became popularised instead, such as paracetamol, non-steroidal anti-inflammatories (NSAIDs), and opioids for pain, and benzodiazepines for insomnia and anxiety (3, 6). In the latter half of the 20th century, the use of cannabis started to rise again as illegal recreational use became more popularised, and scientific interest grew as the various

cannabinoids were isolated, leading to a better understanding of the endocannabinoid system (7, 8). Additionally, the risks of medications such as opioids and benzodiazepines were becoming apparent (8). Commonly referred to as the opioid crisis, prescriptions for opioid medications in the United States peaked at 255 million per year in 2012 after aggressive promotion by pharmaceutical companies. The opioid crisis is believed to have caused nearly 500,000 deaths, resulting from the initial over prescribing of prescription opioids, and the subsequent dependence that led to heroin and fentanyl usage (9, 10). Now well known to be high risk, opioids and benzodiazepines can cause serious adverse events (AEs) including sedation, tolerance, and dependence. As such, there has been a push for alternative medication options with a more favourable risk profile to treat conditions such as pain and anxiety. Cannabis has been proposed as a potential option, with emerging evidence in a range of therapeutic areas including pain, insomnia, epilepsy, and anxiety (8). Laws on cannabis use have since changed around the world, and in 2016 medicinal cannabis became legalised in Australia under certain conditions (11). Additionally, the World Health Organization in 2019 proposed that formulations containing one constituent of cannabis, cannabidiol (CBD), should not be subject to international drug control as there was not any evidence of abuse, public health concerns, and because it is generally tolerated well (12).

Cannabis contains over 100 phytocannabinoids, as well as terpenes and flavonoids, which all have various pharmacological properties resulting in cannabis' diverse clinical possibilities (13). The two most abundant, and therapeutically utilised phytocannabinoids isolated from cannabis are Δ^9-tetrahydrocannabinol (THC), and CBD (13, 14). The isolation and research into the pharmacology of THC led to the discovery of components of the endocannabinoid system (ECS) (15).

1.2. The endocannabinoid system

The ECS in the human body is ubiquitous and its function is complex. Overall, the ECS contributes to homeostasis by regulating various neurological and immunological bodily processes. The key components of the ECS are the cannabinoid receptor type 1 (CB_1), cannabinoid receptor type 2 (CB_2) (16-18), as well as the endogenous ligands, known as endocannabinoids, anandamide (AEA) and 2-arachindonoylglycerol (2-AG) (19). Other components of the ECS include the enzymes that synthesise, facilitate cellular uptake, and metabolise the endocannabinoids (19, 20).

The CB_1 receptors are mainly expressed in the central nervous system (CNS) and are typically found on the terminals of central and peripheral neurons, where their activation facilitates the inhibition of neurotransmitter release (21). There is also some expression of CB_1 receptors in the periphery on immune cells and peripheral tissues, such as throughout the gastrointestinal tract, adipose tissue, adrenal glands, and in the liver; however, they are predominantly found in the CNS (22). The CB_1 receptors are $G_{i/o}$-protein coupled receptors, where they are coupled negatively to adenylate cyclase, positively to mitogen-activated protein kinase, and also to some types of potassium and calcium channels. The CB_1 receptors can also act through G_s-proteins to activate adenylate cyclase (23). The distribution of the CB_1 receptors in the CNS likely explains the role that CB_1 receptors have in the control of motor function, cognition and memory, and analgesia (22). The activation of CB_1 receptors also produces psychoactive effects (22, 23).

The CB_2 receptors are mainly expressed on peripheral organs that are involved in immune function, as well as on circulating immune cells (22). When the immune system has been activated, cells such as lymphocytes, dendritic cells and macrophages release cytokines, chemokines, and the endocannabinoids AEA and

2-AG are attracted to leukocytes to eliminate the antigen. During this response, it appears that CB_2, as well as CB_1, receptors are upregulated to modulate immune cell migration and cytokine release, regulating the immune response once the antigen has been eliminated (24). Through similar mechanisms, CB_2 receptors have an integral role in chronic, inflammatory pain due to the inhibition of inflammatory mediators that target nociceptors (25). The expression of CB_2 receptors has also been shown in the brain and it was initially thought only to be associated with the inflammatory processes in Alzheimer's disease (26), multiple sclerosis (27) and brain tumours (28). However, other studies have shown that CB_2 receptors are also present in healthy brain cells, so the role of these in CNS diseases is not conclusive (29). Similar to the CB_1 receptors, CB_2 receptors are $G_{i/o}$-protein coupled negatively to adenylate cyclase and positively to mitogen-activated protein kinase (23).

1.3. Endocannabinoids

Whilst the endocannabinoids AEA and 2-AG have different pharmacological properties, they are both retrograde transmitters. Synthesised on demand in post-synaptic terminals, AEA and 2-AG are released into the synaptic space where they can interact with the pre-synaptic cannabinoid receptors, leading to their inhibitory neurological or immunological effects (30).

Anandamide is a hydrophobic molecule that easily moves through membranes and is rapidly broken down (31). Anandamide is stored in lipid membranes as its precursor *N*-arachidonoyl phosphatidylethanolamine (NAPE). When needed, the enzyme phospholipase D synthesises AEA from NAPE making it available to bind to endocannabinoid receptors within that cell, or it may be carried to other targets by

carrier proteins (32-34). The major pathway for AEA degradation is hydrolysis via fatty acid amide hydrolase (FAAH) (35, 36).

Similar to AEA, 2-AG is a freely diffusing hydrophobic molecule that is stored in lipid membranes as 2-arachidonoyl-containing phospholipid precursors. When needed, it is primarily synthesised by a sequential action of phospholipase C-β, and diacylgycerol lipase (37, 38). There are many enzymes responsible for 2-AG degradation, most notably by monoacylglycerol lipase and α/β domain hydrolases 6 and 12 (37, 38).

2-Arachindonoylglycerol is found in much higher concentrations than AEA and acts as a full agonist of CB_1 and CB_2 receptors, whereas AEA is only a partial agonist at these receptors, with a slightly higher affinity for CB_1 (30). In addition to CB_1 and CB_2 receptors, endocannabinoids interact with other targets such as peroxisome proliferator activated receptors (PPAR), transient receptor potential (TRP) channels, and G protein-coupled receptors (GPR) 18 and 55. These receptors are considered by many to be a part, or at least an extension of, the ECS (37-39).

In addition to AEA and 2-AG, there are also other minor endocannabinoids and cannabimimetics that have been identified, such as *N*-arachidonyl dopamine, and palmitoylethanolamide (30). Cannabimimetic molecules are said to mimic certain actions of cannabinoids, but are not categorised as a cannabinoid. They can interact with components of the ECS, such as endocannabinoid receptors or enzymes, but they also have other pharmacological targets outside of the endocannabinoid system (40, 41).

1.4. Δ^9-Tetrahydrocannabinol

1.4.1. THC pharmacology and clinical use

Mainly located in the flowering female heads, THC is predominantly responsible for the psychoactive effects of cannabis (42). Δ^9-tetrahydrocannabinol is a partial agonist of both CB_1 and CB_2 receptors; however, it is also believed to act on the other putative receptor targets of the ECS (43, 44). Being a partial agonist of the cannabinoid receptors, THC can act as either an agonist or antagonist depending on factors such as the type of cell the receptor is expressed on, and the presence of other agonists or endocannabinoids (45). The complex actions of CB_1 and CB_2 and the endocannabinoid system means that THC (and CBD) have a myriad of possible pharmacological actions.

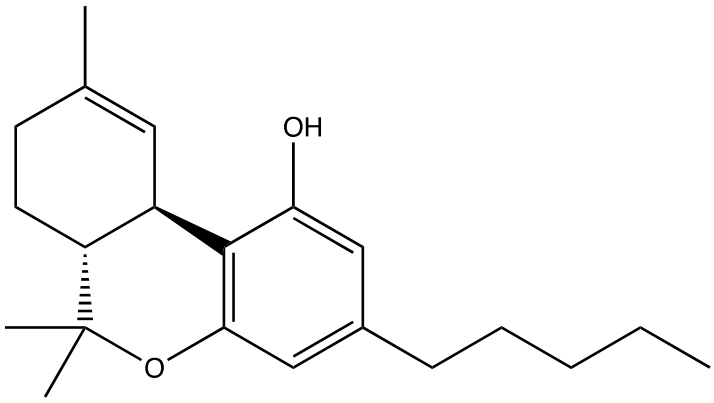

Figure 1. The chemical structure of Δ^9-tetrahydrocannabinol.

The well-known psychoactive effects of cannabis are mediated through the activation of CB_1 receptors by THC, which include euphoria, distortion of sensory perception, and memory impairment (39, 46). Activation of CB_1 receptors by THC also produces analgesic effects, anti-emesis, appetite stimulation, and either anxiolysis or angiogenesis, which is thought to be dose dependent (39, 46). Lower doses of THC are reported to produce effects such as relaxation and euphoria, whereas higher doses can result in panic, dysphoria, or paranoia (47). This also appears to vary between

individuals, where some are more likely to be predisposed to either positive or negative effects, and other factors including route of administration, environmental factors, and tolerance (48-52). It is through interaction with receptors such as CB_2 and PPAR-γ that THC has anti-inflammatory, antispastic, and neuroprotective properties (46).

Due to these pharmacological actions, THC is prescribed for analgesia, spasticity, anxiety, appetite stimulation, and antiemesis (53). From a safety perspective, some patients may be more sensitive to THC, particularly its anxiogenic properties, intoxication, and sedation (54). Furthermore, it has also been shown to increase blood pressure and heart rate, and it is not recommended in pregnancy or breastfeeding (55). Because of these issues, THC needs to be used with caution and titrated carefully, and potentially re-considered in patients with psychiatric conditions including people who experience anxiety and psychosis, cardiovascular diseases, and if they need to drive a motor vehicle or operate heavy machinery (55).

1.4.2. THC pharmacokinetics

Absorption

Δ-9-tetrahydrocannabinol is commonly administered via inhalation or orally; however, it has also been injected as part of pre-clinical and clinical studies (56). The route of administration affects the pharmacokinetic properties of THC, including the rate of absorption, peak concentrations in the plasma and brain, and the formation of the important active metabolite 11-hydroxy-Δ^9-THC (11-OH-THC). As a consequence, patient-perceived psychoactive effects are also influenced by the route of administration. After inhalation, the bioavailability of THC is reported to be between 10–35% (57), influenced greatly by factors including inter- and intra-subject differences in smoking dynamics, inhalation volume, hold time, spacing of puffs, and anticipation

of a drug reward (58). The oral bioavailability of THC has been estimated to be between 10-20%, affected by the vehicle in which it is administered (59). Oral absorption is slower than inhalation, and the peak THC concentrations are delayed (58). Due to the low oral bioavailability of THC, alternate routes of administration have been developed, including sublingual and oromucosal formulations which bypass the significant first pass-effects (58).

Distribution

After inhalation, THC plasma concentrations are quickly decreased as the lipophilic molecule is rapidly distributed into highly perfused tissues such as the brain and liver. Importantly, THC uptakes readily into fat stores, with the concentration and duration of uptake increased with prolonged exposure (58). In addition, the metabolism of THC into its active metabolite 11-OH-THC further reduces THC plasma levels (58). This metabolite penetrates the blood brain barrier (BBB) more rapidly and accumulates to higher concentrations when compared to THC (59, 60). Tetrahydrocannabinol readily crosses the placenta, particularly in early pregnancy, and significantly concentrates in breast milk (58).

Metabolism

After administration, THC is metabolised via hydroxylation via cytochrome P450 (CYP) 2C9 and CYP2C19 to form the psychoactive metabolite 11-OH-THC, and to a lesser extent 8β-hydroxy-THC and 8α-hydroxy-THC through minor pathways (61). The active metabolite, 11-OH-THC, is then further hydroxylated by CYP2C9 to form the inactive metabolite 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol. This inactive metabolite undergoes glucuronidation via glucuronosyltransferase (UGT) enzymes UGT1A1 and UGT1A3 to form the major end product of THC metabolism, 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol-glucuronide (61). Tetrahydrocannabinol-glucuronide is stored in

fatty tissues and is released slowly overtime, detectable in human urine for several weeks after cannabis use (43).

Significant differences in the quantity of psychoactive 11-OH-THC formed from the initial hydroxylation of THC via CYP2C9 has been found to be dependent on the route of administration, which is likely to alter its physiological, psychological, and behavioural effects (56, 61). After oral dosing, higher ratios of 11-OH-THC are formed compared with intravenous administration due to these first pass metabolism effects (59). This is likely to contribute to the psychoactive effects of orally administered THC, where 11-OH-THC penetrates the BBB more rapidly and accumulates to higher concentrations when compared to THC (59, 60).

Differences in the pharmacokinetics and accumulation of THC and 11-OH-THC has also been observed between the inhaled vs injectable routes (56). Inhalation led to higher plasma THC concentration at the 15 minute time point, whereas there was no difference at other time points. There was also no difference in peak plasma concentrations; however, inhalation did lead to higher brain THC levels, likely due to rapid absorption and uptake into tissues (such as the brain), and the bypass of first pass metabolism. Peak brain levels were shown to be at 30 minutes following inhalation, whereas injection resulted in a peak brain concentration at 90 minutes (56). Of note, this corresponds to the peak “high” reported in humans 30 minutes after inhalation of cannabis (56, 62). On the other hand, injection resulted in higher plasma and brain concentrations of 11-OH-THC when compared with inhalation, possibly resulting in a more robust and sustained pharmacological effect. Overall, there is a higher initial THC brain concentration after inhalation, but injection results in higher and sustained 11-OH-THC in the blood and brain (56).

Elimination

Tetrahydrocannabinol and its metabolites are excreted mostly in the faeces (> 65%), and to a lesser extent in the urine (approximately 20%) (59).

1.5. Cannabidiol

1.5.1. CBD pharmacology and clinical use

Cannabidiol, the other main phytocannabinoid isolated from the glandular hairs of cannabis, has been shown to have low affinity, and even weak antagonistic effects at both CB_1 and CB_2 receptors (45, 63). Key pharmacological targets of CBD lie outside of the cannabinoid receptors and include GPR18 and GPR55, various serotoninergic receptors, PPAR-γ receptors, adenosine A1 receptors, glycine receptors, $GABA_A$ and various TRP channels (45, 63). Despite the action of CBD at these receptors, the clinical effects of CBD may also result from its complex interaction with the ECS. It has been shown that CBD is a negative allosteric modulator of THC and 2-AG, and inhibits the cellular update of AEA. Because of this, CBD has indirect modulatory action at CB_1 and CB_2 receptors (45).

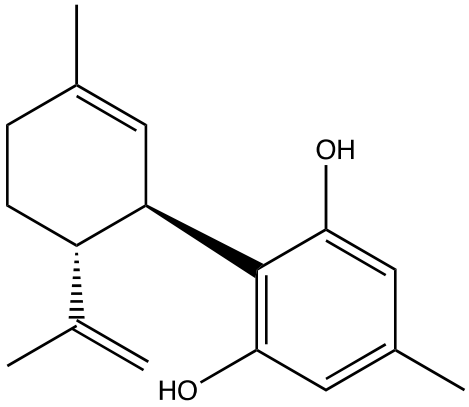

Figure 2. The chemical structure of cannabidiol.

Being non-psychoactive, CBD is often favoured for certain conditions for its non-intoxicating effects (64). The interaction of CBD with its receptor targets has resulted in anti-inflammatory, immunosuppressive, analgesic, anti-convulsive, and anxiolytic properties (65). In saying this, it is still generally regarded that the mechanism of action (MoA) of CBD remains largely unclear (45). Furthermore, it has also been shown that CBD may counteract the intoxicating effects of THC, a clinically relevant observation and a proposed benefit of prescribing CBD and THC combination products (66, 67). However, there are also studies that depict the opposite; the addition of CBD increased intoxication from THC, potentially through pharmacokinetic interactions such as the inhibition of CYP450 enzymes (68, 69). Cannabidiol is regarded as safe and generally well-tolerated; however, it has been potentially implicated in transaminase elevation and hepatic injury. Other side effects patients may experience include somnolence, sedation, appetite changes, and increased seizure frequency (70).

1.5.2. CBD Pharmacokinetics

Absorption

The bioavailability of CBD varies between studies and route of administration. Oral CBD has a low bioavailability of approximately 4%, which can increase 4-fold when administered with high-fat and caloric food (71). The bioavailability of inhaled CBD has been reported to be approximately 31%, or between 11 and 45% (57, 72, 73). The C_{max} is likely dose-dependent, whereas the T_{max} is not, occurring between 1 and 4 hours (72). Transdermal and topical creams have shown promising delivery of CBD in animal studies and are proposed as an alternate route of administration (72).

Distribution

Cannabidiol has a high apparent volume of distribution shown in healthy volunteers, and in vitro studies have shown high plasma protein binding (>94%) of CBD and its metabolites (70).

Metabolism

Cannabidiol is metabolised into its active metabolite, 7-hydroxy-CBD (7-OH-CBD), primarily by CYP2C19. CYP3A4 then metabolises this into an inactive metabolite, 7-carboxy-CBD (74, 75). This is followed by glucuronidation to form 7-carboxy-CBD-glucuronide (61). Studies have shown that CBD is a potent inhibitor of CYP2C19 and CYP3A4, and a weaker inhibitor of CYP2D6 (69, 76, 77).

Elimination

Despite significant first pass effects, a considerable amount of CBD is excreted unchanged into faeces (73). After inhalation, 7-OH-CBD is only a minor transformation product, with the majority being excreted in the urine as unchanged CBD, or as glucuronidated CBD (61).

1.6. Cannabis access and use in Australia

In 2016, the Australian *Narcotic Drugs Act* (1967) was amended which changed cannabis from a Schedule 9 (Prohibited) to a Schedule 8 (Controlled drug) product, allowing for the cultivation and manufacture of medicinal cannabis under strict conditions overseen by the Office of Drug Control within the federal Department of Health (11). Since then, many cannabis pharmaceutical products have become available; however, as most are not yet on the Australian Register of Therapeutic Goods (ARTG), medical practitioners need additional approvals in order to prescribe.

The pathways in which patients and prescribers can access medicinal cannabis in Australia is through the Special Access Scheme (SAS), the Clinical Trials Scheme, or the Authorised Prescribers Scheme. By far the most accessible and common route in which patients are accessing medicinal cannabis products is through the SAS. In order to prescribe, a medical practitioner must have already considered products that are on the ARTG. These products are encouraged to be used first line as they have been tested to ensure they meet the standards of quality, safety, and effectiveness. If the ARTG products are then found to be not clinically suitable, then the medical practitioner can apply to have access to unapproved medications, such as medicinal cannabis products, through the SAS on a case-by-case basis. As of 2023, there have been over 325,000 SAS category B (SAS-B) approvals for medicinal cannabis, for conditions including chronic pain, anxiety, sleep disorders, and neuropathic and cancer-related pain (78, 79).

Medicinal cannabis in Australia is either a schedule 4 or schedule 8 pharmaceutical product, depending on the THC content. In Australia, medicines are scheduled according to a national classification system that controls how medicines are made available to the public. Schedule 4 medicines are known as “prescription only medicines”, and are available to the public through a valid prescription through a pharmacist. Schedule 8 medicines, also known as “controlled drugs”, are only available with a valid prescription to a pharmacist, but also are subject to tight restrictions due to their potential to cause addiction (80, 81). Products that contain THC ≥ 1.0 % w/w or w/v are schedule 8, whereas all other formulations are schedule 4 (82). In September 2020, the Australian Therapeutic Goods Administration (TGA) announced that products containing only CBD can be eligible for schedule 3 status, meaning they can be sold over the counter in pharmacies, given that the product is provided in an

oral dosage formulation at a dose not more than 150 mg per day and for less than 30 days' supply (83). This dose was extrapolated by a review conducted by the TGA where they found 60 mg/day to be potentially clinically useful, safe and tolerable, whilst also acknowledging the potential drug-drug interactions (84). Despite the establishment of schedule 3 cannabis, at the time of writing this thesis, no products had demonstrated sufficient efficacy to gain ARTG approval, which means that Australia is behind many other countries that have CBD readily available without a prescription (85).

As most medicinal cannabis products are not listed on the ARTG, clinical trials must be conducted either under the Clinical Trial Notification (CTN) or the Clinical Trial Approval (CTA) schemes. Under the CTN scheme, the scientific and ethical review of clinical trial documentation is conducted by a Human Research and Ethics Committee (HREC), and then the TGA is notified of the clinical trial. For the CTA scheme, the TGA reviews the scientific data and then must provide an approval for the clinical trial before it is reviewed by a HREC. The CTA scheme is generally for high-risk or novel treatments with limited or no safety data. After HREC approval, some clinical trial sites may require additional local governance approval. The clinical trial can then be commenced at the site approved on the HREC application in accordance with the approved protocol, Good Clinical Practice, NMHRC guidelines, and other local regulations. These specify requirements such as safety and efficacy monitoring and reporting, data collection and handling, and storage of investigational products (86).

Importantly, even if a medicine is listed on the ARTG, the classification of an unapproved good can include various aspects of a product, such as the dose form, formulation, indication, directions for use, name, and the container in which it is packaged (86). This means that if one cannabis product were to be listed on the ARTG,

it would be specific to the one product manufactured by a specific company, including factors such as indication, dose form, and direction for use. Other companies would need to conduct their own studies on their product in order for it to be considered for the ARTG. An example of this is Epidiolex (Cannabidiol), approved in Australia specifically for adjunct use in Dravet Syndrome or Lennox-Gastaut.

In Australia, medicinal cannabis is regulated in the same way as any other pharmaceutical medicine, in contrast to most other countries where it is considered a herbal product (87). Because of this, there are strict quality and manufacturing requirements for medicinal cannabis in Australia. The Australian Therapeutic Goods Order (TGO) 93 – Standard for Medicinal Cannabis, outlines these requirements. In terms of the cannabinoid concentration, the upper and lower limits of medicinal cannabis that is sold in a dried flower/herbal form is 80% and 120% of the stated active pharmaceutical ingredient (API) content, together with any corresponding acids. For medicinal cannabis that is sold as a tablet, capsule, or any other dosage form, the average content of each cannabinoid must be within 90% to 110% of the stated dose, together with any corresponding acids. The TGO93 states that any cannabinoid that is provided at a dose at a concentration ≥ 2.0% (w/w or w/v), is considered an API, with the exception of THC, where it is considered an API at a concentration of ≥ 1.0% (w/w or w/v). The TGO93 also outlines the requirements for how manufacturers must decontaminate and test their products, how they should identify their cannabis plants, and also limits the use of any excipients to ensure that adulteration of the product does not occur (82). These standards ensure that medicinal cannabis products are provided at a high quality, despite not yet being registered on the ARTG. All medicinal cannabis products must be manufactured in a TGA approved Good Manufacturing Practice (GMP) approved facility.

The TGA released a report in September 2020 detailing their findings of laboratory testing of the top 25 medicinal cannabis products sold at the time in Australia, to test their compliance to the TGO93. Of these 25 products, 22 were available and given to the TGA for testing, at which stage it was found that five products failed to meet TGO93 requirements. Of those, three were found to have less CBD or THC content than stated on the label, and two had higher CBD or THC content (88).

1.7. Current clinical applications

The strongest evidence for medicinal cannabis is for epilepsy and multiple sclerosis-related spasticity, both of which have approved products on the ARTG in Australia and many other countries (Epidyolex® and Sativex®, respectively) (70, 89-91). Robust evidence for the use of medicinal cannabis in other conditions is lacking, namely due to the small number of well-designed clinical trials published in the literature. There are several important considerations for conducting clinical trials with cannabis products. Firstly, researchers must consider how to maintain participants' blinding in placebo-controlled studies with cannabis products containing THC. Participants may correctly identify that they are taking the active product due to the recognisable psychoactive effects, breaking the blind and potentially influencing their responses. It has been suggested that methodologies to counteract unmasking should be implemented, such a parallel study design or the use of an active placebo. Additionally, participants should be asked which treatment they believe they have received to compare with random guessing, and test whether these beliefs have influenced study outcomes (92). The length of time medicinal cannabis can persist in plasma is unclear and may be significant, so a washout period is important at baseline for any clinical trial for previous cannabis users, and during cross-over studies, to ensure there is no residual cannabis

in a participant's system (93). Inter-patient variability in the response to cannabis has been attributed to a number of factors. These include exposure factors such as the route of administration, dosage regimen and duration, and interactions with food and other drugs. Individual factors that affect variability in response are age and sex, and susceptibility factors are genetic polymorphisms and epigenetic regulation.

Genetic polymorphisms in cannabinoid receptors have been linked to phenotypes of cannabis use, such as adolescent cannabis use or cannabis dependencies, or response outcomes such as anxiety, anger, or depression. Genetic polymorphisms also affect THC and CBD metabolising CYP enzymes. For example, cannabis users who carry a variant in CYP2C9 have shown reduced enzyme activity, in an increased exposure to THC (94). On the other hand, there was no major differences found in plasma exposure between CYP2C19 intermediate and ultra-rapid metabolisers when compared to extensive metabolisers (70).

Systematic reviews that have looked at indications such as neuropathic pain, cancer-related pain and its associated symptoms, and rheumatic diseases all call for further research before any conclusions can be made (95). A common limitation of the studies that have been published in this field is the lack of detail with regard to the specific CBD and THC content, and the overall dosing information.

Despite the inconclusive evidence for medicinal cannabis, the two most common indications for which it is prescribed in Australia are chronic non-cancer pain and anxiety (53, 79). Both THC and CBD have distinct proposed MoA in chronic pain and anxiety, with a possibility of synergism and improved safety when administered together (96). Evidence suggests that CBD and THC (and other minor cannabinoids and cannabis constituents) can work synergistically, and that CBD may offset some of the negative, intoxicating side effects of THC (66, 67, 97). The clinical use of cannabis

is further complicated as dosing has been shown to be highly individualised according to the patients' response, as well as tolerance to any AEs. Typically, a low dose is initially prescribed, and the patients given instructions on how and when to increase their dose as appropriate (98). Furthermore, tolerance to the behavioural and psychogenic effects of THC has been observed, which may have clinical implications when prescribed long term (99). A vast number of unapproved cannabis products are available for prescribing, and product selection may depend on prescriber or patient preference, the CBD and/or THC content, and the inclusion of other minor cannabinoids and terpenes (53).

Overall, there has been high uptake of medicinal cannabis products in Australia despite the complexities surrounding clinical evidence and product selection. With medicinal cannabis already implemented and widely used in prescribing practices in Australia, real-world data has become of increased importance to monitor for effectiveness and safety. Importantly, this data can be used to justify and inform clinical trials, which will be crucial in order to have products placed on the ARTG. The two most prominent indications, chronic pain and anxiety conditions, are two key areas in need of therapeutic advancement for which both CBD and THC have shown some promise. Despite frequent prescribing, it generally regarded that the evidence for medicinal cannabis in these indications remains insufficient (53).

1.8. Hypothesis/aim

In this thesis, I aimed to explore current prescribing practices and real-world outcomes of patients using medicinal cannabis for chronic pain and anxiety, and determine demographic, safety, and effectiveness outcomes. Furthermore, I designed clinical

trials from the results obtained from analysing real-world data, to facilitate the collection of essential robust efficacy outcomes.

Chapter two of this thesis reports observational outcomes of the tolerability and effectiveness of medicinal cannabis prescribed to patients with chronic, refractory pain, with a separate analysis on those who reported having arthritis. The AEs reported by these patients and their concomitant medications, cannabis product, and dose are further explored in chapter three. Chapter four presents the design and approval of an ongoing clinical trial to explore the pharmacokinetics of transdermal CBD and PEA, and its efficacy in patients with osteoarthritis. Cannabidiol, and its possible use in aromatase-inhibitor associated musculoskeletal symptoms is thoroughly reviewed in chapter five to form an Investigator's Brochure to supplement the clinical trial protocol designed as part of this thesis in chapter six. Chapter seven reviews whether medicinal cannabis may be effective in anxiety conditions, and chapter eight describes observed effectiveness and tolerability of medicinal cannabis in patients prescribed medicinal cannabis for anxiety. Finally, chapter nine concludes the findings of this thesis and makes suggestions for future works.

CHAPTER TWO

Medicinal Cannabis for Australian Patients with Chronic Refractory Pain including Arthritis

CHAPTER 2: MEDICINAL CANNABIS FOR AUSTRALIAN PATIENTS WITH CHRONIC REFRACTOR PAIN INCLUDING ARTHRITIS

2.1. 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 (n = 296), 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 = 92) 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 AE cohort (n = 718) 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.

2.2. 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 (100). One common cause of chronic pain is arthritis, where the most prevalent type, osteoarthritis, affects more than 240 million people worldwide (101). Overall, approximately one in five people experience chronic pain, where they face long lasting physical, psychological, social, and financial issues. Chronic pain also puts a financial burden onto the wider economy due to factors such as the high cost of disease management and increased absenteeism (102-104).

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 (105). 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) (105). In particular, the AEs of opioid medications, including respiratory depression, tolerance, and dependence limit their long term use (106). Despite this, opioid use remains problematic, and the current opioid epidemic necessitates the search for better and safer alternatives (107). There is some emerging evidence of the effectiveness of medicinal cannabis, particularly in the management of chronic pain that is refractory to conventional treatment (25, 108, 109).

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 (19). The CB_1 receptors, which are predominantly found on central and peripheral neurons, affect cognition, memory, motor function, analgesia, and can cause psychoactive effects (23). 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 (23, 25, 110). 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 (25, 54). 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 (25, 111, 112). While the mechanism through which CBD provides antinociception is not completely understood, it is likely to involve reducing levels of circulating pro-inflammatory cytokines (113, 114).

Although legalised in Australia in 2016 (115), 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 (116). 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.

2.3. Methods

2.3.1. 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 patients signed the Patient Information and Consent Form prior to any study related activities.

2.3.2. 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, e.g. a CBD-dominant product could comprise CBD 10 mg/mL and THC 5 mg/mL. The THC-dominant group includes patients 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. Medicinal cannabis products were used in addition to any conventional treatments prescribed.

2.3.3. Study Population

The study population were patients seeking medicinal cannabis treatment through CA Clinics who were enrolled in CACOS. Thus, patients 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 using questionnaires (Supplementary Document 1), between December 2018 and May 2020, and stored using Research Electronic Data Capture. Figure 1 details the analysis cohort selection process.

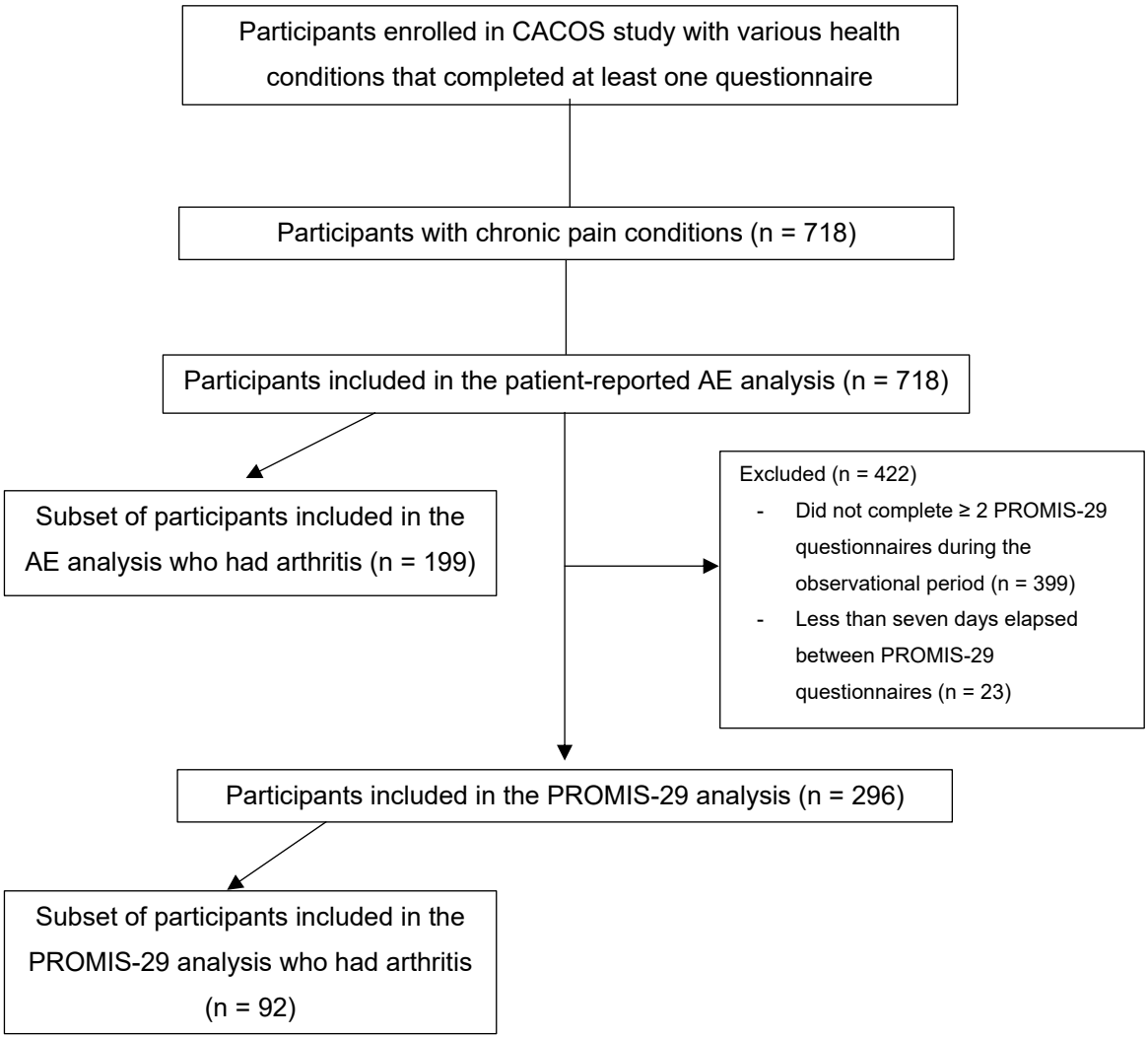

Figure 1. Cohort inclusion flow chart for the AE and PROMIS-29 analyses from the CACOS patients with chronic pain.

2.3.4. Adverse Event (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 patients

before each clinic visit. The patient-reported AEs were categorised according to MedDRA System Organ Classes (SOC) for analysis (117).

2.3.5. Patient Reported Outcomes Measurement Information System (PROMIS) analysis

The 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 (118, 119). It has been used as a primary measure of change in HRQoL (119).

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 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 (119). Pain impact scores were calculated according to the National Institutes of Health Task Force recommendations (120). 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 (120), physical function was 1.9 (120, 121), anxiety was 2.3 (122), depression was 3.0 (122),

fatigue was 2.5 (123), and pain impact score was 3.0 (120). Sleep disturbance and social functioning had no published MCID, so a default score of 2.0 was used (121-123).

2.3.6 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 Analysis of Variance (ANOVA) 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.

2.4. Results

2.4.1 Patient demographics

There were 718 patients 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 patients were eligible to be included in the PROMIS-29 analysis, and 92 of these patients had an arthritis condition (Table 1 and 2). Across each cohort analysed, the most commonly reported chronic pain indications were arthritis, musculoskeletal pain,

neuropathic pain, and fibromyalgia. Further patient demographics including age, sex, pain indication, and the length of the observational period are given in Tables 1 and 2. Patients 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.

Table 1. Cohort demographic data for patients 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	414 (57.7)	182 (61.5)
	Male	304 (42.3)	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)[1]		81.2 (42.3–225.6)	91.1 (42.8–231.4)

[1] 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 patients 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)[1]		110.2 (177.7)	113.1 (55.4–232.1)

[1] 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.

2.4.2 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) (Table 3 – 4, Supplementary Table 1 – 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).

Patients 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.

Patients taking a balanced product also saw significant improvements in multiple PROMIS-29 categories. Overall, for the chronic pain patients, 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 patients, respectively. In the arthritis subset, patients 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).

Patients 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).

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. Patients 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, patients 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 ($p = 0.005$)

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.

PROMIS-29 domain			**Chronic pain**				
			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.

PROMIS-29 domain			**Arthritis subset**				
			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)

2.4.3 Patient-reported adverse events

A total of 1232 AEs were reported across all the medicinal cannabis product categories from a total of 718 patients included in the chronic pain cohort (Table 5). At least one AE was reported by 51% of patients (n = 364). In the arthritis subgroup, 48% (n = 96) of the patients reported at least one AE. The median (Q1–Q3) reported number of AEs over the entire observational period by each patient 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 was dry mouth, somnolence, and fatigue (Table 5, Supplementary Table 3). This was the same in the overall arthritis subset, and in patients taking a CBD-dominant or balanced product. Patients 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, Supplementary 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)

2.5. Discussion

This analysis of the existing CACOS patient 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).

2.5.1 Self-reported adverse events 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 patients 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) (124), 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%) (125). 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.

2.5.2. 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, patients 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 (126). There is preliminary human clinical trial data demonstrating CBD to reduce pro-inflammatory cytokines during a lipopolysaccharide challenge (127). 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 (128). 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 (129).

Patients 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 (130), is relatively consistent with the balanced products in this study. Studies examining the use of nabiximols in pain conditions have produced mixed results (131, 132). 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 (133). 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% (134). Other trials for pain associated with conditions such as spinal cord injury and diabetes have produced negative outcomes (132).

We did not find statistically significant changes in any PROMIS-29 domain reported in patients 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.* on patients with fibromyalgia found that their CBD-dominant product (Bedrolite) 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 (135). 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 (136). 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 (134). 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 (137, 138).

2.5.3 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 (139), 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. Given that medicinal cannabis in this study was prescribed in addition to conventional treatments, it is unknown if any pharmacokinetic or pharmacodynamic factors may have influenced AE reporting. 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.

2.6. Conclusions

Overall, the 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. This analysis indicates that arthritic conditions warrant further exploration with clinical trials. Furthermore, AEs should be studied with regard to concomitant medications and their possible pharmacokinetic and pharmacodynamic interactions with medicinal cannabis.

CHAPTER THREE

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

CHAPTER 3: MEDICINAL CANNABIS FOR PATIENTS WITH CHRONIC NON-CANCER PAIN: ANALYSIS OF SAFETY AND CONCOMITANT MEDICATIONS.

3.1. 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 ($p = 0.036$), and 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.

3.2. 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 (104). Chronic pain originates and extends beyond an initial injury or disease and is recognised as an independent condition of its own accord (140, 141). 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 (105, 142). Medicines commonly used include paracetamol, non-steroidal anti-inflammatory drugs, opioids, antidepressants, gabapentinoids, and benzodiazepines (105). 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 (106).

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 (8, 53). Derived from the *Cannabis sativa* plant, cannabis products contain many different active compounds, including phytocannabinoids, terpenes, and flavonoids (13, 129). 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 (13, 143). 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 (19). Tetrahydrocannabinol is an agonist at both CB_1 and CB_2 where it produces its antinociceptive and intoxicating effects (25, 54). Cannabidiol has a low affinity for CB_1 and CB_2 receptors, but may indirectly interact with them by enhancing the levels of endocannabinoids (31, 144). Overall, CBD is likely to be effective in chronic pain conditions by reducing levels of circulating pro-inflammatory cytokines (113, 114). Cannabis is generally regarded as well tolerated, with CBD having fewer safety issues when compared with THC (129). Both have been implicated in pharmacokinetic and pharmacodynamic interactions; however, the clinical consequences of such are not well established (145, 146).

There is a possible synergistic effect between cannabis and opioids (147, 148), and when administered together patients have been shown to reduce their opioid use (128, 149, 150). There have been multiple mechanisms proposed for the synergism (151) 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 (151-153). However; the safety of prescribing of cannabis with opioids and other analgesics is not well known (129), 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 (154). 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.

3.3. Methods

3.3.1. Study design

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

3.3.2. 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 (155). Questionnaires were provided to each patient enrolled to collect their reported outcomes before each routine clinic visit (Supplementary Document 1). 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.

3.3.3. Patients

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 was collected between December 2018 and May 2020 and stored in the Research Electronic Data Capture (REDCap) clinical database.

3.3.4. Variables and data sources/measurement

3.3.4.1. Medicinal cannabis products

Cannabis products were selected by the prescriber and included all pharmaceutical grade cannabinoid containing products, including CBD, THC, a combination of CBD/THC, and other cannabinoid minors (156). Only oral formulations were included in this analysis. Non-oral formulations (vapourised 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.

3.3.4.2. 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 5th level chemical subgroup of the World Health Organization Anatomical Therapeutic classification system (157). The 20 most prescribed

concomitant medicines were reported. Other concomitant medicines of potential clinical significance were those reported to have CYP450 interactions with cannabis (98).

3.3.4.3. Adverse event reporting

Adverse events 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).

3.3.5. 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.

3.3.6. 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.

3.3.7. Statistical methods

The data was 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 $p \leq 0.05$.

3.4. Results

3.4.1. 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).

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

Demographic		**Number of patients (n = 275)**
Age, years, mean (Standard Deviation 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.

3.4.2. 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 ten 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 the fatigue (p = 0.048; RR = 3.612, CI: 0.924–14.127) when compared with those who were on fewer medications.

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 reuptake inhibitors	52 (19)
10	Anti-emetics	48 (18)
11	Tricyclic antidepressants	45 (16)
12	Statins	44 16)
13	Selective serotonin reuptake 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)

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).

3.4.3. 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 5). 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).

Table 3. Comparison of incidence of AEs that occurred before the second clinic^ visit depending if (yes/no) patients were co-prescribed a gabapentinoid and tricyclic antidepressant.

		Total	**Gabapentinoids** (n = 99)				**Tricyclic antidepressants** (n = 45)			
MedDRA system organ class		n=275	Yes (n=99)	No (n=176)	p^^	Relative risk (RR) (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)
Gastro-intestinal 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 ≤ 1

Table 4. Comparison of incidence of AEs 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 reuptake inhibitor.

^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 and only statistically significant variables are reported.
^^^Relative risk not applicable if n ≤ 1.

3.4.4. Comparison of 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) 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).

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

		Cannabinoid product			
MedDRA system organ class		THC containing (n = 123)	CBD-only (n = 152)	p^	RR (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

3.4.5. 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).

Table 6. Summary of logistic regression analyses for whether CBD and THC dose predict whether 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)		
Gastro-intestinal 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.

3.4.6. Multivariate analyses of key adverse events

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 6).

3.5. 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 generalisability 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 (158).

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 (159); 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 (129, 160).

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 patients taking nabiximols, that 51.0% (n = 408) of patients were taking 10 or more other medications (133), demonstrating a trend of polypharmacy in chronic pain cohorts seeking cannabis. Although in many instances polypharmacy is clinically necessary to treat patients with co-morbidities, 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 (161). 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 (129, 160).

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

(154, 162). 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 (98, 163). Cannabis produces intoxicating effects such as sedation and psychomotor impairment which may potentiate, or be potentiated by, other CNS depressants (163). Our study showed no increased incidence of AEs with concomitant opioids, benzodiazepines, or SNRIs. Opioids were the most common concomitant medication, 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 (164, 165), and sedation and anxiety are reported with tricyclic antidepressants (166).

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 (129). Cannabis exerts psychoactive and intoxicating effects through activation of the CB_1 receptors by THC in the CNS (54). An intoxicating dose of THC has been reported to be 10–20 mg (129), 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. Cannabidiol's lower affinity for the CB_1 receptors means it is less likely to produce

intoxicating effects, as seen in our findings (167). 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 (145, 146). 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 (69, 76, 129, 168-170). Tetrahydrocannabinol is less associated with drug interactions compared with CBD; however, it is still metabolised by, and can inhibit, CYP450 enzymes (171, 172). 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 (173), and polypharmacy in a majority of our chronic pain cohort, clinical pharmacokinetic studies are needed to guide prescribers on important drug-drug interactions.

3.5.1 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. Alternate routes of administration, such as transdermal or sublingual, should be considered in future studies as this may reduce pharmacokinetic interactions by avoiding first pass metabolism.

3.6. Conclusions

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.

CHAPTER FOUR

A protocol for a phase II pilot study to determine the pharmacokinetics, safety, and optimal dose of CBD and PEA applied via the transdermal route to humans

This study has received ethics approval from Western Sydney Local Health District Human Research Ethics Committee (Ref: 2021/ETH12168), and has been registered (Ref: ACTRN12622000723785).

CHAPTER 4: A PROTOCOL FOR A PHASE II PILOT STUDY TO DETERMINE THE PHARMACOKINETICS, SAFETY, AND OPTIMAL DOSE OF CBD AND PEA APPLIED VIA THE TRANSDERMAL ROUTE TO HUMANS.

4.1. Abstract

Background. Osteoarthritis (OA) is a chronic joint condition with pharmacological treatments often limited by their safety and efficacy. Cannabidiol (CBD) and palmitoylethanolamide (PEA) both have shown some efficacy in preclinical and clinical studies. Limited by their low bioavailability and first pass metabolism, transdermal application of CBD and PEA is an alternate route that may result in systemic absorption. In this study, we aim to determine the pharmacokinetics, safety, optimal dose, and efficacy of transdermal creams containing CBD and PEA.

Methods. This study will be completed in two stages. Stage one will be an open label, single ascending dose study where a maximum of 30 participants will be enrolled in up to five dose escalation cohorts. A starting dose of 62.5 mg CBD or PEA will be applied to participants, and blood samples will be taken to measure plasma CBD and PEA concentrations over time. The dose will be escalated until the target plasma concentration is achieved. Stage two will be a randomised, double-blind, placebo-controlled, three-arm cross-over study to examine the efficacy and tolerability of CBD and PEA in OA pain. Seventy-two participants assigned to six cohorts will apply each treatment for four weeks, and changes in OA pain and other quality-of-life measures will be compared.

Conclusion. There is a need to expand our current knowledge on alternate delivery routes of CBD and PEA. This study will provide further understanding into the absorption of CBD and PEA through the skin and their efficacy for treating OA pain.

4.2. Background

Osteoarthritis (OA) is one of the most prevalent chronic joint conditions in the world and its incidence is increasing, with 10% of people over the age of 60 estimated to be affected (174-176). The prevalence of OA differs depending on which joint is affected, with knee OA being the most common, followed by hand OA and then hip OA (175). Pathologic mechanisms also differ, with hand OA, associated with systemic inflammation, whereas knee and hip OA have been linked to injuries and excessive joint load (176).

Although OA is commonly referred to as a degenerative disease, it is now understood that the pathogenesis of OA involves inflammatory, mechanical, and metabolic factors which lead to damage of the synovial joint. These processes result in an imbalance between the repair and destruction of tissues in the joint (175). Pain is the dominant symptom affecting people with OA, alongside other symptoms including morning stiffness, joint instability, swelling, crepitus and muscle weakness, and fatigue (175, 177). Pain signals can arise from peripheral nociceptive pathways, which become increasingly sensitised from the ongoing joint inflammation and structural changes associated with OA (178). Pain signals can also occur through neuropathic pain pathways, and central pain mechanisms (179, 180).

The treatment of OA is primarily aimed at improving symptoms of affected joints (175). Non-pharmacological options are encouraged as first line treatments, such as exercise, weight loss, and assistive devices (i.e. walking canes and braces) (175, 181).

Analgesics are often used in OA; however, there are often limitations regarding effectiveness and safety. Paracetamol and non-steroidal anti-inflammatories (NSAIDs) are the two most common pharmacological methods recommended for OA (175).

Only discovered in the late 20th century, the endocannabinoid system is a complex and widespread neuromodulatory pathway, with potential clinical applications yet to be completely recognised (19, 20). The endocannabinoid system includes the endocannabinoid type 1 (CB_1) and type 2 (CB_2) receptors, their endogenous ligands anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes that synthesise, facilitate cellular uptake, and metabolise these ligands (19, 20). The endocannabinoid system was discovered during research into the constituents and actions of cannabis (15).

Cannabis consists of cannabinoids, terpenes, and flavonoids which all work synergistically to provide a wide range of effects. The two main constituents of cannabis are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) (14). These both have different actions in the body, with CBD being non-psychoactive and THC producing the well-known “high” effects of cannabis (25, 54). Although CBD has some action at the CB_1 and CB_2 receptors, its main mechanism lies independently of these receptors, acting on targets such as transient receptor potential vanilloid (TRPV) and serotonin 5HT1a receptors to produce effects such as reduced pain, inflammation and anxiolysis (167). These anti-inflammatory effects, with the added benefit of being non-psychoactive, makes CBD a promising emerging therapy for various inflammatory and painful chronic pain conditions.

Palmitoylethanolamide (PEA) is an endogenous compound in the human body, and found in foods such as egg yolks and peanuts (182). It is a fatty acid amide that is produced and required in the lipid bilayer of all tissues of the human body. Structurally

analogous to the endocannabinoid AEA, PEA acts locally in tissues and is thought to maintain homeostasis in response to cellular injury. From this, PEA has been shown to exhibit anti-inflammatory and immunomodulatory effects mediated through receptors such as TRPV channels, peroxisome proliferator-activated receptor- α, and G-Protein coupled receptor 55 (183). In addition, PEA has indirect action at the CB_1 and CB_2 receptors by inhibiting and preventing further break-down of AEA (182).

Despite some good preclinical results and the endocannabinoid system identified as an important therapeutic target (184-186), there is yet to be strong evidence shown for the use of CBD for OA in humans (135, 187-189). Limitations and differences reported in these studies include the addition of other cannabinoids, terpenes, or flavonoids into the formulations, possible sub-therapeutic dosing, a low number of participants, and a short duration of dosing (190). Cannabidiol is also known to be an inducer and inhibitor of various Cytochrome P450 enzymes, and possible drug-drug interactions have been identified with many commonly used anti-rheumatic medications, such as opioids, corticosteroids, disease modifying agents, and antidepressants (191). Transdermal administration of CBD has been proposed to overcome its significant first-pass metabolism (192), and has been studied in a rat model of arthritis (193). Palmitoylethanolamide has shown some preliminary effects in randomised controlled trials to reduce pain and inflammation associated with OA in humans (194-196); however, bioavailability remains a challenge due its lipophilic and large molecular size (197).

It is well accepted that the transdermal application of compounds can avoid the first pass-metabolism and improve bioavailability, and topical preparations of CBD and PEA have been shown to be well-tolerated (198).

4.2.1 Objectives/hypotheses

We propose to determine the pharmacokinetics, safety, optimal dose, and efficacy of CBD and PEA as transdermal preparations. We hypothesise that transdermal application of preparations containing these compounds will result in adequate plasma concentrations shown in preclinical studies to be effective for OA. Using the optimal dose found in the pharmacokinetic studies, we will determine if CBD and PEA applied topically are more effective than placebo in reducing pain, and if CBD and PEA are as tolerable as placebo.

4.3. Methods

4.3.1. Study design

This will be a two-stage phase IIa single site clinical trial conducted in Australia. The first stage will be an open-label, parallel-group, single ascending dose study. The second stage will be a randomised, placebo-controlled double-blind cross-over study of tolerability and efficacy.

4.3.2. Participants

For stage one, eligible participants will be healthy volunteers' adults over the age of 18, or people with OA pain. For stage two, eligible participants will have OA who experience pain. Diagnosis of OA will be defined by X-ray evidence of joint damage; age 30–90; disease duration of two years or more; and continued pain in any or more of the knee, hip, hands, or lower lumbar spine joints, despite oral medications. Participants who are taking OA medication or are treatment naïve will be eligible and the investigational product will be used in addition to any current treatments. Other inclusion criteria are: no previous use of oral or smoked cannabinoids for pain

management; able to complete a questionnaire; and are able to attend outpatient clinic at monitoring and follow-up time points. Participants will be excluded if they have a history of psychiatric disorders; history of drug dependency; known sensitivity to cannabinoid agents; history of epilepsy; participant pain explained by fibromyalgia; recurrent or recent malignancy; pregnancy or breastfeeding; change of pain medication in the preceding four weeks; or severe renal or liver dysfunction (participant excluded if there is an elevation of baseline liver enzymes); prior or current cannabis use; or current use of valproate, clobazam, topiramate, and/or rufinamide.

4.3.3. Study settings

This study will take place at the Rheumatology Department of Westmead Hospital, Australia in 2022 and 2023. This protocol has received ethics approval from Western Sydney Local Health District Human Research Ethics Committee (Ref: 2021/ETH12168), and the trial has been registered (Ref: ACTRN12622000723785).

4.3.4. Screening, recruitment, and consent

Participants will be identified from outpatient clinics at Westmead Hospital; patients waiting to have joint replacement surgery; members of arthritis NSW Foundation (5,000 members), and local newspaper advertisements. A clinical trials nurse coordinator (CNC) will provide study information, obtain informed consent, and conduct a medical history and physical exam to ensure suitability and safety. The CNC will be responsible for liaising with the clinical lead to relay clinical and safety database updates; blood and urine sample collection; hospital lab test ordering; and completion of all study pro-forma with safety and clinical data. The CNC, after having been notified of identified

participants, will then invite the potential participants, supplying study information sheets, either face-to-face at their next scheduled appointment or by mail.

4.3.5. Randomisation

For the stage one open label study, participants will be randomised upon enrolment into either the CBD or PEA group at a ratio of 1:1 by the CNC. For stage two, eligible participants will be randomised into six groups by a member of staff not involved with the study activities. Randomisation will be double-blinded using freeware Sealed Envelope (https://www.sealedenvelope.com, London, UK).

4.3.6. Interventions

Stage 1. Six participants will be enrolled and assigned to either the CBD or PEA group by the CNC. The starting dose of 62.5mg CBD or PEA will be applied to the participant's forearm. Blood will be drawn at the following time points; 0, 1, 2, 4, 8 hr. A sixth blood level will be taken at 24 hr to check hepatic and renal function. Adverse events will be reported to the CNC and documented into the study file. The blood samples will be analysed to determine CBD and PEA plasma concentrations. If the target plasma concentrations are not reached, six new participants will be enrolled for the next dose escalation, where the dose of CBD and PEA will be doubled to 125 mg. The same dose escalation strategy will be repeated on newly recruited participants until the target plasma concentration is reached. Dose escalations will be capped at a total of 5 escalations, to a maximum of 1000 mg CBD or PEA applied to the skin.

Stage 2. Eligible participants will be randomised into six groups by a member of staff not involved with study activities. Randomisation will be double-blind using freeware

Sealed Envelope. In period one, groups one and two will receive CBD, groups three and four will receive placebo, and groups five and six will receive PEA for eight weeks. After this period, there will be a washout period of one week. Then for period two each group will receive their next assigned cream for eight weeks, then there will be another one week wash out. Participants will then receive their final cream for period three for eight weeks (Table 1). Application of the cream will be daily except in the wash out periods. The creams will be sourced from Canngea Pty Ltd (Sydney, NSW, Australia) and provided to participants in jars fitted with metered dose pumps. Each pump of cream will contain a specified quantity of cream at a dose informed by the stage one data.

Table 1. Treatment assignments for the six cohorts (n = 10) in the stage two cross-over study with three 8-week treatment periods and two one-week washout periods.

Group	**1**	**2**	**3**	**4**	**5**	**6**
Period 1	CBD	CBD	Placebo	Placebo	PEA	PEA
Washout 1						
Period 2	PEA	Placebo	CBD	PEA	CBD	Placebo
Washout 2						
Period 3	Placebo	PEA	PEA	CBD	Placebo	CBD

Clinical data from the Visual Analogue Scale (VAS), Western Ontario and McMaster Universities Arthritis Index (WOMAC) score, and adverse events, as well as laboratory samples will be collected for each participant at baseline and at weeks 4, 8, 10, 14 and 18 after trial commencement (Table 2). Participants will be followed up every two weeks for four weeks after exiting the trial, with continuing assay of drug metabolites.

Table 2. Summary of study assessments for the stage two cross-over study.

Study Assessments	Screening	Treatment Period											Follow up Period	
Visit	**1**	**2**	**3**	**4**	**N/A**	**5**	**6**	**7**	**N/A**	**8**	**9**	**10**	**11**	**12**
Week	**-1**	**0**	**4**	**8**	**9**	**10**	**14**	**18**	**19**	**20**	**24**	**28**	**30**	**32**
Informed Consent	X				**WASHOUT**				**WASHOUT**					
Inclusion/exclusion criteria	X													
Medical History, including prior medication history	X													
Physical Examination	X	X		X		X		X		X		X	X	X
Height and Weight for BMI	X													
Vital Signs	X	X	X	X		X	X	X		X	X	X	X	X
Laboratory sample collection*	X		X	X		X	X	X		X	X	X	X	X
Randomisation		X												
X-Ray**	X													
Questionnaires														
WOMAC	X	X	X	X		X	X	X		X	X	X	X	X
VAS	X	X	X	X		X	X	X		X	X	X	X	X
EQ-5D-5L		X		X		X		X		X		X		
Adverse Events		X	X	X		X	X	X		X		X	X	X
Concomitant Medications	X		X	X		X	X	X		X		X	X	X

*Clinical chemistry, haematology

** X-ray of the joint for osteoarthritis diagnosis and staging. Accepting X-rays reports from up to one year prior to screening, otherwise, an x-ray will be ordered

CBD and PEA dose justification. In published research, rats (260-280 g body weight) with induced arthritis were applied with CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day), and were studied for efficacy, safety, and plasma CBD concentrations. For the first three dose levels there was a linear relationship between dosing and CBD plasma concentration. Dose dependent improvements in pain and inflammatory markers were also observed, where 6.2 and 62.3 mg/day were concluded to be effective doses (193). For an average 270 g rat, the doses of 6.2 and 62.3 mg/day produced plasma concentrations of 33.3 ng/mL and 1626.9 ng/mL, respectively.

In healthy humans, plasma concentrations of up to 782 ng/mL were well tolerated after a single 6,000 mg oral dose of CBD. Plasma concentrations of up to 541.2 ng/mL were also well tolerated after CBD at a dose of 1,500 mg given orally to healthy participants twice daily for seven days (199).

From the known pharmacokinetic safety data of CBD in humans, and the preclinical rat study showing safety and efficacy and linear pharmacokinetics up to 6.2 mg/day, we propose a target therapeutic plasma concentration in our study to be 33.3 ng/mL.

To achieve this dose, the human equivalent dose (HED) will be calculated from 6.2 mg/day, which was calculated using the following equation (200):

HED (mg/kg) = (Animal no-observed-adverse event level (NOAEL) mg/kg) × $(Weight_{animal}\ [kg]/Weight_{human}\ [kg])^{(1-0.67)}$. This gave a lower limit of 257 mg/day and an upper limit of 2568 mg/day for a 70 kg participant. The calculated HED has not been adjusted by the safety factor of 10 as this is not a first in human study. The starting dose has been selected conservatively, below the HED derived from preclinical studies, at 62.5 mg.

For PEA, a 300 mg single oral capsule dose in humans reached 23 pmol/mL (10,235.87 ng/mL) after two hours, accompanied by increases in 2-AG, which reduced pain and inflammation (201). As this study demonstrated increased 2-AG biomarkers at approximately 10,000 ng/mL, we propose this to be our target therapeutic plasma concentration. There is little data on transdermal PEA pharmacokinetics, so a transdermal equivalent dose was unable to be calculated. Given the favourable safety profile of topical PEA in humans (198, 202-204), the same dose of 62.5 mg was selected for PEA.

Therefore, the starting dose of CBD and PEA in stage one will be 62.5 mg, and the target plasma concentrations will be 33 ng/mL and 10,000 ng/mL, respectively. The dose that will be used in the stage two cross-over study will be decided by the investigators based on the data of stage one.

CBD and PEA topical formulation. Topical formulations of CBD and PEA will be obtained from Canngea Pty Ltd (Sydney, NSW, Australia). The CBD or PEA will be dissolved in a topical cream resulting in a 60 mg/mL concentration. The topical cream base will contain the following ingredients: water, cetearyl alcohol (and) polysorbate 60, prunus amygdalus dulcis (sweet almond) oil, simmondsia chinensis (jojoba) seed oil, dimethyl sulfoxide, butyrospermum parkii (shea) butter, glycerin, stearic acid, tocopheryl acetate, phenoxyethanol (and) ethylhexylglycerin.

Blood sampling. Blood samples (10 mL) will be taken through an indwelling cannula from the forearm at $t = 0$ (before cream application), 1, 2, 4, 8 and 24 h after administration. Blood will be collected in lithium heparin tubes and centrifuged immediately (1900 g, 10 min, at 15 °C). Plasma will be separated and stored in aliquot

tubes at −80 °C until analysis. Liver function studies, full blood count and electrolytes, urea and creatine will be performed using the blood sample taken at 24 h of cream application.

Analysis of CBD and PEA concentration in blood samples. Blood samples collected at the 0, 1, 2, 4, 8 hours will be analysed at the School of Pharmacy at the University of Sydney (NSW, Australia) using LC-MS/MS to determine the plasma concentrations of CBD and PEA. LC-MS/MS quantitation of CBD and PEA concentrations will be determined using a C18-reverse phase column and a mobile phase of (A) 10 mM ammonium formate buffer with 0.1% formic acid, and (B) methanol, in the ratio 10:90 (A:B). The sample injection volume will be 10 µL, and an isocratic elution at a flow rate of 750 µL/min for 13 min. Drug detection will be undertaken in positive electrospray ionisation mode for parent ions at 314 m/z for CBD (retention time 3.5 min), with daughter ions at 123, 193, and 259 m/z and a parent ion at 300 m/z for PEA (retention time 5.4 min), with a daughter ion at 62 m/z.

Data collection and clinical measurements (stage two). Participants will have their history taken at the initial interview, then will undergo physical examination and recording of vital signs and baseline information. Their pain will be measured by VAS (0–10) and WOMAC (patient-based questionnaire). Measurements for the secondary outcomes will include patient-perceived improvement (EQ-5D-5L tool) and adverse events. Other measurements explored will be clinician assessment of joint swelling and tenderness, health assessment questionnaire, mental health questionnaire, and patient assessment of disease activity.

Routine blood analysis will include measurement of electrolyte, urea, and creatinine levels; full blood count; liver function tests (aspartate transaminase, alanine transaminase, alkaline phosphatase, and bilirubin); C-reactive protein; and erythrocyte sedimentation rate. These will be performed at the initial visit, mid-study, and at the end of the study. Electrocardiogram will be performed at the initial appointment.

4.3.7. Outcomes

The primary endpoint of stage one is to determine the pharmacokinetics, safety, and optimal dose of CBD and PEA applied via the transdermal route. Dose escalations will be performed until the target plasma concentration of CBD and PEA are reached, which is 33.3 ng/mL and 10,000 ng/mL, respectively. Adverse events recorded by the CNC in the electronic medical records will be reported.

The primary end point for stage two is to determine the efficacy of CBD and PEA in reducing pain scores associated with OA as a proof-of-concept study to facilitate the design and follow on of more comprehensive clinical trials. Secondary endpoints are to assess the efficacy of CBD and PEA in improving quality of life outcomes in patients with OA, and to assess the treatment emergent adverse events and display them in the form of listings, frequencies, summary statistics, graphs, and statistical analyses where appropriate.

4.3.8. Statistical analysis plan

Sample size. In stage one, six participants will be enrolled into each cohort, three assigned to CBD, and three assigned to PEA. A total of five cohorts may be recruited as there are five possible dose escalations, depending on the pharmacokinetic results. Therefore, the sample size of stage one can accumulate up to 30 participants.

For stage two, the required sample size has been calculated with the assumptions of no period effect and no other period by treatment interaction. The proposed study design will provide an estimate based on 4n subjects for each of the three pairwise differences in WOMAC scores, namely (CBD-PEA), (CBD-placebo) and (PEA-placebo). Sample size estimates which achieve 80% power of detecting a specified within-subject difference have been calculated. Bonferroni-correction has been applied to maintain an overall 5% level of significance (with paired T-Tests). For a mean difference of three, standard deviation (SD) (within subject difference) = 10 for each group. (Total n = 60). Then, accounting for a 20% attrition we will have to recruit extra people for a total of 72 subjects.

Stage one outcomes. For stage one, the CBD and PEA concentration data will be used to calculate pharmacokinetic parameters, including: Area Under the Curve $(AUC)_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, K_{el}, $T_{1/2}$, and clearance (CL). Descriptive statistics will be provided for AEs.

Stage two outcomes. WOMAC and VAS. The primary outcomes will be calculated from pairwise differences in WOMAC and VAS scores, namely (CBD-PEA), (CBD-placebo) and (PEA-placebo). Comparisons will be made from treatment commencement, week two, and treatment conclusion (week four).

EQ-5D-5L. Responses from the EQ-5D-5L questionnaire will be converted to an index value. Pairwise differences between the start and finish of each treatment period (CBD, PEA, and placebo) will be compared to assess for quality-of-life outcomes. Additionally, the EQ-5D-5L scores will be applied to standardised weighted value sets

to calculate quality of adjusted life years. This can then be further applied to calculations of the cost-utility analysis of the CBD and PEA.

Other measures. Descriptive statistics will be provided for demographic and exploratory outcomes. Analysis of variance (ANOVA) or non-parametric test equivalents will be used to examine differences in the efficacy of CBD, PEA, and placebo. Logistic regressions will be used to explore relationships between efficacy and adverse event outcomes and potential confounding variables that are identified during the study.

4.4. Conclusion

Outlined is a two-stage study protocol for a dose-finding pharmacokinetic study for transdermal application of CBD and PEA, and a double-blind placebo controlled cross-over efficacy study. Oral administration can lead to limitations in safety and efficacy including gastrointestinal side effects like nausea, vomiting and diarrhea, and poor pharmacokinetics including low bioavailability, inconsistent plasma levels and significant first-pass liver metabolism. By using a transdermal dosage formulation, these effects will be minimised.

There is a need to expand our current knowledge on alternate means of delivery of CBD and PEA. This study will provide a novel understanding into the absorption of CBD and PEA through the skin and the level of systemic exposure that results. The results of stage one will be used to inform the stage two randomised controlled clinical trial to test the efficacy of these transdermal formulations to reduce the pain and inflammation associated with OA. Given the broad possible anti-inflammatory actions

of CBD, future studies should consider investigating the potential of CBD in other inflammatory arthralgia conditions.

This study protocol has been approved by Western Sydney Local Health District Human Research Ethics Committee (Ref: 2021/ETH12168), and been registered on the Australian clinical trials database (Ref: ACTRN12622000723785).

CHAPTER FIVE

Cannabidiol for aromatase inhibitor associated side effects: Investigator's Brochure

CHAPTER 5: CANNABIDIOL FOR AROMATASE INHIBITOR ASSOCIATED SIDE EFFECTS: INVESTIGATOR'S BROCHURE.

5.1. Abstract

Background: The use of aromatase inhibitors has been associated with musculoskeletal symptoms such as arthralgia and myalgia. The upregulation of cytokines and inflammatory pathways has been proposed as a possible mechanism by which these symptoms occur. The effectiveness of medicinal cannabis in various immunological and inflammatory conditions is an emerging area, and the main non-psychoactive component of cannabis, cannabidiol (CBD), has been demonstrated to exhibit anti-inflammatory properties. Cannabidiol has been proposed as an investigational product in treating aromatase-inhibitor associated musculoskeletal symptoms (AIMSS). This paper aims to provide a comprehensive review of CBD and AIMSS in the format of an Investigator's Brochure which will be used to inform a clinical trial protocol.

Findings: The investigational product will contain 75 mg CBD in a hard gelatine capsule to be given twice daily. Cannabidiol has vast pharmacological properties, acting both within, and outside, the endocannabinoid system. Some key inflammatory mediators associated with AIMSS that CBD has shown to modulate in preclinical studies are eotaxin, interleukin (IL)1- β, IL-6, monocyte chemoattractant protein-1, and tumour necrosis factor-α. The non-clinical and clinical pharmacokinetics of CBD has been well reported in the literature and product information for Epidyolex®, and in a safety review conducted by the Therapeutic Goods Administration (TGA). The TGA concluded that at doses of 150 mg/day CBD has an acceptable safety and tolerability profile. The TGA identified that the main risks are the inhibition of cytochrome P450

and drug efflux transporters, and potential pharmacodynamic interactions of additive adverse events with other CNS depressants.

Conclusion: The Investigator's Brochure summarises the current pre-clinical, clinical, and safety evidence of CBD. This information will support a clinical trial protocol examining the use of CBD in patients experiencing aromatase inhibitor associated arthralgia

5.2. Introduction

The investigational medicinal product used in this clinical trial is called cannabidiol broad spectrum extract (CBD extract). The product is derived from the *cannabis sativa* plant, which contains cannabinoids, flavonoids, and terpenes. The active pharmaceutical ingredient (API) within this product that is being investigated is cannabidiol, a phytocannabinoid that has been demonstrated to exhibit anti-inflammatory properties. We hypothesize that the CBD extract will reduce joint pains associated with aromatase inhibitor (AI) use in women undergoing treatment for breast cancer.

The aetiology of aromatase-inhibitor associated musculoskeletal symptoms (AIMSS) has been attributed to a number of potential factors; pharmacogenetics, decline of oestrogen synthesis, vitamin D levels, and the upregulation of cytokines and inflammatory pathways (205). The decline in the synthesis of oestrogen has also been associated with structural changes in joints, increased inflammatory cascades, and the reduction in oestrogens anti-nociceptive properties (206, 207). Studies suggest that oestrogen deficiency may induce an increased production of inflammatory cytokines such as interleukin (IL)-1β and Tumour Necrosis Factor (TNF)-α (208). The decline in oestrogen synthesis from AI therapy has demonstrated increased levels of IL-6 which may be due to the inhibitory activity of aromatase on the expression of this cytokine

(209). The involvement of inflammatory processes in AIMSS has also been shown in clinical settings, such as ultrasound and magnetic resonance imaging of the affected joints (210). In addition, arthralgia symptoms in AIMSS were associated with increased serum concentrations of C-reactive protein (CRP), eotaxin, monocyte chemoattractant protein-1 (MCP-1), and vitamin D binding protein (VDBP) in human trials (207).

Our research approach is to utilise the anti-inflammatory properties of CBD, as outlined in this Investigator's Brochure, to target the inflammatory processes that are implicated in AIMSS.

5.3. Physical, chemical, and pharmaceutical properties and formulation

The extract contains the phytocannabinoid cannabidiol (CBD). Other excipients in the product may include flavonoids, terpenes, and small concentrations of other cannabinoids. The API in this product is cannabidiol (> 98%) 75 mg in hard gelatine capsules.

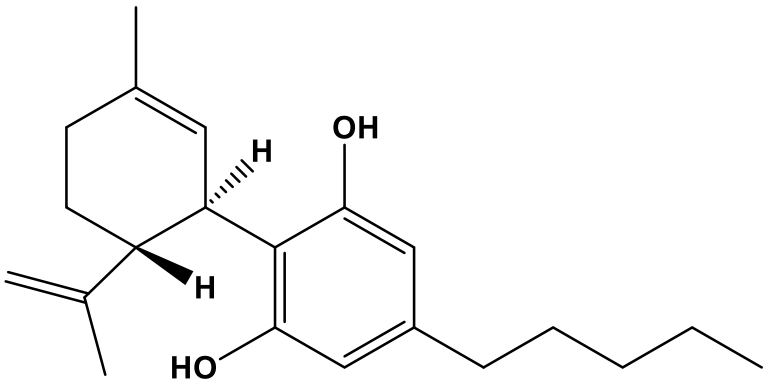

Figure 1. The chemical structure of CBD.

The CBD extract is a plant derived oil encapsulated in hard gelatine capsules that needs to be stored in the original container provided and kept below 25 °C.

Phytocannabinoids are physiologically active substances found within the *cannabis sativa* plant. Cannabinoids are substances that have the typical C_{21}

terpenophenolic skeleton, as well as their derivatives and transformation products (211). There have been at least 104 phytocannabinoids isolated from *cannabis sativa* (211), and the investigational medicinal product in this study contains CBD, which belongs to the cannabinoid-type family of phytocannabinoids found in the plant. There are also hundreds of non-cannabinoid constituents found in cannabis belonging to eight different chemical classes; flavonoids, steroids, phenanthrenes, fatty acids, spiroindans, nitrogenous compounds, xanthones, and biphenyls (211).

5.4. Non-clinical studies

5.4.1. Non-clinical pharmacology

Cannabidiol has been shown to exert its pharmacological actions through targets both within, and outside the endocannabinoid system. The main components of the endocannabinoid system are the cannabinoid receptor type 1 (CB_1), cannabinoid receptor type 2 (CB_2), their endogenous ligands, also referred to as endocannabinoids, anandamide (AEA) and 2-arachindonoylglycerol (2-AG), as well as the enzymes that synthesize, facilitate cellular uptake, and metabolise the endocannabinoids (19, 20). In addition to the CB_1 and CB_2 receptors, endocannabinoids have also been found to target many other receptors, resulting in the widespread and complex function of the endocannabinoid system, believed to be a major neurological and immunological regulatory system contributing to our overall homeostasis (19, 20).

The endocannabinoid AEA is a hydrophobic molecule that readily passes through plasma membranes and is quickly broken down (31). Anandamide itself cannot be stored, instead it is stored as its phospholipid precursor, *N*-arachidonoyl phosphatidylethanolamine (NAPE), by the catalysing enzyme *N*-acyltransferase (33). When needed, AEA is synthesised on demand from NAPE by the enzyme

phospholipase D, where it is now available to bind with the endocannabinoid receptors either within the same cell it was released from, or it is taken to other targets via carrier proteins (32-34). Anandamide signalling is stopped when it is hydrolysed by fatty acid amide hydrolase (FAAH), the main enzyme that regulates anandamides' effects (35, 36).

Many animal studies suggest that a key mechanism of action of CBD is increasing available AEA levels by inhibiting FAAH, the enzyme that would otherwise breakdown AEA (212, 213). Other research states that the inhibition of FAAH may be species dependent, and that in humans, the increase in anandamide is likely through CBD binding with AEA's transporting protein called fatty acid binding protein (FABP) (144). Fatty acid binding proteins are intracellular proteins that mediate the transport of AEA to FAAH for enzymatic breakdown. It is speculated that CBD and AEA compete to bind to FARPs, which may account for the increase in circulating levels of AEA when CBD is administered (144). Another suggested mechanism is that CBD may increase the protein tyrosine phosphatase non-receptor type 22 enzyme which catalyses phospho-anandamide to anandamide (214). It is through the increase in AEA that CBD may have CB_1 and CB_2 receptor mediated effects (31).

Predominantly found on central and peripheral neurons, the CB_1 receptors inhibit the release of a range of neurotransmitters resulting in changes to motor function, cognition, and producing psychoactive effects (23). On the other hand, the CB_2 receptors are mostly found on immune cells where they can modulate immune cell migration and the release of cytokines (23, 25, 110). Cannabidiol has been shown to have some CB_1 and CB_2 mediated effects; however its main direct pharmacological actions are elsewhere, including receptor ion channels, enzymes, and cellular uptake processes (167) (Table 1).

Table 1. In vitro targets of CBD that have been reported and their EC_{50} values (167).

Receptor and ion channels	Enzymes	Cellular uptake or other processes
CB1 receptor < 1 μm: Blockade 1-10 μm: Displacement of other cannabinoid	Cytochrome P450 (CYP) 1A1 < 1 μm: Inhibition	Adenosine uptake (Via cultured microglia and macrophages) < 1 μm: Inhibition
CB2 receptor < 1 μm: Blockade 1-10 μm: Displacement of other cannabinoid	CYP1A2 1-10 μm: Inhibition	Calcium uptake into synapses < 1 μm: Inhibition
G-protein coupled receptor (GPR) 55 < 1 μm: Blockade	CYP1B1 1-10 μm: Inhibition	Dopamine uptake into synapses 1-10 μm: Inhibition
5-hydroxytryptamine (5HT) 1a < 1 μm: Potentiation > 10 μm: Activation	CYP2C9 1-10 μm: Inhibition	5HT uptake into synapses 1-10 μm: Inhibition
5HT3A ligand gated ion channel (allosteric modulation) < 1 μm: Blockade	CYP2D6 1-10 μm: Inhibition	y-aminobutyric acid uptake into synapses 1-10 μm: Inhibition
Transient receptor potential (TRP) M8 cation channel < 1 μm: Blockade	CYP3A5 1-10 μm: Inhibition	Anandamide cellular uptake 1-10 μm: Inhibition
TRPA1 cation channel < 1 μm: Activation	Mg^{2+}-ATPase 1-10 μm: Inhibition	P-glycoprotein 1-10 μm: Inhibition
TRPV4 cation channel < 1 μm: Activation	Arylalkylamine *N*-acetyltransferase 1-10 μm: Inhibition	Choline uptake by rat hippocampal homogenates >10 μm: Inhibition
Peroxisome proliferator active receptor (PPAR)y 1-10 μm: Activation	Indoleamine-2,3-dioxygenase 1-10 μm: Inhibition	
Ca_V3 t-type Ca^{2+} voltage gated ion channels 1-10 μm: Inhibition /antagonism	15-lipoxygenase 1-10 μm: Inhibition	
TRPV1 cation channel 1-10 μm: Activation	Phospholipase A_2 1-10 μm: Activation	
TRPV2 cation channel 1-10 μm: Activation	Glutathione peridoxase 1-10 μm: Activation	
TRPV3 cation channel 1-10 μm: Activation	Glutathione reductase 1-10 μm: Activation	
α3 glycine ligand-gated ion channel 1-10 μm: Potentiation	CYP2A6 >10 μm: Inhibition	
GPR18 >10 μm: Activation or blockade	CYP3A4 >10 μm: Inhibition	
μ and δ opioid receptors (allosteric modulation) >10 μm: Blockade	CYP3A7 >10 μm: Inhibition	
α1 and α1β glycine ligand-gated ion channels >10 μm: Potentiation	Fatty acid amide hydrolase >10 μm: Inhibition	
	Cyclooxygenase >10 μm: Inhibition	
	5-lipoxygenase >10 μm: Inhibition	
	Superoxide dismutase >10 μm: Inhibition	
	Catalase >10 μm Inhibition	
	NAD(P)H-quinone reductase >10 μm: Inhibition	
	Progesterone 17α-hydroxylase >10 μm: Inhibition	
	Testosterone 6β-hydrolase >10 μm: Inhibition	

	Testosterone 16 α -hydrolase >10 μm: Inhibition	
	Phosphatases Induction >10 μm: Inhibition	

The extensive list of CBD targets means it has many potential pharmacological uses, most notably perhaps is regarding inflammatory and immunological pathways. It is hypothesized that it is through these immunological and inflammatory pathways that CBD is effective in reducing joint pain (126), and may be of use in reducing the adverse effects associated with aromatase inhibitors. Table 2 lists the identified receptors which mediate the immunomodulatory effects of CBD, adapted from Nichols and Kaplan 2020 (114).

Table 2. Identified receptors which mediate cannabidiol immunomodulatory effects (114).

Receptor	Activity	Immunomodulatory effects	Reference
CB_1	Agonist*	Expressed on B cells, Natural Killer (NK) cells, Cluster of Differentiation (CD)8+ T cells, monocytes, and CD4+T cells.	(212, 215)
CB_2	Agonist*	Expressed on B cells, NK cells, monocytes, neutrophils, and T cells.	(216-218) (215)
Fatty acid amide hydrolase (FAAH)	Inhibition	The inhibition of FAAH** stops the breakdown of anandamide, thereby increasing its availability to exert its actions.	(65, 144, 212-214, 219, 220)
Peroxisome proliferator-activated receptor-gamma (PPAR-γ)	Agonist	Attenuates expression of pro-inflammatory cytokines, and shifts immune cell differentiation toward anti-inflammatory phenotypes.	(221-227)
Transient receptor potential vanilloid 1 (TRPV1)	Agonist	CBD activates and subsequently desensitises TRPV1, a receptor that is involved in nociceptive pain transduction, and immune signalling cascades.	(65, 213, 218, 219, 228-236)
Adenosine A_{2A}	Activation	CBD may enhance endogenous adenosine signalling, facilitating endogenous immunosuppressive pathways.	(237-241)
Serotonin 1a receptor (5-HT1a)	Agonist	Modulation of macrophages and cytokine release.	(216)
G-protein coupled receptor 55 (GPR55)	Antagonist	A pro-nociceptive/inflammatory novel endocannabinoid receptor	(242, 243)

*Other studies have shown that CBD negligible, and possibly weak antagonism at CB_1 and CB_2 receptors (45).
**It has been proposed that in humans, the increase in anandamide levels by administration of CBD is via fatty acid binding proteins, rather than FAAH.

The CB_2 receptors are well-known for their expression on immune cells, however CB_1 receptors also have a role in immune function. Research has shown CB_1 to be expressed on B cells, NK cells, CD8+ T cells, monocytes, and CD4+T cells, and CB_2 receptors to be expressed on B cells, NK cells, monocytes, neutrophils, and T cells. Interaction with CB_2 receptors inhibits the production of cytokines such as TNF- α, IL-6, and IL-8 in human monocytes and macrophages, and TNF- α, IL-2, interferon-γ in activated human peripheral lymphocytes (215). Cannabidiol may have some direct

activity with the CB_1 and CB_2 receptors or may interact with these receptors indirectly through increasing AEA levels; however, other critical receptors have also been identified (Table 2).

5.3.1.1. Peroxisome proliferator-activated receptor- γ (PPAR-γ)

The peroxisome proliferator-activated receptors are a family of ligand gated transcription factors that is overall, responsible for lipid storage and glucose metabolism. The PPAR-γ sub-type has been identified to have a key role in immune responses where activation of the receptor inhibits the expression of pro-inflammatory cytokines, and can shift immune cell differentiation toward anti-inflammatory phenotypes (244). The endocannabinoids AEA and 2-AG, as well as CBD, have all been shown to agonise PPAR-γ, with their effects being reversed by using PPAR-γ antagonists (114).

5.3.1.2. Transient receptor potential vanilloid 1 (TRPV1)

Transient receptor potential vanilloid 1 is a critical receptor through which CBD acts on the inflammatory and pain signalling pathways. Cannabidiol agonises TPRV1, a receptor that when activated, transduces the depolarisation of neurons in nociceptive pathways leading to a pain response, as well as releases pro-inflammatory cytokines such as interleukin (IL)-1 α, IL-6, and tumour necrosis factor-α (TNF)-α. It is speculated that repeated CBD exposure may cause desensitisation of these TRPV1 receptors and reduce pain signalling and the release of pro-inflammatory cytokines (245-247). Additionally, the endocannabinoid AEA has been shown to have a similar action to reduce TRPV1 responsiveness (248). These effects are believed to be particularly prominent in the regulation of pain and immune signalling in the synovial space of

joints, resulting in a promising potential mechanism of action of both CBD and AEA in joint-pain conditions (65).

5.3.1.3. Adenosine A_{2A}

Adenosine A_{2A} receptors are found on nearly all immune cells, and they respond to adenosine that is released from damaged cells in the context of inflammation or tissue injury (249). Activation of adenosine receptors promotes immunosuppressive pathways to reduce tissue injury and inflammation (237, 249). Research has shown that reductions in TNF-α after administration of CBD have been reversed by A_{2A} antagonists, suggesting that this a key receptor in the immunomodulation of CBD, particularly with regard to TNF-α (114).

5.3.1.4. Serotonin 5-HTP1a receptor (5-HTP1a)

Immune cells have been found to express 5-HTP1a receptors (114), and serotonin signalling both in the periphery and central nervous system is believed to play a role in immunomodulation. Serotonin modulation has been shown to effect macrophage function and cytokine secretion (250), and the agonising effects of CBD at the 5-HTP1a is thought to exert anti-inflammatory actions (216).

5.3.1.5. GPR55

The g-protein coupled receptor 55 (GPR55) has been shown to control motility of the gastrointestinal tract, angiogenesis, neuropathic pain, a range of intracellular signalling pathways, and the modulation of inflammatory processes (215). Proposed as a novel cannabinoid receptor, studies suggest that AEA may interact with GPR55 at similar concentrations to CB_1 and CB_2 (242, 251). Research has shown GPR55 to have a pro-

nociceptive role, and that antagonism of this receptor by CBD may reduce nociception and inflammation (252).

As CBD can directly, or indirectly through increasing AEA levels, interact with the receptors that have been listed above, CBD is able to produce a wide range of immunomodulatory actions via various immune cells. As mentioned, CRP, eotaxin, IL1- β, IL-6, MCP-1, TNF- α, and VDMP levels have been shown to be increased in patients with AIMSS. Table 3 lists these inflammatory markers, and whether or not CBD has been shown to attenuate them *in vivo*.

Table 3. Inflammatory processes implicated in AIMSS and pre-clinical evidence for CBD's efficacy

Inflammatory mediators associated with AIMSS	Evidence for CBD?	References
CRP	X	-
Eotaxin	✓	(217)
IL1- β	✓	(225, 253-259)
IL-6	✓	(254, 256, 259)
MCP	✓	(255, 259)
TNF- α	✓	(126, 193, 224, 225, 254-256, 260-267)
VDMP	X	-

The attenuation of inflammatory mediators by CBD is critical in its mechanism of action for inflammatory conditions such as AIMSS; however, studies have also shown that AEA is associated with changes in cytokine levels. The endocannabinoid system may also be implicated in the progression of multiple sclerosis, and there may be benefits of administering cannabinoid agonists (256, 268). UCM707 is a selective anandamide re-uptake inhibitor that increases availability of anandamide. In a murine model of multiple sclerosis, UCM707 resulted in decreased production of TNF- α, IL-B and IL-6,

and highlighted that agents that are able to increase endocannabinoids are of promising therapeutic potential (256). In another multiple sclerosis murine model, researchers examined an agent that inhibits the transportation and inactivation of anandamide, and they found that there was a reduced production of IL-1b (257).

There are extensive pre-clinical animal model studies using CBD that has shown efficacy in modulating the key inflammatory mediators that are also in AIMSS, found in Tables 4–9 (114).

Table 4. In vivo studies that demonstrate efficacy of CBD to attenuate the inflammatory marker eotaxin.

Indication	Subjects			CBD administration			Results	Proposed Mechanism of Action (MOA)	Reference
	Species	Sex	Number of subjects	Dose	Interval	Route			
Allergic asthma	Mice	-	49	5–10 mg/kg	Three times	Intraperitoneal (IP)	Eotaxin	Mediated via CB_1 and CB_2	(217)
Autoimmune hepatitis mice	Mice	Female	6	10–50 mg/kg IV once	Once	IP	Eotaxin	Experiment showed involvement of TRPV1	(231)

Table 5. In vivo studies that demonstrate efficacy of CBD to attenuate the inflammatory marker IL-1β.

Indication	Subjects			CBD administration			Results	Proposed MOA	Reference
	Species	Sex	Number of subjects	Dose	Interval	Route			
Alzheimer's Disease	Mice	-	-	2.5–10 mg/kg/day	7 days	IP	IL-1β	Hypothesized to be mediated by CB2 receptors	(253)
Colitis	Mice	Male	-	1-10mg/kg daily	6 days	IP	IL-1β	-	(258)
Autoimmune endocarditis	Mice	Male	49	10 mg/kg	46 days	IP	IL-1β	Theorised to be via helper and cytotoxic T cell infiltration	(259)
Alcoholic liver disease	Mice	Female	16 - 28	5 or 10 mg/kg	11 days	IP	IL-1β	Reduces expression of M1 macrophage related genes	(255).
Haloperidol induced inflammation	Mice	Male	36 - 40	60 mg/kg twice daily	21 days	IP	IL-1β	Hypothesised to be via agonising PPARy	(225)
Hypoxic-ischaemic brain damage	Piglets	Male	24	1 mg/kg	Once	IV	IL-1β	5-HTP1a involvement	(269)
Inflammatory pain	Rats	Male and female	40	10 mg/kg twice daily	3 days	IP	IL-1β	-	(270)
Periodontitis	Rat	Male	30	5 mg/kg/day	30 days	IP	IL-1β	Hypothesised to be via increasing AEA	(271)
Kidney ischemia/ reperfusion	Rat	Male	-	5 mg/kg	Once	IV	IL-1β	Hypothesised to be via adenosine receptors	(272)

Table 7. In vivo studies that demonstrate efficacy of CBD to attenuate the inflammatory marker IL-6.

Indication	Subjects			CBD administration			Results	Proposed MOA	Reference
	Species	Sex	Number of subjects	Dose	Interval	Route			
Myocardial ischemic reperfusion injury	Mice	Male	50	5 mg/kg/day	Two doses	IP	IL-6	Theorised to be via adenosine receptors	(260)
Autoimmune endocarditis	Mice	Male	49	10 mg/kg	46 days	IP	IL-6	Theorised to be via helper and cytotoxic T cell infiltration	(259)
Autoimmune hepatitis mice	Mice	Female	6	10–50 mg/kg IV once	Once	IP	IL-6	Experiment showed involvement of TRPV1	(231)
Acute lung injury	Mice	Male	36-45	20 mg/kg	Once	IP	IL-6	Experiment showed involvement of adenosine 2A receptor	(240)
Acute pancreatitis	Mice	-	36	0.5 mg/kg	Twice	IP	IL-6	Experiment showed increased GPR55 expression	(273)
Asthma	Rat	Male	21	5 mg/kg	Twice	IP	IL-6	-	(274)
Acute lung injury	Mice	Male	16 - 20	20 and 80 mg/kg	Once	IP	IL-6	Unspecified immunomodulation	(275)
Malaria	Mice	Female	24	30 mg/kg/ day	3–7 days	IP	IL-6		(276)
Inflammatory pain	Mice	Female	-	1 mg and 100 µg topical 1 – 100 µg IP	once	Topical	IL-6	-	(277)
Colitis	Rats	Male	36	1 mg/kg/day	5 days	IP	IL-6	Shown to be through GPR55	(278)

Table 8. In vivo studies that demonstrate efficacy of CBD to attenuate the inflammatory marker MCP-1.

Indication	Subjects			CBD administration			Results	Proposed MOA	Reference
	Species	Sex	Number of subjects	Dose	Interval	Route			
Autoimmune endocarditis	Mice	Male	49	10 mg/kg	46 days	IP	MCP -1	Theorised to be via helper and cytotoxic T cell infiltration	(259)
Alcoholic liver disease	Mice	Female	16 - 28	5 or 10 mg/kg	11 days	IP	MCP-1	Reduces expression of M1 macrophage related genes	(255)
Autoimmune hepatitis mice	Mice	Female	6	10–50mg/kg IV once	Once	IP	MCP-1	Experiment showed involvement of TRPV1	(231)
Acute lung injury	Mice	Male	36-45	20 mg/kg	Once	IP	MCP-1	Experiment showed involvement of adenosine 2A receptor	(240)
Acute lung injury	Mice	Male	16 - 20	20 and 80 mg/kg	Once	IP	MCP-1	Unspecified immunomodulation	(275)

Table 9. In vivo studies that demonstrate efficacy of CBD to attenuate the inflammatory marker TNF-α.

Indication	Subjects			CBD administration			Results	Proposed MOA	Reference
	Species	Sex	Number of subjects	Dose	Interval	Route			
Diabetic cardiomyopathy	Mice	Male	44	1, 10, and 20 mg/kg	Daily for 11 weeks	IP	TNF-α	-	(261)
Hepatic encephalopathy	Mice	Female	50	5 mg/kg	Daily for 4 weeks	IP	TNF-α	Adenosine A2A receptor or 5HTP1a	(262)
Delayed allergic hypersensitivity	Mice	Male	20	1–10 mg/kg	5 days	IP	TNF-α	Attenuation of Type 1 T Helper (Th1) cytokines. Th1/Type 2 T Helper (Th2) balance change	(263)
Inflammatory bowel disease model	Mice	Male	12	10 mg/kg	Two doses	IP	TNF-α	Shown to be associated with PPAR-y	(224)
Liver Ischemia reperfusion injury model	Mice	Male	70 - 120	3 and 10 mg/kg	Once	IP	TNF-α	Suppression of TNF-a release from Kupffer cells	(264)
Sepsis related encephalitis model	Mice	-	27	1 mg/kg and 3 mg/kg	Once	I.V.	TNF-α	Hypothesised general immune-suppression	(265)
Meningitis	Rat	Male	16	2.5 mg – 10 mg/kg	Once and up to 9 days	IP	TNF-α	Hypothesised to be via PPAR	(266)
Osteoarthritis	Rat	Male	35	6.2 – 62 mg/day	4 days	Transdermal	TNF-α	Hypothesised to be via GPR55 or TRPV1	(193)
Cerebral artery occlusion	Rat	Male	5	50–200 ng/rat	5 days	Intra-cerebroventricular	TNF-α	Hypothesised to be via PPARy pathway	(267)
Diabetes	Mice	Female	125	5 mg/kg day	5 times a week	IP	TNF-α	Shift to Th2	(254)
Arthritis	Mice	Male	79	5 mg/kg/day IP 25 mg/kg/day oral	Daily for 10 days	IP and oral	TNF-α	Th1 suppression	(126)
Alcoholic liver disease	Mice	Female	16 - 28	5 or 10 mg/kg	11 days	IP	TNF-α	Reduces expression of M1 macrophage related genes	(255)
Haloperidol induced inflammation	Mice	Male	36 - 40	60 mg/kg twice daily	21 days	IP	TNF-α	Hypothesised to be via agonising PPARy	(225)
Autoimmune hepatitis mice	Mice	Female	6	10–50 mg/kg IV once	Once	IP	TNF-α	Experiment showed involvement of TRPV1	(231)

Acute lung injury	Mice	Male	36-45	20 mg/kg	Once	IP	TNF-α	Experiment showed involvement of adenosine 2A receptor	(240)
Acute pancreatitis	Mice	-	36	0.5 mg/kg	Twice	IP	TNF-α	Experiments showed increased GPR55 expression	(273)
Asthma	Rat	Male	21	5 mg/kg	Twice	IP	TNF-α	-	(274)
Acute lung injury	Mice	Male	16 - 20	20 and 80 mg/kg	Once	IP	TNF-α	Unspecified immunomodulation	(275)
Malaria	Mice	Female	24	30 mg/kg/ day	3 – 7 days	IP	TNF-α		(276)
Inflammatory pain	Rats	Male and female	40	10 mg/kg twice daily	3 days	IP	TNF-α	-	(270)
Inflammatory pain	Mice	Female	60	5 mg/kg	once	IV	TNF-α	-	(279)
Periodontitis	Rat	Male	30	5 mg/kg/day	30 days	IP	TNF-α	Hypothesised to be via increasing AEA	(271)
Kidney ischemia/ reperfusion	Rat	Male	-	5 mg/kg	Once	IV	TNF-α	Hypothesised to be via adenosine receptors	(272)
Inflammatory pain	Mice	Female	-	1 mg and 100 µg topical 1 – 100 µg IP	once	Topical	TNF-α	-	(277)

5.4.2. Non-clinical pharmacokinetics

In vitro studies show that CBD is metabolised by, and can inhibit and induce, various cytochrome P450 (CYP) enzymes.

5.4.2.1. Metabolism of CBD

According to the product information for the medicine Epidyolex®, CBD is a substrate for CYP3A4, CYP2C19, UGT1A7, UGT1A9, and glucuronosyltransferase (UGT) 2B7 (70). Other studies have shown that CBD is also metabolised by CYP1A1, CYP1A2, CYP2C9, CYP2D6, and CYP3A5 (75).

5.4.2.2. Inhibition by CBD

The product information for Epidyolex® states that vitro data suggest CBD is an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A9, and UGT2B7 at clinically relevant concentrations (70, 76, 77, 280, 281). Other studies have also shown CBD to inhibit CYP1A1, CYP1B1, CYP3A4, and CYP3A5 (69, 280). In vitro at clinically relevant concentrations, a metabolite of CBD, 7-carboxy-cannabidiol (7-COOH-CBD), is an inhibitor of UGT1A1, UGT1A4, and UGT1A6. It has also shown to be a P-glycoprotein (P-gp) and multidrug resistance mutation 1 substrate and may also inhibit breast cancer resistance protein, organic anion transporting (OAT) P1B3, and OAT3. It is not yet confirmed whether CBD may inhibit P-gp mediated efflux in the intestines (70).

5.4.2.3. Induction by CBD

Cannabidiol has been shown to induce CYP1A2 and CYP2B6 at clinically relevant concentrations (70). The product information for Epidyolex® states that cannabidiol and metabolites has been shown not to interact with following (70):

Cannabidiol and metabolite 7-OH-CBD: renal/hepatic uptake transporters do ***not*** interact with:

- OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, OATP1B1, and OATP1B3.
- P-gp/MDR1, BCRP, or BSEP at clinically relevant concentrations

Cannabidiol does ***not*** interact with:

- Brain transporter: OATP1A2 and OATP2B1

5.5. Effects in humans

5.5.1. Pharmacokinetics

5.5.1.1. Absorption

Cannabidiol is rapidly absorbed, with a time to maximum plasma concentration of 2.5–5 hours at steady state, which is reached after 2–4 days of twice daily dosing. Taking cannabidiol with a high-fat meal resulted in a 5-fold increase in C_{max} and a 4-fold increase in Area Under the Curve (AUC) (70).

5.5.1.2. Distribution

In vitro studies show that >94% CBD and its phase I metabolites were bound to plasma proteins, with preference to human serum albumin. Apparent volume of distribution was high in healthy volunteers, at 20,963 L to 48,849 L. It was shown to be greater than total body water, which suggests that cannabidiol has a wide distribution in the body (70).

5.5.1.3. Metabolism

Cannabidiol is subject to significant first pass effects. Healthy volunteer studies showed the half-life of cannabidiol in plasma was 56-61 hours after twice daily dosing for 7 days in healthy volunteers. Metabolism of CBD occurs via CYP450 and UGT enzyme pathways. The CYP2C19 and CYP3A4 isoforms are responsible for phase I metabolism, and the UGT1A7, UGT1A9, and UGT2B7 are responsible for phase II conjugation (70). Cannabidiol is also metabolised by CYP1A1, CYP1A2, CYP2C9 and CYP2D6 (98). Healthy volunteer studies did not show major changes in cannabidiol exposure in CYP2C19 intermediate, ultra-rapid, and extensive metabolisers (70).

5.5.1.4. Excretion

Cannabidiol is mostly cleared by metabolism in the liver and gut and then excreted in faeces, and a small proportion is renally cleared. The plasma clearance of cannabidiol following a single 1500 mg dose was found to be 1111 L/h (70).

5.5.2. Bioavailability

Some studies has shown the bioavailability of CBD to be as low as 6% due to significant first pass metabolism; however, this may increase 4-fold when CBD is taken with high-fat foods (71).

5.5.3. Special patient groups

5.5.3.1. Elderly

Pharmacokinetics have not been studied in people over the age of 55 (70).

5.5.3.2. Paediatrics

Pharmacokinetics have not been studied in children under 2 years of age; however, data has been collected in children aged 4–10 years old (282) (Table 2).

5.5.3.3. Renal impairment

No effects on C_{max} or AUC were seen when a single dose of cannabidiol 200 mg was administered to patients with mild, moderate, or severe renal impairment when compared to normal renal function. End stage renal disease was not studied (70).

5.5.3.4. Hepatic impairment

No effects on C_{max} or AUC were seen when a single dose of cannabidiol 200 mg was administered to patient with mild hepatic impairment. Subjects with moderate to severe hepatic impairment were observed to have 2.5- to 5.2-fold higher plasma concentrations of CBD compared to those with normal hepatic function. Cannabidiol should be used with caution in patients with moderate to severe hepatic impairment (70).

Table 10 below lists the original research trials that inform the above data. A systematic review has concluded that there are some discrepancies in the pharmacokinetic data between trials, and further research is needed to understand properties such as half-life and bioavailability between formulation types (72).

Table 10. Summary of trials evaluating pharmacokinetic outcomes of oral CBD in humans.

CBD used	Total n, sex	T 1/2	Absorption			Distribution (Volume distribution) (L/h)	Metabolism	Excretion (plasma clearance) L/h	Bioavailability	Special patient group data?	Reference
			T max (median, range), hrs	C max (mean, SD), ng/mL	AUC_{0-t} (mean, SD)h x ng/mL						
10 mg/kg/day 10 weeks	15, M+F	2-5 days	-	-	-	-	-	-	-	-	(283)
20 mg ONCE, repeated over 5 separate visits	6, M+F	-	2.17 (1-4)	2.05 (0.92)	2.60 (3.45)	-	-	-	-	-	(284)
400 mg + Fentanyl (Over two sessions)	6, M+F	-	Session 1: 3hr	181.2±39.8 ug/L	704±283	-	-	-	-	-	(285)
			Session 2: 1.5hr	114.2±19.5 ug/L	482±314						
CBD 800 mg + fentanyl (over two sessions)	6, M+F	-	Session 1: 3hr	222.1±35.6 ug/L	867±304	-	-	-	-	-	
			Session 2: 4hr	157.1±49.0 ug/L	722±443						
800 mg once	8, M+F		Mean 3 (2 - 6)	77.9	-	-	-	-	-	-	(286)
10 mg sublingual	15, M	2.95 (2.58)	3 (2 – 4)	3.22 (1.28)	9.64 (3.99)	-	-	-	-	-	(287)
5 mg/kg/d	10	-	-	-	241	-	-	-	-	Yes – children included	(282)
10 mg/kg/d	8				722						
20 mg/kg/d	9				963						
1500 mg single dose	6 M+F	terminal 14.43 (36.1)	4.00 (3.00–5.00)	292.4 (87.9)	1517 (78.2)	20,963 (55.3)	-	1111 (67.2)	-	-	(199)
3000 mg single dose	6 M+F	14.39 (14.9)	5.00 (3.00–5.00)	533.0 (35.1)	2669 (36.4)	23,357 (32.9)	-	1121 (30.5)	-	-	

4500 mg single dose	6 M+F	16.61 (18.7)	5.00 (5.00–5.00)	722.1 (52.3)	3215 (50.3)	36,575 (66.8)	-	1445 (52.6)	-	-	
6000 mg single dose	6 M+F	15.42 (29.0)	5.00 (3.00–5.02)	782 (83.0)	3696 (79.9)	36,575 (66.8)	-	1909 (77.3)	-	-	
750 mg BD for 7 days	9 M+F	56.41 (32.6)	3.00 (2.50–5.00)	330.3 (40.8)	1745 (38.4)	-	-		-	-	
1500 mg BD for 7 days	9 M+F	60.54 (20.2)	3.00 (2.00–4.00)	541.2 (53.7)	3236 (44.0)	-	-		-	-	
30 mg single dose (water soluble formulation)	10 M+F	152.35	0.9 hr	2.82 ng/ml	408.11	32,445	-	Ke = 0.011	-	-	(127)
30 mg single dose (lipid soluble formulation)		137.95	1.5 hr	0.65 ng/mL	90.52	63,334	-	Ke = 0.012	-	-	
30 mg as tincture	15 M+F	-	3.29±0.61	2.20±1.88	4.58±3.88	-	-	-	-	-	(288)

5.5.4. Drug interaction studies

Cannabidiol has been shown *in vitro* to affect many common metabolising and transporting targets, so there is a relatively high potential for drug-drug interactions to affect both CBD, and its concomitant medicines (75). There have been some human studies to examine the clinical consequences of these, most of which are in the context of CBD use in combination with anti-epileptic medications in certain seizure disorders.

Stott *et al* conducted a phase I healthy volunteer study examining the effect of CBD on CYP3A4 and CYP2C19. The study consisted of 36 men who were given Sativex® (CBD and THC) in combination with rifampicin (CYP3A4 inducer), ketoconazole (CYP3A4 inhibitor), and omeprazole (CYP2C19 inhibitor). The results showed rifampicin to reduce CBD concentrations by 52%, ketoconazole (CYP3A4 inhibitor) to increase CBD concentrations by 89%, and there was no significant change associated with omeprazole use. These results show consideration should be given when administering CYP3A4 inducers and inhibitors and dose titration and adjustment may be required (289).

Another trial by Geffrey *et al* had 25 total patients with refractory epilepsy, and 13 of whom were on clobazam, an antiepileptic metabolised by CYP3A4, CYP2C19, and CYP2B6. Both CBD and clobazam concentrations were increased by one another, with CBD levels increasing by 70%, and clobazam levels by 60%. This study shows clinically relevant inhibition of various CYP enzymes by CBD, as well as CBD itself falling victim to CYP interactions (290).

Gaston *et al* examined the use of CBD and antiepileptic medications in 39 adults and 42 children and found significantly changed clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine levels. These interactions are believed to have occurred as clobazam is metabolised by CYP2C19, topiramate is metabolised by

CYP2C9 and CYP2C19, and zonisamide is metabolised by CYP3A4. The interaction between CBD and eslicarbazepine and rufinamide is largely unexplained in this study, and it is hypothesised that it may have arisen from an interaction of the antiepileptic drugs to the CBD oil carrier (291).

In addition to the above findings from clinical trial data, there have also been some case reports published concerning CBD and drug-drug interactions. There have been a total of three case reports published that has shown administration of cannabis in patients who are taking warfarin to have increased INR values (168, 292, 293). These case reports were investigated *in vitro* by Yamaori et al., who concluded that CBD, THC, and cannabinol, but not polycyclic aromatic hydrocarbons, cause a direct, concentration-dependent inhibition of CYP2C9, the enzyme that hydroxylates warfarin for excretion (281).

To conclude, the potential for drug-drug interactions should be considered in this study particularly with CYP3A4 and CYP2C19 medicines, and additional monitoring should take place. In the CAIMSS study, women who are on the aromatase inhibitor exemestane have been excluded due to its metabolism by CYP3A4.

5.5.5. Safety

In April 2020, the Australian Therapeutic Goods Administration (TGA) conducted a safety review and concluded that CBD at doses of up to 150 mg/day have an acceptable safety and tolerability profile and are rarely associated with adverse events, leading to the decision to allow CBD 150 mg/day to become a schedule 3 medicine. Their report identified the main risk of CBD use is its inhibition of various CYP and drug efflux transporters, and potential pharmacodynamic interactions of additive adverse events with other CNS depressants.

5.5.6. Withdrawal from clinical trials

A meta-analysis of randomised controlled clinical trials assessing CBD by Chesney *et al* shows withdrawal from trials are dependent on the dose of CBD. High doses of CBD (1400–3000 mg) was associated with 12.9% drop out rate, medium doses (600–1000 mg) was associated with 8.8% drop out, and low doses (20–400 mg) was associated with 4.3% drop out, which was a similar rate to placebo (3.5% drop out) (294).

5.5.7. Summary of serious adverse events

The meta-analysis by Chesney *et al* concluded an increased odds ratio (OR) of pneumonia (OR 5.37, 95% confidence interval (CI): 1.17–24.65) and abnormal liver function tests (OR 11.19, 95% CI: 2.09–60.02), which are evident only in studies of children with epilepsy (294). A majority of participants in the clinical trials assessing CBD for childhood epilepsy were also taking other anti-epileptic medicines, which is likely contributing to the differences in adverse events outcomes (294). Another systematic review assessed serious adverse events related to cannabidiol use in randomised controlled clinical trials, and concluded they are rare and comprise of elevated liver enzymes, convulsions, sedation, lethargy, and upper respiratory tract infections. Elevated liver enzymes were found to be related to concomitant valproate use, and sedation, lethargy, and upper respiratory tract infections are related to concomitant clobazam use (295).

5.5.8. Summary of clinical trials assessing adverse events (AE) of CBD

The meta-analysis by Chesney *et al* has shown the OR for experiencing an AE with CBD is 1.55 (95% CI: 1.03–2.33). Overall, 67.6% of participants who were taking CBD in randomised controlled trials experienced an AE, compared to 54.5% of people

treated with placebo. Importantly, this likelihood differed depending on the clinical treatment group, where studies involving children with epilepsy were more likely to have AEs associated with CBD in comparison to non-childhood epilepsy studies ($p = 0.04$). The dose of CBD was strongly correlated with the likelihood of experiencing an AE ($p = 0.0023$). The meta-analysis overall showed that for all the included RCTs, there was a greater OR for decreased appetite, (OR 3.56, 95% CI: 1.94–6.53), diarrhoea (OR 2.61, 95% CI: 1.46–4.67), sedation (OR 4.21, 95% CI: 1.18–15.01) and somnolence (OR 2.23, 95% CI: 1.07–4.64). In only the non-epilepsy studies, the only adverse event that was more frequent with CBD was diarrhoea (OR 5.03, 95% CI: 1.44–17.61) (294). Another systematic review concluded that CBD is generally well tolerated and AEs are usually mild to moderate (296).

Table 11. Summary of randomised controlled clinical trials of oral cannabidiol that assessed adverse events.

Indication	Number of participants	Dose used	Length of time	Fed/ fasted	Common treatment-related adverse events	Serious adverse events	Ref
Huntington's Disease	18	10 mg/kg	6 weeks	Fasted	No statistical difference reported between placebo and CBD group.		(283)
Fatty liver disease	25	200 mg, 400 mg, 800mg	8 weeks	Fasted	Diarrhoea (n = 4/7, 200mg daily group)	0	(297)
Type II diabetes	27	200 mg	13 weeks	Fasted	Decreased appetite (n = 2/13)	0	(298)
Crohn's Disease	19	20 mg sublingual	8 weeks	-	No statistical difference reported between placebo and CBD group.		(299)
Dravet Syndrome (GWPCARE1)	120	20 mg/kg	11 days titration + 12 weeks maintenance	-	Diarrhoea (n = 19/67), vomiting (n = 9/67), fatigue (n = 12/67), pyrexia (n = 9/67), somnolence (n = 22/67).	Status epilepticus (n = 3/67), elevated LFTs (n = 12/67).	(300)
Schizophrenia	41	600 mg	6 weeks	-	Sedation (n = 4/18)	0	(301)
Schizophrenia	88	1000 mg	6 weeks		Diarrhoea (n = 8/43), nausea (n = 3/43).	0	(302)
Clobazam interaction study	20	20 mg/kg	10 day titration + 12 week maintenance	-	Diarrhoea (n = 6/16), nausea (n = 3/16), vomiting (n = 3/16).	Seizure cluster (n = 1/16)	(303)
Dravet Syndrome (GWPCARE1 – Dose ranging)	34	5/10/20 mg/ kg	3, 7 or 11 days titration, 21 day maintenance, 10 day taper	-	Somnolence (n = 5/27), decreased appetite (n = 5/27), sedation (n = 4/27), vomiting (n = /27), ataxia (n = 3/27)	Pyrexia (n = 2/8), convulsion (n = 1/8), elevated LFTs (n = 4/6 in the 20mg/kg group).	(282)
Lennox-Gastaut Syndrome (GWPCARE3)	225	10 or 20 mg/kg	7 or 11 days titration, 12 week maintenance, 10 day taper	-	Somnolence (n = 18/143), decreased appetite (n = 17/143), and diarrhoea (n = 13/143).	Elevated LFTs (n = 4/143), somnolence (n = 1/143), seizure (n = 1/143), status epilepticus (n = 1/143), lethargy (n = 1/143), constipation (n = 1/143), cholecystitis (n = 1/143).	(304)
Lennox-Gastaut Syndrome (GWPCARE4)	171	20 mg/kg	11 days titration, 12 weeks maintenance, 10 day taper	-	Diarrhoea (n = 9/86), somnolence (n = 5/86), decreased appetite (5/86), and vomiting (n = 3/86).	Elevated LFTs (n = 11/86), pneumonia/ acute respiratory failure (n = 2/86)	(305)
Healthy adult	24	1500 mg or 3000 mg per day	1 week	-	Diarrhoea (n = 27/66), headache n = 21/66)	0	(199)
Cannabis use disorder	10	800 mg	6 weeks	-	0	0	(306)
Persecution ideation and anxiety in paranoid group	32	600 mg	Once	-	Tiredness/ sedation (n = 5), light headedness/ dizziness (n =	0	(307)

					2), nausea (n = 2), abdominal discomfort (n = 1), increased appetite (n = 2).		
Mild/moderate ulcerative colitis	75	50 mg up to 250 mg daily	10 weeks	-	Dizziness (n = 12/29), somnolence (n = 9/29), nausea (n = 7/29)	Attention disturbance (n = 1/29), dizziness (n = 1/29), joint swelling (n = 1/29), muscle twitching (n = 1/29).	(308)
Parkinson's Disease	21	75 mg and 300 mg daily	6 weeks	-	Not assessed	0	(309)
Healthy adults	26	600 mg/day	1 week		Reduced appetite (n = 1/26), headache (n = 1/26), insomnia (n = 1/26), hyperactivity (n = 1/26), dysuria (n = 1/26).	0	(310)
Healthy adults	21	1500 mg/day	2 weeks	-	Diarrhoea (n = 4/9), nausea (n = 2/9), headache (n = 2/9)	0	(311)

On the basis of previous studies, anticipated AEs in the CAIMSS study are likely to be mild to moderate, with the most likely being diarrhoea. Other mild/moderate AEs have been reported in clinical trials using higher doses and with concomitant antiepileptic drugs, however they should still be monitored for in the CAIMSS study. These include nausea, appetite changes, sedation, and somnolence. Serious adverse events are unlikely and have been found to be associated with concomitant antiepileptic use, but may comprise of elevated liver enzymes, or intolerable sedation/somnolence.

5.5.9. Efficacy

Cannabidiol has not been studied in humans or animal models for aromatase inhibitor associated musculoskeletal symptoms. Pre-clinical animal studies show promising efficacy for CBD in reducing the inflammatory mediators that may be implicated in aromatase inhibitor musculoskeletal symptoms (312). Additionally, research is currently underway for the use of CBD as an anti-inflammatory agent in other joint-related conditions in humans, such as arthritis (312, 313). A clinical trial using a final mean daily dose of CBD 13.5 mg and THC 14.6 mg has shown medicinal cannabis to be more effective than placebo in reducing pain symptoms in participants with rheumatoid arthritis (314). A prospective cohort study examining 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 (128).

Hobbs *et al*, as part of their healthy volunteer study, also examined the anti-inflammatory potential of CBD. They collected peripheral blood mononuclear cells (PBMCs), which are immune blood cells such as lymphocytes, monocytes, and erythrocytes at baseline, and then 90 minutes after ingestion of CBD 30 mg. The PBMCs from both baseline and after CBD ingestion were challenged with lipopolysaccharide, a pro-inflammatory elicitor, and they found that there was

significantly reduced expression of TNF after treatment with CBD. It is thought this is the first trial that has shown reduction in pro-inflammatory cytokines in humans, and shows promising preliminary viability for the use of CBD in inflammatory conditions (127).

5.6. Marketing experience

Cannabidiol Broad Spectrum Extract that will be used in this trial is not approved for use in Australia or any other country. Cannabidiol (Epidyolex®) is currently available and approved for use in Australia for Dravet Syndrome and Lennox Gastaut Syndrome. Epidyolex® is an oral liquid containing cannabidiol 100 mg/mL. The starting dose is 2.5 mg/kg twice daily for one week, increasing to a maintenance dose of 5 mg/kg twice daily, with a maximum recommended dose of 10 mg/kg twice daily (70).

<u>Very common adverse reactions (70):</u>

- Metabolism and nutrition disorders (decreased appetite)
- Nervous system disorders (somnolence)
- Gastrointestinal disorders (diarrhoea, vomiting)
- General disorders and administration site conditions (pyrexia, fatigue)

<u>Common adverse reactions (70):</u>

- Infections and infestations (pneumonia, bronchitis, nasopharyngitis, urinary tract infection)
- Metabolism and nutrition disorders (increased appetite)
- Psychiatric disorders (irritability, insomnia, aggression, abnormal behaviour, agitation)
- Nervous system disorders (Lethargy, drooling, tremor)

- Respiratory, thoracic, and mediastinal disorders (cough)
- Hepatobiliary disorders (AST increased, ALT increased, GGT increased, liver function test abnormal)
- Skin and subcutaneous tissue disorders (rash)
- General disorders and administration site conditions (weight decreased)

5.7. Conclusion

This Investigator's Brochure summarises the current pre-clinical, clinical, and safety evidence to inform a pilot clinical trial examining the use of CBD in patients experiencing aromatase inhibitor associated arthralgia.

CHAPTER SIX

A protocol for a randomised, placebo-controlled cross-over trial of cannabidiol extract for aromatase inhibitor associated musculoskeletal symptoms

CHAPTER 6: RANDOMISED, PLACEBO-CONTROLLED CROSS-OVER TRIAL OF CANNABIDIOL EXTRACT FOR AROMATASE INHIBITOR ASSOCIATED MUSCULOSKELETAL SYMPTOMS

6.1. Abstract

Background. Aromatase inhibitors (AI) are used in the treatment of hormone receptor positive breast cancer in post-menopausal women. Approximately 30% of those taking an AI will discontinue this medication due to adverse events (AEs), including associated musculoskeletal symptoms such as arthralgia and myalgia, and other symptoms including hot flushes and night sweats. It has been suggested that the upregulation of inflammatory pathways may be implicated in these AEs, and there is emerging evidence for medicinal cannabis, in particular, cannabidiol (CBD) in some of these inflammatory pathways. This research aims to assess whether a CBD broad spectrum extract: (1) Reduces patient-reported average joint pain severity; (2) Reduces patient-reported average joint pain interference; (3) Change patients' self-perceived impression of health status; (4) Improves post-menopause health-related quality of life symptoms.

Methods. This study will be a cross-over randomised placebo-controlled clinical trial on patients with hormone receptor-positive breast cancer prescribed aromatase inhibitors (excluding exemestane) who are experiencing new or increased arthralgia since commencement of therapy. The trial will consist of two study periods of 4 weeks with a 3-week washout in between. There will be two arms (n = 20), arm one (n = 10) will receive CBD extract in the first study period, and then placebo in the second study period. Arm two (n = 10) will receive placebo in the first study period and CBD in the second study period. Outcomes will be measured at baseline and at the conclusion of 4 weeks.

Conclusion. The high discontinuation rates of those taking an AI calls for effective treatments that address the underlying pathophysiology. The results of this study will determine whether a CBD extract can improve the AEs associated with AI treatment, potentially leading to improved adherence and outcomes.

6.2. Background

6.2.1. Disease Background

Aromatase inhibitors (AIs) are first-line adjuvant agents used in the treatment of hormone receptor positive breast cancer in post-menopausal women. This class of drugs are typically continued for five to ten years after initial treatment as a hormone blockade; however, despite their proven efficacy in reducing 10-year breast cancer mortality, there is a high discontinuation rate (315, 316). Over 30% of patients will stop an AI due to adverse events, the most common being musculoskeletal symptoms, such as arthralgia and myalgia. Aromatase inhibitor associated musculoskeletal symptoms (AIMSS) occurs in approximately 50% of all patients (316). Other adverse events associated with AIs are menopausal symptoms including vasomotor AEs such as hot flushes, night sweats, vaginal dryness, mood disorders, and difficulty sleeping (316). Currently, patients are advised to manage AIMSS with non-pharmacological options such as physiotherapy, weight loss, exercise, and application of heat to the affected areas. These strategies can be used alongside pharmaceutical analgesia, including paracetamol, non-steroidal anti-inflammatories, and opioids. Despite these options being available to patients, they do not address the underlying cause of the condition, discontinuation rates remain high, and effective interventions are needed to ensure patients are able to adherence to their AI therapy (317).

The exact aetiology of AIMSS remains uncertain, however, research shows it is likely related to pharmacogenetics, the decline of oestrogen synthesis, vitamin D levels, and the upregulation of cytokines and inflammatory pathways (205). The reduction of the synthesis of oestrogen has also been associated with impaired cartilage maintenance, reduction of estrogen's anti-nociceptive properties, tenosynovial changes (206), and inflammatory cascades (207). Evidence from research into rheumatological conditions shows high estrogen levels can reduce pro-inflammatory cytokine production, therefore estrogen deficiency may induce an increased production of inflammatory cytokines such as interleukin (IL)-1β and Tumour Necrosis Factor (TNF)-α (208). Increased levels of IL-6 was also shown during AI therapy which may be due to the inhibitory activity of aromatase on the expression of this cytokine (209). The involvement of inflammatory processes in AIMSS has also been shown in clinical settings, such as ultrasound and MRI imaging of the affected joints (210). In addition, arthralgia symptoms in AIMSS were associated with increased serum concentrations of C-reactive protein (CRP), eotaxin, Monocyte chemoattractant protein-1 (MCP), and Vitamin D binding protein (VDMP) in human trials (207).

Medicinal cannabis therapy is an emerging area of interest for many therapeutic indications, one of which is for its immunomodulatory and anti-inflammatory properties. Acting on the endocannabinoid system, and other targets, medicinal cannabis has many potential pharmacological targets which could reduce inflammation and provide analgesia, and this has been demonstrated in both pre-clinical and animal studies (23, 25, 110, 313, 318). Medicinal cannabis derived is from the *cannabis sativa* plant, and it contains many compounds, including cannabinoids, terpenes, and flavonoids. The two main constituents of cannabis are the cannabinoids cannabidiol (CBD), and tetrahydrocannabinol (THC), and it is CBD that has been shown to have

immunosuppressive effects (114). The receptors that CBD target which facilitate immune responses are listed in Table 1. Through these, CBD has been shown to reduce in vivo levels of TNF-α, IL-1β, IL-6, and interferon-gamma. With activity against these pro-inflammatory cytokines, CBD is regarded as a potent anti-inflammatory agent with many potential clinical applications (312, 313). In addition, a clinical trial has shown medicinal cannabis to be more effective than placebo in reducing pain symptoms in patients with rheumatoid arthritis (314). We hypothesise that CBD can reduce AIMSS through its immunosuppressive effects.

Table 1. Identified receptors which mediate cannabidiol immunomodulatory effects (114).

Receptor	**Activity**
CB_1	Agonist
CB_2	Agonist
Fatty acid amide hydrolase (FAAH)	Inhibition
Peroxisome proliferator-activated receptor-gamma (PPAR-gamma)	Agonist
Transient receptor potential vanilloid 1 (TRPV1)	Agonist
Adenosine A_{2A}	Activation
Serotonin 1a receptor (5-HT1a)	Agonist
G-protein coupled receptor 55 (GPR55)	Antagonist

Other menopausal adverse events associated with AI use such as mood changes and hot flashes result from the decline of oestrogen synthesis. Oestrogen has been shown to facilitate the production of neurotransmitters such as serotonin, and it is thought that the withdrawal of estrogen during the menopausal period can lead to various symptoms that relate to the reduced production of such neurotransmitters. Serotonin has been implicated in both the mood changes during menopause, and the central

events that trigger hot flashes (319, 320). As CBD has been shown to agonise 5-HT1a and reduce symptoms of anxiety, we hypothesise that CBD may assist with the mood changes and hot flushes experienced during AIMSS (321).

This clinical trial will test cannabidiol broad spectrum extract (CBD extract). This will contain 98% or higher cannabidiol, and fewer than 2% of other cannabinoids, terpenes, and flavonoids.

6.2.2. Rationale for performing the study

This research aims to improve adherence and outcomes in patients with hormone receptor positive breast cancer who are experiencing musculoskeletal symptoms and other adverse events from ongoing aromatase inhibitor therapy (excluding exemestane). Medicinal cannabis is an emerging area of clinical and research interests, with cannabidiol particularly becoming increasingly available in Australia. Unfortunately, evidence from randomised-controlled clinical trials is lacking and this research may assess the potential for CBD extract to reduce pain and inflammation in this setting.

6.3. Study objectives

6.3.1. Primary Objective*

a) To assess whether treatment with CBD extract decreases average joint pain severity in patients with AIMSS, as measured at 4 weeks by the Brief Pain Inventory Short Form (BPI-SF);

6.3.2. Secondary objectives

a) To assess whether treatment with CBD extract decreases average joint pain interference of daily living activities in patients with AIMSS, as measured at 4 weeks by the Brief Pain Inventory Short Form (BPI-SF);
b) To assess whether CBD extract treatment affects patients' self-perceived impression of health status as measured by the global rating of change scale (GRCS) of average pain since in the last week;
c) To assess whether CBD extract treatment improves post-menopausal health-related quality of life symptoms such as sleep, mood, and hot flushes according to the Menopause-Specific Quality of Life (MENQOL) questionnaire;

6.3.3. Additional explorative objectives

d) To assess whether CBD extract increases or decreases the use of other analgesic drugs as measured by the medication quantification scale;
e) To investigate whether CBD extract increases adherence and/or reduces discontinuation rates of aromatase inhibitor therapy

6.4. Study design

6.4.1. Design

Randomised placebo-controlled double-blind cross over phase IIA clinical trial

6.4.2. Study Groups

Table 2. The two study groups, number of participants and dosing schedule

Arm One n = 10 minimum	**Arm Two** n = 10 minimum
Receives CBD extract 75 mg BD for 4 weeks, then a 3-week washout period, then receives placebo BD for 4 weeks	Receives placebo BD for 4 weeks, then a 3-week washout period, then receives CBD extract 75 mg BD for 4 weeks

6.4.3. Number of participants

The minimum number of participants required to enrol in the study is n = 20.

6.4.4. Number of sites

Single-centre study. All participants will be recruited at:

The SAN Clinical Trial Unit

185 Fox Valley Road

Wahroonga NSW 2076

6.4.5. Duration

Total duration of study will be 11 weeks (4 weeks of first study period + 3 weeks wash out + 4 weeks second study period).

6.5. Participant section

6.5.1. Inclusion criteria*

6.5.1.1. Disease criteria

a) Women with histologically confirmed oestrogen receptor or progesterone receptor positive breast cancer (Stage I-III) with no evidence of metastatic disease (M0).
b) Patients must have undergone and recovered from mastectomy or breast sparing surgery. If the patient was treated with initial chemotherapy and/or radiation therapy, these must be completed at least 28 days prior to registration for the trial. Patients should be recovered from all Grade 2 or higher side effects except for alopecia and peripheral neuropathy. Concurrent bisphosphonate and trastuzumab therapies are allowed.

6.5.1.2. Clinical criteria

a) Women must be post-menopausal, defined by at least one of the following:
    1. ≥ 12 months since last menstrual period, OR
    2. Patient has undergone a bilateral oophorectomy, OR
    3. Prior hysterectomy with one or both ovaries left in place AND (unless ≥ years of age) FSH values consistent with post-menopause, OR
    4. Patient has been on luteinizing hormone-releasing hormone agonist for at least 3 months, and oestradiol levels drawn within 28 days of registration are consistent with post-menopause.

b) Patients must be receiving one of the following aromatase inhibitor therapies for at least 21 days prior to registration and plan to continue for at least 180 days after registration:
    1. Anastrozole 1 mg daily, or
    2. Letrozole 2.5 mg daily.

c) Patients must be experiencing AIMSS that began or increased after initiation of AI therapy. Musculoskeletal pain should not be associated with fracture or traumatic injury.

d) Patients should have completed the Brief Pain Inventory Short Form within 7 days of enrolment into the study and have an average baseline pain of at least 4 out of 10

e) Laboratory parameters:

Normal liver function: Aspartate aminotransferase 10-40 U/L and alanine aminotransferase 7-56 U/L

Normal renal function: Serum creatinine <133 μmol/L and eGFR ≥ 60

f) Regular narcotic medications should be stabilized for at least 14 days prior to registration

6.5.1.3. Specimen Submission Criteria

a) Patients must be willing to submit blood samples for baseline samples prior to beginning the protocol treatment.

6.5.1.4. Regulatory Criteria

b) All patients must be willing to participate in the study and be informed of its investigational nature. Written informed consent will be required and the ability to fill out the questionnaires in English.

6.5.2. Exclusion criteria

a) Patients must not have a diagnosed inflammatory autoimmune arthritis condition. (Patients with existing osteoarthritis that have had an increase in symptoms since commencement of AI are eligible)
b) Patient must have no known allergy or hypersensitivity to cannabis or cannabinoids.
c) Patients must not have any contraindicated medical conditions to cannabis treatment, including any one of the following:
    - Life-time history of the psychiatric disorders schizophrenia or bipolar disorder as classified in DSM 5;
    - Previous psychosis with or intolerance to cannabinoids;
    - Current substance use disorder according to DSM 5;
    - Life-time history of dependence on cannabis or diagnosis of cannabis use disorder according to DSM 5; or
    - Current or history of suicidal ideation.

d) Patients using prescribed or recreational cannabis products within 90 days of the study and are unwilling to abstain for duration of study.
e) Inability to understand and comply with the instructions of study.
f) Participation in another clinical trial within 30 days of this commencement of this trial.
g) Hepatic or renal impairment.

6.6. Study outline

6.6.1. Study Flow Chart

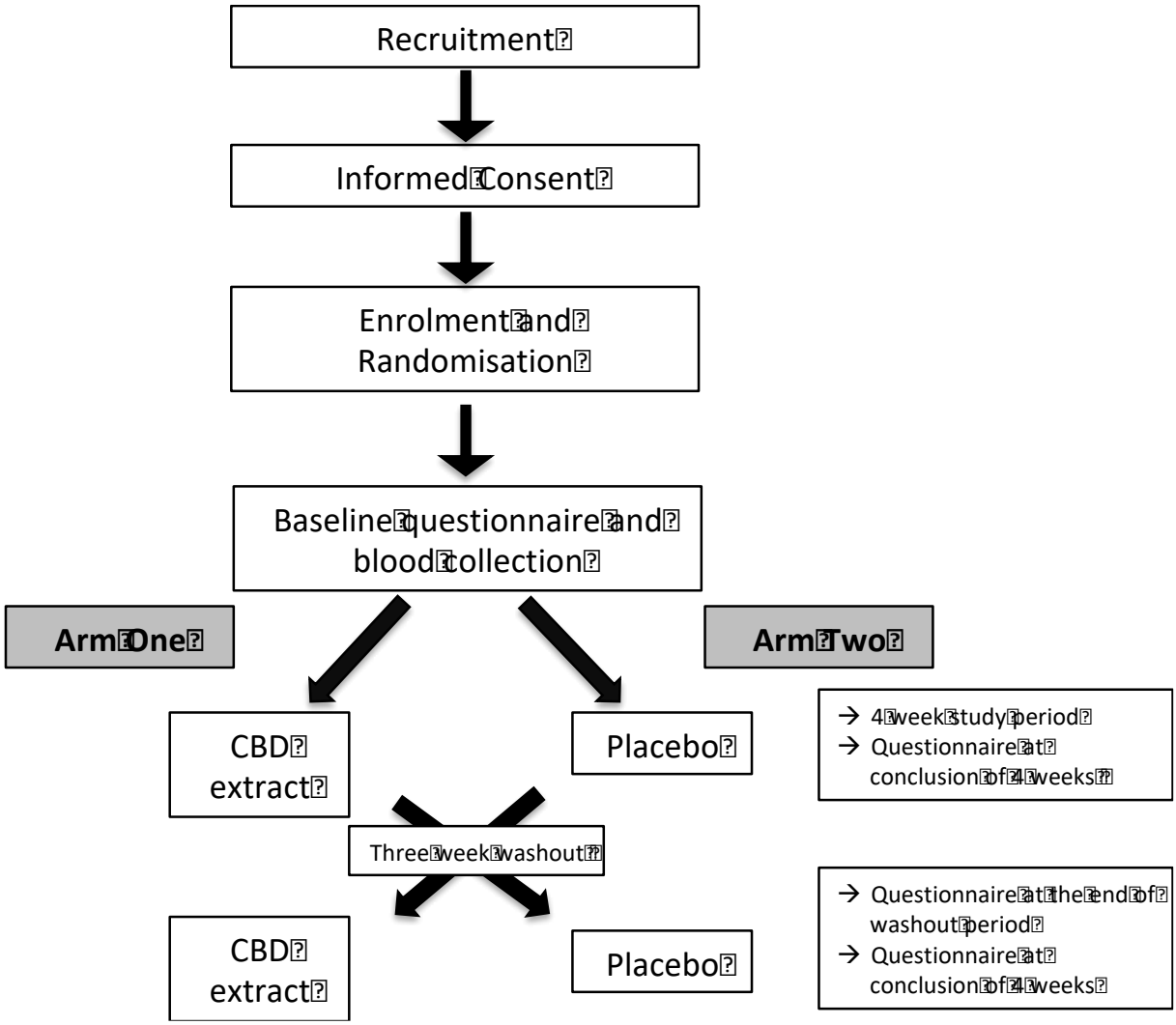

Figure 1. Study flow chart

6.6.2. Investigation plan

Table 3. Investigation plan with planned interventions at each visit

List Interventions	**Visit One^**	**Visit Two (Enrolment visit)**	**Visit Three (End of first study period)**	**Visit Four (End of washout)**	**Visit Five (End of second study period)**
Informed Consent	✓				
Inclusion / Exclusion criteria	✓				
Physical examination	✓		✓	✓	✓
Blood samples	✓^^				
Adverse Event & Serious Adverse Event Assessment			✓	✓	✓
Questionnaire		✓ (Baseline Questionnaire 1)	✓ (Questionnaire 2)	✓ (Baseline Questionnaire 3)	✓ (Questionnaire 4)
Product given to patient		✓		✓	
Randomisation		✓			

^Visit one may not be necessary if the participant has had a recent physical exam blood samples taken.

^^Baseline bloods for inclusion/exclusion criteria purpose

6.7. Methodology

Patients will be recruited through The SAN Integrated Cancer Centre. Patients who are experiencing arthralgia associated with AI use will be informed of the trial. Patients will return for visit one, where informed consent will be obtained, inclusion and exclusion screening commenced including baseline physical examination and blood samples if needed. On visit two, patients will be enrolled into the trial and randomised to their first product (either placebo or CBD). A questionnaire will be provided to the patient to complete on site. After 4 weeks, patients will return to fill out questionnaire 2, at which time adverse event will be recorded. Patients will then return home for a 3 week wash out period. After the wash out period is complete, patients will come for visit 3, where the baseline questionnaire 3 is given, and product number 2 provided. After the 4-week study period ends, patients will return for the final questionnaire.

6.8. Data collection

Adverse events data will be obtained on site during scheduled visits and stored as per standard practice. Demographic and medical history will be obtained from patient profiles from the site. Participants will be given a participant-specific code to use when returning surveys. Surveys will be stored on site. All data will be entered into Research Electronic Data Capture (REDCap), accessed through the University of Sydney. Information gathered will be:

a) Demographics
    - Re-identifiable participant code
    - Date of birth
    - Gender
    - Background medical information

- Medication history

b) Pain scores caused by arthralgia

c) Overall impression of health change since commencing the treatment

d) Menopause symptoms experienced

e) Quantity/types of analgesic medications used

f) Adverse events

6.9. Impact and/or response to participant withdrawal

Patients are freely able to withdraw consent at any time during the study. Statistical power calculations allow for 5% drop out. If over 5% drop out, we will attempt recruitment of additional participants.

6.10. Outcome measures

6.10.1. Brief Pain Inventory – Short Form (BPI-SF)

The BPI-SF is a validated questionnaire which assesses the severity of joint pain, and the impact it has had on a patient's functioning. The short form provides a score between 0-10. A change in 2 or more units is considered clinically meaningful (322).

6.10.2. Global Rating of Change Scale (GRCS)

The GRCS will be used to measure overall self-perceived improvement or deterioration of joint pain. This will be undertaken using an 11-point scale ranging from -5 (very much worse) to +5 (completely recovered). A change in 2 or more units is considered clinically meaningful (323-325).

6.10.3. Menopause-specific Quality of Life (MENQOL) questionnaire

The MENQOL questionnaire is a self-administered tool which consists of 29 items in a Likert-scale format which assesses the impact of domains of menopause symptoms; vasomotor, psychosocial, physical, and sexual (326).

6.10.4. Medication Quantification Scale version III (MQS III)

The MQS III is a tool used to quantify medications used in chronic pain populations; the drug class, dosage, and the risk of using them (327).

6.11. Study Procedure Risks

The Therapeutic Goods Administration lists the most commonly reported adverse effects that have been associated with the use of cannabidiol. These are:

- Diarrhea
- Tiredness
- Changes in appetite/weight
- Transaminase elevations
- Sedation
- Sleep disturbances
- Infections
- Anaemia

The TGA lists cannabidiol as generally well tolerated and not associated with serious adverse events. Heart rate, body temperature, blood pressure, psychological and psychomotor functions have not been shown to be adversely affected by cannabidiol treatment. Transaminase elevation and hepatocellular injury has been shown to occur at higher doses (CBD 620 – 1240 mg), and not shown to occur in lower dosing ranges (84).

Cannabidiol (Epidyolex®) is registered in Australia for use in the treatment of Lennox-Gastaut syndrome and Dravet syndrome as an adjunct therapy. Adverse events reported in the product information of Epidyolex® are*:

Very common (over 10% of participants)

- Decreased appetite
- Somnolence
- Diarrhoea, vomiting
- Pyrexia
- Fatigue

Common (over 1% of participants)

- Infections (pneumonia, bronchitis, nasopharyngitis, urinary tract infection)
- Increased appetite
- Irritability, insomnia, aggression, abnormal behaviour, agitation
- Lethargy, drooling, tremor
- Cough
- Hepatocellular injury/abnormal LFTs à AST increased, ALT increased, GGT increased
- Rash
- Weight decreased

*These adverse events were reported in trials of cannabidiol as an adjunct for epilepsy at a dose of 5 mg/kg body weight which is up to two-fold higher than the dose for this study. Cannabidiol was used as an adjunct, concurrently prescribed with other antiepileptics such as clobazam and valproate. The concurrent use of these anti-epileptics with cannabidiol may affect the adverse events recorded in the trials and are

also subject to pharmacokinetic drug-drug interactions via CYP450 (328). Expected adverse events in this trial may be limited to diarrhoea.

A recent systematic review concluded that cannabidiol is well tolerated across a wide range of dosages and is rarely associated with adverse events. Outside the treatment of epilepsy, diarrhoea is the only adverse event that has a higher incidence than placebo (294).

- Cannabidiol Broad Spectrum Extract
- Approved therapeutic indication, dosage/duration in Australia: N/A – This product will be an unapproved therapeutic good. Will require clinical trials notification.
- Believed mode of action: Anti-inflammatory
- Dosage regimen: 75 mg BD for 4 weeks
- Mode of excretion: CYP450 metabolism then excretion through in faeces and to a lesser extent renally.
- Known adverse events: Diarrhoea, tiredness, changes in appetite/weight, transaminase elevations.
- Known contra-indications or warnings: Nil

6.12. Recruitment and Screening

People will be recruited through The SAN clinical trial oncology unit where their treating practitioners will inform their patients who are receiving AI therapy of this trial if they are experiencing AIMSS. Screening will be performed by the principal investigator who will utilise a medical history and baseline blood samples.

6.12.1. Informed Consent Process

Informed consent will be obtained on visit one by signing a Patient Information and Consent Form (PICF). Participation in the research will be voluntary and they will be provided with sufficient information to ensure they have an adequate understanding of both the proposed research and the implications for participating in it. Participants will be informed of the purpose, methods, demands, risks, and potential benefits of the research in a way that is suitable to each participant. The participant will be given the opportunity to ask questions and discuss the information and decision if they wish.

The following information will be communicated to the patient:

a) Alternatives to participation;
b) How the research will be monitored;
c) Provision of services to participants adversely affected by the research;
d) Contact details of a person to receive complaints;
e) Contact details of the researchers;
f) How privacy and confidentiality will be protected;
g) The participants right to withdraw from further participation at any stage, along with any implications of withdrawal, and whether it will be possible to withdraw data;
h) The amounts and sources of funding for the research;
i) Financial or other relevant declarations of interest of researchers, sponsors, or institutions;
j) Any payments to participants;
k) The likelihood and form of dissemination of the research results, including publication;
l) Any expected benefits to the wider community;

m) Any other relevant information, including research specific information.

People who elect not to participate in the research may do so without giving any reason for doing so. Participants may withdraw their consent at any stage during the research period. If a participant chooses to withdraw, all previous data collected will be discarded. We will request they return any unused medication to the pharmacy department for disposal (329).

6.12.2. Enrolment Procedure

The participant will be enrolled into the study after the informed consent process has been completed and the participant has met all inclusion criteria and none of the exclusion criteria. The participant will receive a study enrolment number, and this will be documented in the participant's medical record and on all study documents.

6.12.3. Randomisation Procedure

Participants will be randomised by the pharmacy department on visit two after all inclusion and exclusion criteria are met. At this visit participants will be randomised either to arm one or arm two and assigned a Randomisation Number allocated by pharmacy.

6.13. Safety

Any possible adverse event will be assessed at each visit throughout the study, and any evidence of a clinical and/or laboratory adverse event will be documented in the participants' medical file. The principal investigator will assess the seriousness and the likelihood that it is related to the investigational medical product. Adverse events will

be followed up on their duration and where it is resolving up to 2 weeks after the end of the trial period.

An adverse event is any unfavourable or unintended sign, symptom, or condition and/or observation that may or may not be related to study treatment.

A serious adverse event is defined as any adverse event that results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability/incapacity or congenital/birth defect, condition requiring medical or surgical intervention.

The Principal Investigator will record all adverse events and will arrange for tabulation of all SAEs for reporting.

6.13.1. Adverse Event Reporting

6.13.1.1. Adverse event

An adverse event for medicines is also referred to as an adverse experience, any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP.

6.13.1.2. Serious adverse event

A serious adverse event (SAE), also referred to as serious adverse drug reaction, is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;

- requires in-patient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is a medically important event or reaction.

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe.

All safety and monitoring will adhere to the National Health Medical Research Council guidance for safety monitoring and reporting in clinical trials involving therapeutic goods (330). Any AEs and SAEs in participants taking the IMP will be categorised according to the safety reporting assessment listed by the National Health Medical Research Council (330).

In this study, the sponsor/investigator will:

a) Keep detailed record of all adverse events and maintain up-to-date line listings;

b) Communicate safety information to investigators and/or Human Research Ethics Committee (HREC) and clarify the impact of each report on patient safety, trial conduct or trial documentation;

c) Assess and categorise the safety reports received from investigators and report all suspected unexpected serious adverse reactions (SUSARs) occurring to the Therapeutic Goods Administration:

   - Fatal or life-threatening SUSARs will be reported immediately, but no later than 7 days after being made aware of the case, with any follow up information within a further 8 calendar days;

- All other SUSARs will be reported no later than 15 calendar days after being made aware of the case.

d) Notify the TGA, HREC and investigators of all significant safety issues that adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. Urgent safety measures should be notified within 72 hours, and all other significant safety issues should be notified within 15 calendar days of the sponsor being made aware.

e) Capture and assess all AEs that occur at the site;

f) Report to the sponsor within 24 hours of becoming aware of the event:
   - All SAEs, except those that are identified as not needing immediate reporting
   - All urgent safety measures instigated by the site

g) Report to the sponsor
   - All critical safety events
   - Any additional requested information relating to reported deaths

h) Report to the institution within 72 hours of becoming aware of the event:
   - All significant safety issues
   - SUSARs arising from the local site

6.13.2. Data safety and monitoring board

The data safety and monitoring board (DSMB) (or identified person/committee who has suitable expertise to assist and advise the institution and/or review body in carrying out their safety monitoring procedures) will report directly to the HREC that provides approval for the trial. The DSMB is accountable through the HREC to the National Health and Medical Research Council.

All trial data will be reviewed by the DSMB at the end of the two study periods. If the DSMB feel there may be ethical problems to continue the trial, or if the study team wishes a formal interim analysis to be carried out which has not been foreseen in the Protocol or pose a question of principle (for example modification of an endpoint), then a written request should be made to the HREC.

6.13.3. Early termination

The clinical trial may be terminated if unethical situations arise, including:

a) There are or have been substantial deviations from the trial protocol;
b) Adverse events of an unexpected type, severity, or frequency are encountered; or
c) As the trial progresses, the continuation of the trial would disadvantage some of the participants as determined by the researchers or others monitoring the trial.

If research needs to be terminated early the SAN Clinical Trials Unit will communicate with researchers, HREC and study participants, and reasoning will be given. The researchers and the SAN Clinical Trials unit will compile the final study report, and patients will be unblinded.

6.14. Blinding and unblinding

Blinding will occur through the pharmacy department at the SAN Clinical Trials Unit, where they will receive information on the randomisation of participants and keep records of the study enrolment numbers and to which arm each patient has been allocated. The placebo and investigational medicinal product will both come in the form of an oil-containing capsule, containing the same coloured liquid, with any aromas

masked. The investigational medicinal product and placebo drug will be labelled by the pharmacy department so that it is not possible to determine if they are receiving active or placebo.

6.15. Outcomes and future plans

The collection, preservation, and dissemination of clinical trial data will be according to the standard requirements for Good Clinical Practice-compliant management in clinical trials. The results of this trial will be published in academic literature as outlined in section 9.1. The data and knowledge gained from this clinical trial will be used to inform future research and clinical studies. The data collected from this study may be used for extended related research, as outlined in the PCIF.

6.16. Registrations and publications

The trial will be uploaded and registered with ClinicalTrials.gov prior to patient enrolment. A clinical trials notification will be submitted to the Therapeutic Goods Administration for the use of unapproved cannabidiol and placebo products. The sponsor will apply for permission to conduct the trial with the relevant HREC.

At the conclusion of the trial, a manuscript will be prepared for publication using the results of the study based off this protocol. Publication will be sought in a high impact scientific journal.

In addition to disseminating research in scientific journals, results of the project may be considered in mainstream media, such as social media and news networks.

6.17. Statistical considerations

6.17.1. Sample size power calculation

The sample size required is 20 subjects, 10 randomly assigned to receive placebo followed by CBD, and 10 randomly assigned to receive CBD followed by placebo. This will be sufficient to ensure 90% power to detect a within subject reduction in pain score of 2 or more on CBD versus placebo assuming the standard deviation of the within subject difference is no more than 2.5.

6.17.2. Statistical analysis plan

6.17.2.1. BPI-SF

A clinically meaningful change in the BPI-SF is considered to be a change of ≥ 2. Joint pain and pain interference will be measured at baseline and at 4 weeks after both treatment with cannabidiol and placebo. The difference between outcomes in the cannabidiol and placebo group will be measured by a two-sided paired t-test with 5% significance level.

6.17.2.2. GRCS

A change of ≥ 2 on the 11-point scale from baseline to the completion of 4 weeks will be considered clinically meaningful. The GRCS for joint pain and for joint stiffness will be used to identify patients who report clinically significant worsening (scores from -3 to -5), the same (score of -2 to +2), or better (combining scores of +3 through +5) since the last time they completed the questionnaire. A difference in these categories between treatment and placebo will be measured by the Wilcoxon test with a 5% significance level.

6.17.2.3. MENQOL

A change in MENQOL outcomes will be measured in each participant from baseline to the conclusion of 4 weeks after both cannabidiol and placebo treatment. The difference between outcomes in the cannabidiol and placebo group will be measured by a paired t-test at a 5% significance level.

6.17.2.4. MQS-III

The MQS-III will produce single numerical value for the participants pain medication regimen. The change in this numerical value will be compared in each participant at baseline and at 4 weeks after both cannabidiol and placebo treatment. The difference between outcomes in the cannabidiol and placebo group will be measured by a paired t-test at a 5% significance level.

6.18. Confidentiality and storage and archiving of study documents

Identifiable patient data will be stored on site at the SAN Clinical Trials Unit as per standard of care. Re-identifiable patient data will be stored in REDCap for analysis. After completion of the study, all files containing study documents will be stored by the SAN Clinical Trials Unit for a minimum of 15 years, or according to their storage policy. Data will only be accessed by the delegated study team on site or by the research team at the University of Sydney.

6.19. Other study documents

Copies of the questionnaire tools can be found freely available online. The Patient Information and Consent Form can be found in the Supplementary Materials (Supplementary Document 2).

6.20. Resources

The CAIMMS trial is an investigator-initiated trial by Dr Gavin Marx (Principal Investigator), in close collaboration with the University of Sydney. The investigational medicinal product will be supplied by Canngea Pty Ltd. The SAN Clinical Trials Unit will cover onsite expenses. Research and data preparation and analysis will be undertaken by the University of Sydney. During the development of this protocol and the patient information consent forms, researchers have liaised with a consumer representative from Cancer Voices Australia.

CHAPTER SEVEN

CANNABIS AND ANXIETY: A CAUSE OR A TREATMENT?

CHAPTER 7: CANNABIS AND ANXIETY: A CAUSE OR A TREATMENT?

7.1. Abstract

Purpose of review

Anxiety is a prevalent mental health condition which manifests as a disproportionate response of fear to a perceived threat. Different types of anxiety disorders vary in their pathophysiology, symptoms, and treatments. The causes of anxiety disorders are complex and largely unknown; however, it has been suggested that a number of brain mechanisms and neurotransmitters are involved in the development of these conditions. While there are non-pharmacological treatments for anxiety, many patients are prescribed medications such as selective serotonin reuptake inhibitors, serotonin and noradrenaline reuptake inhibitors, and/or benzodiazepines. Unfortunately, these medications have issues with efficacy and safety, and therefore, there is a continuing need for newer medicines. Anxiety is the second highest indication in Australia that medicinal cannabis is prescribed for, and the constituents, tetrahydrocannabinol (THC), cannabidiol (CBD), and terpenes have been proposed as a potential treatment for anxiety conditions.

Recent findings

Medicinal cannabis constituents act on the endocannabinoid system (ECS) and other targets. The ECS affects several physiological functions through modulation of the central nervous system and inflammatory pathways. In particular, CBD has been suggested to exhibit anxiolytic properties, whereas THC can either have an anxiogenic or anxiolytic effect, depending on the dose, route of administration, and individual

genetic and environmental factors. There is also evidence that terpenes could be effective in anxiety management.

Summary

Currently, there is a gap in the literature as to whether standardised CBD and/or THC preparations can be used for anxiety disorders, despite high levels of prescribing. Further information is required to know the precise doses and CBD-THC ratios from human clinical trials and real-world patient use

7.2. Introduction

Anxiety is a normal emotion that individuals experience in response to situations that they perceive as threatening (331, 332). The Yerkes-Dodson law suggests that there is a relationship between anxiety and performance (333). A moderate level of anxiety or arousal can improve an individual's execution of tasks, but a high level of anxiety can reduce this efficiency (333). Associated physiological symptoms of anxiety include heart palpitations, high blood pressure, and changes to breathing patterns. The physical effects are accompanied with psychological feelings of tension, concern, and impending doom (334).

These reactions serve as a protection mechanism that allow an individual to respond quickly to threats, but can be detrimental when excessive (332). Anxiety disorders occur when there is a persistently high level of anxiousness that is disproportionate to the perceived, or real, threat (331, 332). This prolonged state of fear can impair an individual's functioning and result in avoidance behaviours in an attempt to minimise their symptoms, particularly when challenged with triggering situations (335).

With anxiety disorders under-reported and under-diagnosed, it has been suggested that the prevalence is actually higher than the data shows (336). As a disabling condition with high societal prevalence, anxiety disorders pose a disease burden that is associated with increased morbidity and mortality, and therefore high social and economic costs (336, 337).

7.3. Anxiety pathophysiology

There are a range of brain mechanisms and neurotransmitters that have been implicated in anxiety; however, the exact pathophysiology is unknown (332, 338-340). There are common discrepancies in brain functionality that are observed in patients with anxiety disorders, particularly in the limbic system (332). This system is responsible for emotional processing and associated responsive behaviour, and is comprised of the hypothalamus, amygdala, thalamus, and the hippocampus (341). In particular, the amygdala has been identified as a key structure related to anxiety, as it is responsible for the initial response to, and emotional processing of, threatening stimuli (332, 342). Studies using magnetic resonance imaging have suggested that the amygdala is overreactive in anxiety disorders, causing greater negative emotional processing (343). This has been observed in generalised anxiety disorder (GAD), social anxiety, and specific phobias (338, 342). The hippocampus plays a key role in memory and is believed to contribute to learned responses to fearful situations seen in anxiety, such as patterns of avoidance or panic (337, 342). Abnormalities in the hippocampus can potentially be associated with an increased risk of anxiety disorders, particularly post-traumatic stress disorder (PTSD) (339, 342).

The insular cortex within the brain is thought to be strongly related to the limbic system and has been observed as overreactive in anxiety disorders (342). It is thought

to play a role in fear regulation and is particularly relevant to the pathophysiology of specific phobias and PTSD (344). The prefrontal cortex (PFC) has a range of functions, including social processing, and has also been implicated in anxiety (342). Hyporegulation of the PFC has been suggested to contribute to disturbed emotional regulation (338, 342). The limbic system, particularly the amygdala, and the PFC, are thought to be strongly associated with one another, and dysregulation between the two is a possible mechanism in the pathophysiology of anxiety (338, 342).

An imbalance of neurotransmitters in the brain also may play a role in the development of anxiety (345). The two major central nervous system neurotransmitters are gamma-aminobutyric acid (GABA) and glutamate, which have inhibitory and excitatory effects, respectively (346). As a neurotransmission inhibitor, GABA acts on receptors in specific parts of the brain, such as the structures in the limbic pathway, and reduces the hyperactivity that is observed with anxiety (346). Serotonin imbalances have also been suggested in consideration of the pathophysiology of anxiety, although the exact role of serotonin is unclear (340). Other neurotransmitters that may have a role in a person's response to fear and development of anxiety include adenosine, hormones, and cannabinoids, although their exact mechanisms are under researched and unclear (345).

7.4. The endocannabinoid system

The endocannabinoid system (ECS) is widely distributed throughout the body, including within the central nervous system, immune system, and gastrointestinal system (347). Functions of the ECS include regulation of ion channels, neurotransmitter release, and cellular physiology (37, 348). The ECS refers to the endogenous neurotransmitters and their synthesis, transport, and degradation

processes, as well as the receptors with which they interact (37, 347, 349). Two of the key endogenous cannabinoids are arachidonic acid derivatives; 2-arachidonoyl glycerol (2-AG) and arachidonoyl ethanolamide (AEA) (347). Both 2-AG and AEA are neurotransmitters that act as retrograde messengers (348). While these two primary endogenous cannabinoids are structurally similar, their synthetic processes are different. The synthesis of AEA begins with arachidonic acid which is converted by the enzyme N-acyltransferase into *N*-arachidonoyl-phosphatidylethanolamine, a precursor for the endogenous cannabinoid (347, 349). This precursor is stored in lipid membranes and the subsequent release of AEA is catalysed by a specific phospholipase D (347). Diacetylglycerise lipases catalyse the reaction between arachidonic acid and diacylglycerol to form 2-AG; its primary synthesis pathway (349, 350). The synthesis and release of these cannabinoids occurs when signalled through cell depolarisation, increased calcium concentration, or metabotropic receptor stimulation (349).

Once released, endogenous cannabinoids interact with receptors, most importantly, cannabinoid type 1 receptor (CB_1) and cannabinoid type 2 receptor (CB_2). These are G-protein coupled receptors primarily of the i/o subtypes with inhibitory actions (37). Cannabinoid type 1 receptors are found on both central and peripheral neurons, cardiovascular and reproductive systems, and the gastrointestinal tract (351). Cannabinoid type 2 receptors are found on immune cells, blood cells, and post-synaptically in areas of the CNS (351). Cannabinoid type 2 receptors have been found specifically in the microglia of the brain, and are thought to be upregulated in tissue injury or inflammation (352). Although both CB_1 and CB_2 are found in the brain, CB_1 is more abundant and can produce a range of neuromodulatory effects through its distribution in the cortex, basal ganglia, hippocampus, and cerebellum (352). The

areas in which they are found suggest CB_1 should be considered in the pathophysiology and therapeutic treatment of neuropsychological disorders (353).

7.5. Cannabis

Cannabis sativa (cannabis) is a plant that contains hundreds of chemical constituents, and its therapeutic use dates back thousands of years (13, 354). The major and most extensively researched constituents of cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD) (355). These compounds interact differently with cannabinoid receptors and have different targets outside the ECS, driving their unique therapeutic effects, even though their chemical structures are relatively similar (355). Cannabis has long been listed as an illegal recreational drug and access to cannabis for medicinal purposes in Australia was only legalised in 2016 (53). Since then, a number of pharmaceutical grade products with different THC and CBD ratios have been made available; however, the heterogeneity in the market makes it difficult to compare them and determine optimal therapeutic preparations (356).

7.6. Tetrahydrocannabinol (THC)

Tetrahydrocannabinol is the major psychoactive constituent of cannabis, and produces a psychological response associated with feelings of relaxation and euphoria, also known as a ‘high’, which drives the recreational use of cannabis (13, 356). There are several naturally existing structural conformations of THC. Delta-9-tetrahydrocannabinol (Δ9-THC) is the most common form of THC, and interacts with both CB_1 and CB_2 (13). Delta-8-tetrahydrocannabinol (Δ8-THC), an isomer of Δ9-THC, is not as well researched and has been found to interact with CB_1, but it is unclear whether it interacts with CB_2 (352). The psychoactive properties of THC are due to its

partial agonism of CB_1 in the brain; however, this can be dose dependent (13, 48, 50). The presence of other cannabinoid agonists can change the effect that THC has on these receptors (13). Tetrahydrocannabinol can behave as an inverse agonist, reportedly inhibiting G protein activation of CB_2, and as an antagonist at CB_1 when administered with more efficient agonists of these receptors (13).

Tetrahydrocannabinol has a narrow therapeutic window between its potential therapeutic benefits and unwanted psychological reactions associated with its use, which can make dosing challenging (51). It is commonly reported that THC at lower doses can produce effects such as euphoria, relaxation, and sociability, whereas higher doses can have adverse effects including dysphoria, panic, and phobia (47). This can also vary between individuals, as those who are predisposed to anxiety could be more likely to experience these reactions even with lower doses of THC (48, 49). In addition, the variable effect of THC between people is also influenced by genetic and environmental factors, as well as by the route of administration, with the oral *vs* inhalation routes having different pharmacokinetic pathways and psychoactive properties (50-52). The feelings of anxiousness and panic brought on by THC are thought to originate in the amygdala, a structure of the brain known to exert hyperactivity in anxiety (356, 357).

As the ECS is widespread throughout the body and the brain, THC can have a range of beneficial effects, and therefore therapeutic applications, particularly as an antiemetic or appetite stimulant (50, 51). Dronabinol and nabilone are synthetic compounds of THC that have been developed and approved for these indications (51). Dronabinol is used in the USA for appetite stimulation for acquired immunodeficiency syndrome patients, and as an antiemetic for cancer patients undergoing chemotherapy (51). Nabilone is also used as an antiemetic during chemotherapy, and it is more potent

than dronabinol as it is used at a lower dose and, therefore, is favoured of the two drugs for this indication (356).

7.7. Cannabidiol (CBD)

Cannabidiol is a non-psychoactive constituent of cannabis; however, it still exerts pharmacological activity that can have therapeutic applications (13). Cannabidiol can be extracted from cannabis sativa plants or hemp, which is a cannabis species typically grown for industrial use (358). There are several proposed pharmacological targets of CBD, such as G-protein coupled receptors and ion channels, including the transient receptor potential cation channel, and serotonin 5-HT1a receptor (5-HT1a). Cannabidiol is also a known inhibitor of cytochrome P450 enzymes (13). In addition, it has been observed that while CBD has a low affinity for both CB_1 and CB_2, even at low concentrations it can still interact with these receptors (359). The nature of these interactions varies; at low concentrations it behaves as an inverse agonist and at high concentrations as an antagonist (359). Based on *in vitro* studies it is also hypothesised that CBD may act as a low efficacy agonist at CB_1; however, this has not been demonstrated *in vivo* (13).

Cannabidiol has a range of pharmacological effects and therefore could be a viable treatment for a number of conditions (355). Cannabidiol can interact with ion channels, neurotransmitter transporters and membrane receptors, and these are the proposed mechanism for CBD's anti-epileptic activity (360). There is evidence that CBD can be an effective treatment for Lennox Gastaut syndrome and Dravet syndrome, reducing the frequency of seizures in treated patients (89). It has been suggested that the role CBD plays in mood is due to its interactions with CB_1 in the limbic and paralimbic systems (355). As an antagonist at CB_1, CBD can also block

THC from binding to these receptors, and decrease its psychoactive properties (355). Cannabidiol's antagonism in the brain is a proposed mechanism for the antipsychotic properties it exerts; however, more research is required in this area (359). Inflammation is thought to be mediated by CB_2 in the periphery, and as an inverse agonist it is thought that CBD could affect this, and therefore, could have anti-inflammatory applications (13, 352). The favourable side effect profile of CBD is due to its lacking psychoactive properties, which supports the development of CBD as a medicine (355).

7.8. Terpenes

Terpenes are a diverse group of naturally existing compounds, present in a number of herbs, flowers, and fruits, as well as cannabis plants (361, 362). Terpenes influence the fragrance and taste of these natural products and are utilised commercially in products such as perfumes, essential oils, and food flavourings (361). The number of isoprene units of a terpene molecule effects its pharmacological activity, as well as its classification as a monoterpene, sesquiterpene, diterpene, sesterpene, or triterpene (361). Cannabis contains a number of monoterpenes including limonene, β-myrcene, α-pinene, linalool, and terpinolene, which are responsible for the distinct scent of cannabis (363). Many terpenes can also be used therapeutically, for example, paclitaxel is a natural terpene that has an established role in the treatment of specific cancers (363-365). The properties of terpenes are strain specific, and cannabis terpenes have therapeutic potential in the treatment of epilepsy, anxiety, and inflammation (363, 364).

7.9. Cannabis and anxiety

Cannabis is commonly prescribed for anxiety, however it can exert paradoxical effects (53, 79). Overall, the evidence surrounding cannabis and anxiety is conflicting, with some studies concluding cannabis can induce anxiety, while other studies suggest cannabis has anxiolytic properties (352). Cannabis is reportedly used by individuals who experience anxiousness to alleviate their symptoms (13, 366). Chronic, heavy cannabis use, particularly by adolescents, is a risk factor for the develop of anxiety in later life, potentially because of the down regulation of CB_1 (357, 367). A study of 11 cannabis users and 19 matched healthy control participants used high-resolution research tomography to examine CB_1 function 2 and 28 days after abstinence from the drug. The results showed that dependence on cannabis was associated with the downregulation of CB_1, which rapidly reverses when a person stops using the drug (368).

The different constituents of cannabis (THC, CBD, and terpenes) interact differently with receptors and neurotransmitters in the CNS and ECS (369). Consequently, each of these has different effects on anxiety, and therefore, their individual therapeutic potential needs to be considered (13).

Tetrahydrocannabinol is considered to be primarily responsible for the anxiogenic effects of cannabis (13). Studies have demonstrated that high doses of THC, specifically Δ9-THC, can cause significant levels of anxiety and fear (357). These can be so extreme that they induce panic attacks, even in those without an anxiety disorder (357). Whilst THC is known to induce anxiety, some studies have also reported anxiolytic properties at low doses, thought to be due to binding at CB_1 in the limbic regions of the brain (13, 357). A recent study of 10 Canadian military personnel with PTSD found that nabilone titrated to a dose of up to 3.0 mg over 7 weeks was

effective compared with placebo for PTSD, particularly for reducing nightmares(370). Nabilone was not effective compared with placebo for the treatment of GAD, and a number of the studies that used THC for affective disorders found either no symptom improvement, or increased anxiety (371).

The specific dose of THC required to exert maximal anxiolytic effects without anxiogenic side effects is unclear and thought to be impacted by a number of patient factors such as external stressors, patient tolerance, and whether they are prone to anxiousness (13). Currently, the evidence is lacking as to whether THC is viable as a treatment in isolation for anxiety disorders (13, 371).

Cannabidiol does not have psychoactive effects so it may be an effective treatment for anxiety (371). Human and animal studies have demonstrated the anxiolytic effects of CBD, but the exact mechanism by which this occurs is largely unknown (13). Several studies have proposed that CBD interacts with 5-HT1a and this is a key mechanism behind its anxiolytic effects (13, 357, 371). Serotonin has been implicated as a key neurotransmitter involved in the pathophysiology of anxiety, and current treatments for anxiety address its imbalance. In rodents, CBD increases serotonin release in the prefrontal cortex, an area of the brain of significance when considering anxiety in humans (372). Allosteric modulation of 5-HT1a receptors is also a proposed mechanism of CBD's anxiolytic activity (372). Additionally, it has been suggested that CBD decreases the metabolism of AEA, increasing its interactions with CB_1, a potential mechanism behind the anxiolytic effects (373).

Doses of 25–600 mg of CBD have been shown to alleviate the symptoms of anxiety (372, 373). An exact dose-response relationship is yet to be established, but a key difference to THC is that higher doses of CBD do not result in any anxiogenic side effects (371). It is thought that CBD counters the psychoactive side effects associated

with THC when administered together, and that it could be a viable treatment for anxiety due to its tolerability (371, 373). At high doses it has been found that CBD has a rapid onset of action, which is of clinical relevance for social anxiety, and so, studies have looked at the effects of one-off CBD doses before exposure to threatening situations associated with social anxiety, such as public speaking (374, 375). In one study, a double-blind trial was undertaken with 24 patients with GAD. Half were given a single dose of 600 mg CBD and the other half placebo 1.5 h before a simulated public speaking test. The results showed that CBD reduced anxiety, cognitive impairment, and discomfort (55). In a second study, 10 patients were given 400 mg CBD or placebo; with the CBD group displaying significantly decreased subjective anxiety (56).

The efficacy of CBD has also been observed for GAD using daily doses of 25–125 mg to reduce anxiety levels in diagnosed patients (371, 373). Animal studies have suggested that CBD could also be effective in PTSD, through memory suppression and extinction (376).

Terpenes could also be a possible treatment for anxiety disorders; however, the evidence is conflicting. Linalool is one of the major terpene constituents in cannabis that has been suggested to interact with the CNS, and as such, it may exert anxiolytic activity (377). Previous studies in mice concluded that linalool did not reduce anxiety responses, but could potentially be useful for depression (377). In contrast, a recent study examined the efficacy of linalool in the treatment of GAD. From 539 patients with GAD who were given either 80 or 160 mg silexan (linalool containing oil), 20 mg paroxetine, or placebo once daily for 10 weeks, the study concluded that silexan was superior to placebo and its efficacy was similar to the paroxetine (378).

7.10. Conclusion

Anxiety is a prevalent condition with a high disease burden. Currently, the primary treatments for anxiety disorders are antidepressants and benzodiazepines; however, their use is limited because of issues relating to efficacy and safety. Medicinal cannabis has anxiolytic properties, particularly CBD, and is suspected to be an effective treatment for a number of anxiety disorders; however, rigorous evidence from controlled clinical trials is lacking. Further studies are needed to first, examine the efficacy of standardised preparations of CBD, with or without THC, on different patient populations. These should aim to explore which anxiety disorders medicinal cannabis is effective at treating, at which doses, and examine any factors behind interpatient variability. Second, studies are needed to assess whether medicinal cannabis is more effective for intermittent symptoms of anxiousness and whether it should be used on a when-required basis, or whether it can be used as maintenance therapy for anxiety disorders and taken on a daily basis. Finally, research should also look into formulation design factors in terms of CBD and THC ratios, and the route of the delivery (i.e. capsules, oils, or inhalation). With demand and access to medicinal cannabis increasing, further research is crucial to ensure its safe and effective use.

CHAPTER EIGHT

The effectiveness and adverse effects of cannabidiol and tetrahydrocannabinol used in the treatment of PTSD and other anxiety disorders: a cross sectional analysis of an observational study.

CHAPTER 8: THE EFFECTIVENESS AND ADVERSE EFFECTS OF CANNABIDIOL AND TETRAHYDROCANNABINOL USED IN THE TREATMENT OF PTSD AND OTHER ANXIETY DISORDERS: A CROSS SECTIONAL ANALYSIS OF AN OBSERVATIONAL STUDY.

8.1. Abstract

Background. Anxiety is a prevalent mental health condition for which current treatments are limited by low efficacy and adverse events (AEs). Components of medicinal cannabis, cannabidiol (CBD) and tetrahydrocannabinol (THC), have been proposed as potential treatments for anxiety disorders, specifically post-traumatic stress disorder (PTSD). This study evaluated patient quality of life outcomes following treatment with various medicinal cannabis formulations to determine its effectiveness and associated AEs.

Methods. We conducted a cross sectional analysis of data collected between September 2018 and June 2021 from the CA Clinics Observational Study (CACOS), an ongoing study of patients with various health conditions prescribed medicinal cannabis at the CA Clinics in Australia. PROMIS-29 survey scores of 198 patients with an anxiety disorder were compared across a median (IQR) of 154.4 (246.6) days at baseline, and after treatment with medicinal cannabis, to determine whether there was clinical improvement. The data of 568 anxiety patients was also analysed across a median (IQR) of 55.8 (191.2) days to examine the AEs they experienced as defined by the Medical Dictionary for Regulatory Activities organ system class.

Results. The median doses taken by patients included in the PROMIS-29 analysis were 50.0 mg/day for CBD and 4.4 mg/day for THC. The total patient sample (n = 198) overall reported significantly improved anxiety ($p < 0.001$), depression ($p < 0.001$),

fatigue ($p < 0.001$), and ability to take part in social roles and activities ($p < 0.001$). Those who were diagnosed with PTSD (n = 57) reported significantly improved anxiety ($p < 0.001$), depression ($p < 0.001$), fatigue ($p < 0.001$), and social abilities ($p < 0.001$). The most common AEs reported across the whole patient cohort (n = 568) were dry mouth (n = 185, 32.6%), somnolence (n = 178, 31.3%), and fatigue (n = 105, 18.5%), but incidence varied with different cannabis formulations. The inclusion of THC in a formulation was significantly associated with experiencing gastrointestinal AEs (OR 1.011, $p = 0.003$); specifically dry mouth (OR = 1.010, $p = 0.005$) and nausea (OR = 1.008 $p = 0.008$).

Conclusions. Various formulations of medicinal cannabis significantly improved self-reported scores of anxiety, depression, fatigue, and the ability to participate in social activities in patients with anxiety disorders. A number of AEs were associated with medicinal cannabis; however, more research is needed into the severity and tolerability of these events.

8.2. Introduction

Anxiety is a response that individuals have to situations they perceive as threatening, and anxiety disorders occur when this response is overactive to the point that it impairs a person's functioning (332). The exact pathophysiology of anxiety is unknown; however, it is thought to arise from abnormalities in brain structures including the amygdala and prefrontal cortex (379). The imbalance of neurotransmitters such as serotonin and noradrenaline have also been implicated in the development of anxiety (379). The major types of anxiety disorders are generalised anxiety disorder, social anxiety, panic disorder, phobic disorder, post-traumatic stress disorder (PTSD), and obsessive compulsive disorder (332). Each disorder varies in terms of its causes,

symptoms, pathophysiology, and the treatments available (332). The initial treatment for anxiety disorders is usually non-pharmaceutical, namely cognitive behavioural therapy (380, 381). Where cognitive behavioural therapy is not suitable, or is unsuccessful, pharmaceutical treatment may be considered (382).

Benzodiazepines and antidepressants are the first line pharmaceutical treatments for anxiety disorders as they address the imbalance of various neurotransmitters that are associated with their pathophysiology (380). Benzodiazepines are very effective anxiolytics; however, they have significant risks of dependence, daytime sedation, and memory problems (382). As a result, the use of benzodiazepines for anxiety disorders is limited to acute crisis treatment and short term maintenance therapy (382). Selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors, tricyclic antidepressants, and monoamine oxidase inhibitors are indicated for the ongoing treatment of anxiety (383). Unfortunately, these types of drugs are limited by inconsistent efficacy for anxiety disorders, with SSRIs having a reported response rate of only 60% in patients with PTSD (384). Due to the limited efficacy of these medications, clinicians take side effect profiles and patient preference into consideration when prescribing these treatments (380). As such, there is a continuing need for new medications for anxiety disorders that have both favourable safety and efficacy profiles.

The therapeutic use of cannabis dates back thousands of years for a number of conditions including epilepsy, pain, and anxiety (13). The major cannabinoid constituents of cannabis are cannabidiol (CBD) and tetrahydrocannabinol (THC), which interact differently with the receptors of the endocannabinoid system as well as other receptors in the body, and therefore have different therapeutic applications (356).

It has been proposed that cannabinoids may be useful in the treatment of a number of anxiety disorders (13, 371, 374).

The endocannabinoid system is distributed widely throughout the body and consists of cannabinoid type 1 receptors (CB_1) and cannabinoid type 2 receptors (CB_2) (37). Cannabinoid type 1 receptors are more abundant in the central nervous system and brain, and CB_2 receptors are more widely distributed in the peripheral nervous system (351). Tetrahydrocannabinol interacts with CB_1 in the brain, which causes the psychoactive effects of cannabis, and can produce the associated anxiogenic effects (13). An individual's response to THC is affected by a number of factors, including dose and tolerance (66). High doses of THC are thought to increase the risk of anxiety exacerbations, whereas low doses, less than 30 mg THC per day, could be an effective treatment for anxiety disorders such as PTSD (385). Cannabidiol has anxiolytic properties and doses between 25-600 mg have been shown to decrease anxiety in patients (373). The exact mechanisms behind the anxiolytic properties of CBD are largely unknown; however, it does not interact with CB_1 in the brain and is therefore not associated with anxiogenic effects at higher doses (13).

Medicinal cannabis could be an effective treatment for a number of anxiety disorders, particularly PTSD; however, more research into the efficacy and adverse events (AEs) of CBD and THC is needed. It is unclear which formulation of cannabis, and which specific doses of CBD and THC, are optimal for the treatment of anxiety. Studies have not yet established a relationship between the dose and efficacy of CBD and/or THC at improving different symptoms of specific anxiety types.

8.2.1. Purpose

In this paper we performed a cross-sectional analysis of data collected from an ongoing observational study to assess the effectiveness and safety of medicinal cannabis in the treatment of PTSD and other unspecified anxiety disorders. The effectiveness of medicinal cannabis was examined by evaluating the changes to a number of anxiety-related patient outcomes before and after treatment. Safety was assessed through the analysis of the types and incidence of AEs experienced by patients using different medicinal cannabis formulations.

8.3. Methods

8.3.1. Setting

We performed a cross-sectional analysis of data that had been collected from the CA Clinics Observational Study (CACOS), a large, ongoing, observational study conducted through the CA Clinics, a network of medicinal cannabis prescribers located in Australia. Patients are enrolled prior to their first appointment and return questionnaires before each clinic visit that measures various health-related quality of life outcomes in patients with a range of conditions including epilepsy, pain, and anxiety (Supplementary Document 1). This study was approved by the Bellberry Human Research Ethics Committee (Ref: 2019-04-338).

8.3.2. Medicinal Cannabis Formulations

All the medicinal cannabis formulations that were prescribed to each patient contained either CBD and/or THC. Patients self-reported the medicinal cannabis product(s) they were taking and based on the concentration of each constituent they were classed as CBD- or THC-only, CBD or THC dominant, or balanced formulations. ‘Dominant’ refers

to a concentration of one constituent that is 1.5 times greater than the other; for example, a THC dominant product could contain 3 mg/mL or more of THC and 2 mg/mL CBD. If patients had taken multiple products from different formulation classes, they were included in both groups for analysis. The preparations were also classified based on their formulation as an oral liquid, capsule, flos (whole flower), or granulate (granulated whole flower). This study only included the oral liquid and capsule formulations to ensure consistency when analysing dose and effectiveness, as inhaled formulations have different absorption properties to oral routes (51). Patients also reported the quantity (mL) they were prescribed as 'morning', 'evening', and 'additional' doses. The information was cross checked with clinical records where the written dosage was less than 0.1 mL and/or greater than 2 mL. The total dose of THC and/or CBD the patient had in a day was then calculated (mg/day).

8.3.3. Study Population

Patients that were enrolled in CACOS and were using medicinal cannabis for an anxiety disorder were included in this cross-sectional study. Patients were provided with health questionnaires throughout the course of their treatment with medicinal cannabis. Patients with a baseline survey prior to treatment with medicinal cannabis and at least one survey after they had started treatment were included in the PROMIS-29 analysis (n = 198), a total of 396 surveys. All patients that had completed a survey after they had started treatment, regardless of whether they had a baseline survey, were included in the AE analysis (n = 568), and from these patients there were a total of 1431 surveys. The time between a participant's first and last survey defined their observational period and where there was only one survey, the observational period

was one day. This data was collected between the dates of the 25th of September 2018 and the 29th of June 2021.

8.3.4. Patient Reported Outcomes Measurement Information System (PROMIS) Analysis

The effectiveness of medicinal cannabis for anxiety disorders was measured using the PROMIS-29 (v2.0) survey, a health-related quality of life (HRQoL) tool that evaluates patient health outcomes based on seven domains. Of the seven, excessive anxiety, fatigue, sleep disturbance, and a decreased ability to take part in social roles and activities are symptoms of anxiety disorders so these domains were included in our analysis (335). The depression domain was also considered relevant to anxiety disorders and included in this study, as these disorders often exist concomitantly (386).

Patients were given a raw score across these five health domains for each of their questionnaires that were converted into T-scores using the PROMIS-29 v2.0 conversion tables as a reference (387). The difference between the scores of their baseline survey and final survey was calculated to determine which patient outcomes improved after treatment with medicinal cannabis. A decrease in t-score indicated improvement in anxiety, depression, fatigue, and sleep disturbance outcomes, whereas improvements in ability to participate in social activities are reflected in a t-score increase. Any outcome improvement was also assessed for clinical significance based on Minimal Clinically Important Difference (MCID) scores published in the literature that had also used the PROMIS-29 tool in patients with anxiety disorders. The MCID for the anxiety domain was four (388), but the MCID scores for depression, fatigue, pain impact, sleep disturbance, and social functioning could not be determined and were set to five as a default, following the literature recommendation (389).

Patients were classified as clinically ‘improved’, ‘unchanged’ or ‘worsened’ based on a respective t-score change of greater than or less than the defined MCID.

8.3.5. Adverse Event (AE) Reporting

Patients were able to self-report any AEs they experienced during their treatment with medicinal cannabis in the questionnaires. The AE section began with the question; *“Have you been experiencing any side effects from your medicinal cannabis prescribed by CA Clinics?”.* There were common AEs listed that the patients could tick or a box for ‘none’ if they hadn’t experienced any side effects. There was also an option of ‘other’ where the patient could freely write anything they experienced outside the listed effects. In analysing the data, each AE was then categorised into an organ class based on the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOC) and reported by formulation type (390). Both the incidence of AEs and the number of patients that reported them were collated in the results to account for patients that had more than one survey and reported the same AE numerous times.

8.3.6. Statistical Analysis

Statistical analysis of the data was performed using SPSS. Data was assessed for normality, and where a normal distribution was observed, the mean and standard deviation (SD) were reported. Where data was not normally distributed, the median and interquartile range (IQR) were used instead (391). Paired two-tailed t-tests were performed to compare patient t-scores before and after taking medicinal cannabis across each PROMIS-29 domain to determine the significance of these results. A one-way Analysis of Variance (ANOVA) (391) was conducted to determine whether there were significant differences in t-score changes between formulation types, and a two-

way ANOVA (392) was also used to compare the differences in t-score changes between both formulation categories and different types of anxiety diagnosis.

Fisher's exact tests were used to compare the clinical improvement categorical results of “improved”, “unchanged”, and “worsened” across the PROMIS-29 domains for each total patient subset (393). As this test assumes categories are independent, patients that had only taken a single formulation type were included in the Fisher’s exact tests. If the clinical categorisation for a PROMIS-29 domain was significant for a total patient subset, further analysis using Fisher’s exact tests were undertaken on the different formulation types to determine which specific formulations were related to the outcomes.

Logistic regressions were performed to determine whether there was a relationship between the CBD/THC doses and clinical improvement in the PROMIS-29 domains. Logistic regressions were also performed on the AE MedDRA classes, to determine whether there were any significant relationships between CBD/THC doses and AEs. Where there was a significant association between the CBD/THC doses and AE class, a logistic regression was performed on the individual AEs in this class to determine where the significance was. A logistic regression was also performed on anxiety as an AE to determine whether there was an association between dose and reported increased anxiety symptoms.

8.4. Results

8.4.1. Patient demographics

From the total patients in the CACOS study, 568 people were eligible for this study as they reported using medicinal cannabis for an anxiety disorder or for symptoms of anxiety. All patients were included in the AE analysis and from these, 198 patients

were eligible for effectiveness (PROMIS-29) analysis. Demographic information of the patient sample, which includes sex, age, and observational period, is provided in Table 1. The different types of anxiety were also recorded where specifically reported by the patient.

Table 1. Demographics of patients included in this study.

Demographic feature	**PROMIS-29 analysis** (n = 198)	**Adverse events analysis** (n = 568)
Sex		
Female, n (%)	105 (53.0)	304 (53.5)
Male, n (%)	93 (47.0)	264 (46.5)
Age, years, median (IQR)	48 (24)	48 (24)
Observational period, days, median (IQR)	154.4 (246.6)	55.8 (191.2)
Anxiety type		
PTSD, n (%)	57 (28.8)	158 (27.8)
Unspecified, n (%)	141 (71.2)	410 (72.2)

8.4.2. Analysis of patient outcomes

There were statistically significant changes to patient outcomes observed in the total patient group (n = 198), PTSD subset (n = 57), and unspecified anxiety subset (n = 141) (Table 2 and Appendices 1 and 2, respectively).

Table 2. Effectiveness (PROMIS-29) analysis of all patients with an anxiety diagnosis.

	All anxiety patients					
	All formulations (n = 198)	**CBD-only** (n = 112)	**CBD Dominant** (n = 20)	**Balanced** (n = 96)	**THC dominant** (n = 18)	**THC-only** (n = 10)
CBD dose mg/day, median (IQR)	50.0 (85.0)	100.0 (100.0)	25.0 (43.5)	20.0 (40.0)	6.0 (13.6)	0.0 (0.0)
THC dose mg/day, median (IQR)	4.4 (20.0)	0.0 (0.0)	6.3 (25.7)	20.0 (34.3)	33.8 (61.5)	38.0 (35.7)
Anxiety (MCID=4)						
Score baseline, mean (SD)	64.6 (9.0)	64.6 (8.8)	61.9 (11.3)	64.2 (8.9)	63.1 (8.5)	64.4 (8.0)
Score final, mean (SD)	59.6 (9.0)	60.2 (8.3)	58.9 (6.8)	59.9 (9.7)	58.2 (7.7)	62.4 (8.0)
p value	<0.001*	<0.001*	0.300	<0.001*	0.011*	0.587
Improved, n (%)	104 (52.5)	56 (50.0)	10 (50.0)	46 (47.9)	11 (61.1)	4 (40.0)
Unchanged, n (%)	66 (33.6)	38 (33.9)	5 (25.0)	36 (37.5)	5 (27.7)	3 (30.0)
Worsened, n (%)	28 (14.1)	18 (16.1)	4 (20.0)	14 (14.6)	2 (11.1)	3 (30.0)
p value[1]	0.945					
Depression (MCID=5)						
Score baseline, mean (SD)	61.6 (9.8)	61.3 (9.8)	61.6 (9.5)	61.9 (10.4)	58.5 (10.6)	61.1 (10.2)
Score final, mean (SD)	57.5 (10.0)	58.3 (9.1)	58.3 (6.4)	57.9 (11.0)	53.9 (10.3)	59.3 (13.6)
p value	<0.001*	<0.001*	0.111	<0.001*	0.018*	0.713
Improved, n (%)	84 (42.4)	39 (34.8)	8 (40.0)	43 (44.8)	9 (50.0)	4 (40.0)
Unchanged, n (%)	86 (43.4)	59 (52.7)	8 (40.0)	33 (34.4)	7 (38.9)	2 (20.0)
Worsened, n (%)	28 (14.1)	14 (12.5)	4 (20.0)	20 (20.8)	2 (11.1)	4 (40.0)
p value[1]	0.032					
Fatigue (MCID=5)						
Score baseline, mean (SD)	62.9 (10.0)	63.0 (9.2)	65.5 (8.5)	63.8 (10.4)	62.3 (12.5)	66.4 (9.4)
Score final, mean (SD)	56.9 (11.0)	56.1 (10.2)	58.6 (8.5)	58.2 (11.2)	55.5 (11.8)	57.4 (13.6)
p value	<0.001*	<0.001*	<0.001*	<0.001*	0.033*	0.014*
Improved, n (%)	95 (48.0)	52 (46.4)	10 (50.0)	46 (47.9)	10 (55.6)	8 (80.0)
Unchanged, n (%)	85 (42.9)	52 (46.4)	9 (45.0)	41 (42.7)	5 (27.8)	2 (20.0)
Worsened, n (%)	18 (9.1)	8 (7.1)	1 (5.0)	9 (9.4)	3 (16.7)	1 (10.0)

p value[1]	0.588					
Sleep disturbance (MCID=5)						
Score baseline, mean (SD)	51.6 (5.4)	51.8 (4.1)	52.7 (3.4)	51.5 (6.7)	51.4 (5.8)	50.1 (6.9)
Score final, mean (SD)	51.6 (4.4)	51.7 (3.5)	52.0 (2.4)	51.60 (5.5)	51.4 (2.8)	52.6 (2.1)
p value	0.964	0.830	0.392	0.788	0.991	0.324
Improved, n (%)	26 (13.1)	11 (9.8)	4 (20.0)	16 (16.7)	4 (22.2)	2 (20.0)
Unchanged, n (%)	150 (75.8)	89 (79.5)	16 (80.0)	67 (69.8)	12 (66.7)	8 (80.0)
Worsened, n (%)	22 (11.1)	12 (10.7)	1 (5.0)	13 (13.5)	2 (11.1)	1 (10.0)
p value[1]	0.458					
Ability to take part in social roles and activities (MCID=5)						
Score baseline, mean (SD)	36.5 (9.3)	37.3 (7.0)	36.1 (7.7)	34.9 (6.9)	37.7 (10.0)	34.7 (7.4)
Score final, mean (SD)	41.5 (9.7)	42.8 (9.2)	40.5 (11.3)	38.7 (9.3)	40.8 (10.4)	42.7 (14.6)
p value	<0.001*	<0.001*	0.024*	<0.001*	0.082	0.022*
Improved, n (%)	91 (46.0)	56 (50.0)	6 (30.0)	37 (38.5)	7 (38.9)	5 (50.0)
Unchanged, n (%)	91 (46.0)	49 (43.8)	13 (65.0)	49 (51.0)	9 (50.0)	5 (50.0)
Worsened, n (%)	16 (8.1)	7 (6.3)	1 (5.0)	10 (10.4)	2 (11.1)	0 (0.0)
p value[1]	0.642					

* p-value is statistically significant ($p < 0.05$)

[1]p-value calculated using Fisher's exact tests including patients from the sample that had been on only one formulation

In the total patient sample (n = 198), across all medicinal cannabis formulations, 53% (n = 104) of patients were classified as having had a clinically meaningful improvement in their anxiety levels (a change in score greater than the MCID) (Table 2). Patients overall reported significantly improved anxiety ($p < 0.001$), depression ($p < 0.001$), fatigue ($p < 0.001$), and ability to take part in social roles and activities ($p < 0.001$). The CBD-only ($p < 0.001$), balanced ($p < 0.001$), and THC dominant ($p = 0.011$) formulations were all associated with significant improvements in anxiety symptoms. There were also significant improvements to patients' depression observed in those taking CBD-only ($p < 0.001$), balanced ($p < 0.001$), and THC dominant formulations ($p = 0.018$). Additionally, fatigue significantly improved across all formulation groups, and the ability to take part in social roles and activities was significantly improved in all formulations except for THC dominant.

Similar to the total patient sample, 52.6% (n = 30) of those diagnosed with PTSD (n = 57) reported a clinical improvement in anxiety symptoms, with statistical significance observed for anxiety ($p < 0.001$), depression ($p < 0.001$), fatigue ($p < 0.001$), and social abilities ($p < 0.001$) (Supplementary Table 7). The CBD-only group (n = 35) was the only formulation associated with significant decreases in anxiety ($p < 0.001$), and depression ($p = 0.019$). Symptoms of depression were also significantly more likely to be categorised as clinically improved in patients taking CBD-only ($p < 0.001$) and balanced ($p < 0.001$) formulations. Patients with PTSD also reported significant improvements to their fatigue in the CBD-only ($p < 0.001$), balanced ($p < 0.001$), and THC-only groups ($p = 0.009$), and in their social ability whilst taking a CBD-only ($p < 0.001$) and balanced ($p = 0.003$) formulations.

The unspecified anxiety subset (n = 141) reported that anxiety symptoms significantly improved whilst taking the same medicinal cannabis formulations as the

total patient sample (Supplementary Table 8). Patients in this cohort also reported significantly improved depression whilst taking CBD-only ($p = 0.002$) and balanced formulations ($p = 0.006$). Fatigue was significantly improved for those taking CBD-only ($p < 0.001$), CBD dominant ($p = 0.001$), balanced ($p < 0.001$), and THC dominant ($p = 0.034$) formulations. This was similar for social abilities, except for the THC dominant formulation.

There was not a significant change to sleep disturbance in any formulation group for all patients or any patient subset. A one-way ANOVA determined that there were not significant differences in health outcomes between formulation types, and a two-way ANOVA confirmed that there were also no significant differences when factoring in the different anxiety disorder classification as well. A logistic regression was performed which established there was no relationship between clinical improvement and CBD/THC dose in this patient sample.

8.4.3. Adverse events

The AEs experienced by patients were analysed according to the formulation type(s) they had been prescribed throughout their observational period (Table 3).

Table 3. Adverse events across formulation types by MedDRA system organ class.

MedDRA system organ class		**All formulations** (n = 568)		**CBD-only** (n = 297)		**CBD dominant** (n = 75)		**Balanced** (n = 257)		**THC dominant** (n = 51)		**THC-only** (n = 19)	
		AE^	**n^^**	**AE**	**n**	**AE**	**n**	**AE**	**n**	**AE**	**n**	**AE**	**n**
CBD dose, median (IQR)		40.0 (87.6)		90 (109.1)		27 (46.3)		18.75 (21.3)		4.0 (7.1)		0.0 (0.4)	
THC dose, median (IQR)		5.0 (20.0)		0.0 (0.0)		8.0 (17.8)		19 (20.0)		30.0 (48.0)		33.0 (19.25)	
Gastro-intestinal disorders, n (%)	**Total**	**386 (29.4)**	**220 (38.7)**	**198 (29.4)**	**105 (35.4)**	**46 (21.0)**	**30 (40.0)**	**216 (29.7)**	**124 (48.2)**	**55 (26.6)**	**29 (56.9)**	**17 (23.9)**	**12 (63.2)**
	Dry mouth	274 (20.9)	185 (32.6)	140 (20.8)	87 (29.3)	30 (13.7)	23 (30.7)	152 (20.9)	104 (40.5)	41 (19.8)	25 (49.0)	15 (21.1)	10 (52.6)
	Nausea	61 (4.6)	52 (9.2)	28 (4.2)	24 (8.1)	6 (2.7)	6 (8.0)	38 (5.2)	32 (12.5)	10 (4.8)	9 (17.6)	2 (2.8)	2 (10.5)
	Diarrhoea	20 (1.5)	19 (3.4)	9 (1.3)	9 (3.0)	3 (1.4)	2 (2.7)	13 (1.8)	12 (4.7)	2 (1.0)	2 (3.9)	0	0
	Gastro-intestinal upset	21 (1.6)	18 (3.2)	15 (2.2)	13 (4.4)	7 (3.2)	5 (6.7)	9 (1.2)	8 (3.1)	2 (1.0)	2 (3.9)	0	0
	Vomiting	2 (0.2)	2 (0.4)	1 (0.1)	1 (0.3)	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Constipation	4 (0.3)	3 (0.5)	4 (0.6)	3 (1.0)	0	0	0	0	0	0	0	0
	Flatulence, bloating and distension	4 (0.3)	2 (0.4)	1 (0.1)	1 (0.3)	0	0	3 (0.4)	1 (0.4)	0	0	0	0
Psychiatric, n (%)	**Total**	**498 (37.9)**	**233 (41.0)**	**261 (38.8)**	**119 (40.1)**	**82 (37.4)**	**32 (42.7)**	**271 (37.2)**	**121 (47.1)**	**60 (29.0)**	**29 (56.9)**	**28 (39.4)**	**12 (63.2)**
	Somnolence	239 (18.2)	178 (31.3)	120 (17.8)	88 (29.9)	40 (18.3)	26 (34.7)	136 (18.7)	96 (37.2)	31 (15.0)	24 (47.1)	13 (18.3)	9 (47.4)
	Inappropriate laughter	2 (0.2)	2 (0.4)	1 (0.1)	1 (0.3)	0	0	2 (0.3)	2 (0.8)	0	0	0	0
	Anxiety	71 (5.4)	54 (9.5)	44 (6.5)	34 (11.4)	10 (4.6)	9 (12.0)	30 (4.1)	23 (8.9)	6 (2.9)	4 (7.8)	3 (4.2)	1 (5.3)
	Lack of motivation	1 (0.1)	1 (0.2)	0	0	1 (0.5)	1 (1.3)	0	0	0	0	0	0
	Confusion	34 (2.6)	31 (5.5)	16 (2.4)	15 (5.1)	4 (1.8)	3 (4.0)	21 (2.9)	19 (7.4)	3 (1.4)	3 (5.9)	1 (1.4)	1 (5.3)
	Disorientation	28 (2.1)	27 (4.8)	18 (2.7)	17 (5.7)	4 (1.8)	4 (5.3)	16 (2.2)	16 (6.2)	4 (1.9)	4 (7.8)	1 (1.4)	1 (5.3)
	Depression	31 (2.4)	30 (5.5)	14 (2.1)	14 (4.7)	2 (0.9)	2 (2.7)	14 (1.9)	14 (5.4)	7 (3.4)	6 (11.8)	3 (4.2)	2 (10.5)
	Paranoia	8 (0.6)	7 (1.2)	6 (0.9)	5 (1.7)	3 (1.4)	2 (2.7)	4 (0.6)	4 (1.6)	1 (0.5)	1 (2.0)	1 (1.4)	1 (5.3)

	Euphoria	37 (2.8)	29 (5.1)	22 (3.3)	19 (6.4)	7 (3.2)	2 (2.7)	21 (2.9)	15 (3.8)	6 (2.9)	5 (9.8)	3 (4.2)	3 (15.8)
	Hallucination	5 (0.4)	5 (0.9)	2 (0.3)	2 (0.7)	1 (0.5)	1 (1.3)	3 (0.4)	3 (1.2)	0	0	1 (1.4)	1 (5.3)
	Insomnia	22 (1.7)	21 (3.7)	10 (1.5)	10 (3.4)	5 (2.3)	5 (6.7)	10 (1.4)	9 (3.5)	0	0	0	0
	Psychosis	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	0	0	0	0	0	0	1 (1.4)	1 (5.3)
	Cognitive impairment	1 (0.1)	1 (0.2)	0	0	1 (0.5)	1 (1.3)	1 (0.1)	1 (0.4)	0	0	0	0
	Slowed thinking	2 (0.2)	1 (0.2)	2 (0.3)	1 (0.3)	0	0	2 (0.3)	1 (0.4)	0	0	0	0
	Increased sex drive	1 (0.1)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Racing thoughts	1 (0.1)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Griding teeth	1 (0.1)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Memory loss	9 (0.7)	8 (1.4)	2 (0.3)	2 (0.7)	4 (1.8)	3 (4.0)	6 (0.8)	5 (1.9)	2 (1.0)	2 (3.9)	0	0
	Mood disorders and disturbances	4 (0.3)	4 (0.7)	3 (0.4)	3 (1.0)	0	0	2 (0.3)	2 (0.8)	0	0	1 (1.4)	1 (5.3)
Nervous System disorders, n (%)	**Total**	**95 (7.2)**	**73 (12.9)**	**53 (7.9)**	**36 (12.1)**	**19 (8.7)**	**15 (20.0)**	**49 (6.7)**	**38 (14.8)**	**16 (7.7)**	**9 (17.6)**	**3 (4.2)**	**3 (15.8)**
	Vivid dreams	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	0	0	0	0	0	0	0	0
	Dizziness	69 (5.3)	62 (10.9)	35 (5.2)	29 (9.8)	13 (5.9)	13 (17.3)	35 (4.8)	33 (12.8)	10 (4.8)	9 (17.6)	3 (4.2)	3 (15.8)
	Agitation	5 (0.4)	1 (0.2)	5 (0.7)	1 (0.3)	0	0	5 (0.7)	1 (0.4)	5 (2.4)	1 (2.0)	0	0
	Tingling feeling	3 (0.2)	2 (0.4)	1 (0.1)	1 (0.3)	0	0	3 (0.4)	2 (0.8)	0	0	0	0
	Tremor	1 (0.1)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Headache	16 (1.2)	13 (2.3)	11 (1.6)	8 (2.7)	6 (2.7)	3 (4.0)	5 (0.7)	5 (1.9)	1 (0.5)	1 (2.0)	0	0
Metabolism disorders, n (%)	**Total**	**79 (6.0)**	**62 (10.9)**	**37 (5.5)**	**30 (10.1)**	**18 (8.2)**	**14 (18.7)**	**47 (6.4)**	**35 (13.6)**	**14 (6.8)**	**8 (15.7)**	**6 (8.5)**	**3 (15.8)**
	Increase appetite	60 (4.6)	45 (7.9)	28 (4.2)	22 (7.4)	9 (4.1)	7 (9.3)	37 (5.1)	27 (10.5)	12 (5.8)	7 (13.7)	6 (8.5)	3 (15.8)
	Decreased appetite	19 (1.5)	18 (3.2)	9 (1.3)	8 (2.7)	9 (4.1)	8 (10.7)	9 (1.2)	9 (3.5)	2 (1.0)	2 (3.9)	0	0
Skin disorders, n (%)	**Total**	**2 (0.2)**	**2 (0.4)**	**1 (0.1)**	**1 (0.3)**	**0**	**0**	**0**	**0**	**1 (0.5)**	**1 (2.0)**	**0**	**0**
	Acne	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	0	0	0	0	0	0	0	0

	Skin irritation	1 (0.1)	1 (0.2)	0	0	0	0	0	0	1 (0.5)	1 (2.0)	0	0
General disorders and administration site conditions, n (%)	**Total**	**197 (15.0)**	**131 (23.1)**	**90 (13.4)**	**62 (20.9)**	**43 (19.6)**	**25 (32.3)**	**108 (15.0)**	**69 (26.8)**	**38 (18.4)**	**19 (37.3)**	**10 (14.1)**	**4 (21.1)**
	Fatigue	125 (9.5)	105 (18.5)	56 (8.3)	48 (16.2)	23 (10.5)	20 (26.7)	70 (9.6)	58 (22.6)	22 (10.6)	17 (33.3)	4 (5.6)	4 (21.1)
	Balance problems	48 (3.7)	40 (7.0)	21 (3.1)	17 (5.7)	7 (3.2)	7 (9.3)	24 (3.3)	21 (8.2)	8 (3.9)	6 (11.8)	2 (2.8)	2 (10.5)
	Foggy feeling in head	2 (0.2)	2 (0.4)	1 (0.1)	1 (0.3)	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Feeling of relaxation	4 (0.3)	1 (0.2)	0	0	4 (1.8)	1 (1.3)	4 (0.6)	1 (0.4)	0	0	0	0
	Weight on chest	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	0	0	0	0	0	0	0	0
	Energy increased	2 (0.2)	2 (0.4)	2 (0.3)	2 (0.7)	1 (0.5)	1 (1.3)	0	0	0	0	0	0
	Increased thirst	1 (0.1)	1 (0.2)	0	0	1 (0.5)	1 (1.3)	1 (0.1)	1 (0.4)	0	0	0	0
	Spaced out feeling	4 (0.3)	1 (0.2)	0	0	4 (1.8)	1 (1.3)	4 (0.6)	1 (0.4)	4 (1.9)	1 (2.0)	4 (5.6)	1 (5.3)
	Pain	10 (0.8)	6 (1.1)	9 (1.3)	5 (1.7)	3 (1.4)	1 (1.3)	4 (0.6)	2 (0.8)	4 (1.9)	2 (3.9)	0	0
Eye disorders, n (%)	**Total**	**19 (1.5)**	**5 (0.9)**	**13 (1.9)**	**2 (0.7)**	**6 (2.7)**	**3 (4.0)**	**14 (1.9)**	**3 (1.2)**	**13 (6.3)**	**2 (3.9)**	**4 (5.6)**	**1 (5.3)**
	Vision issues	4 (0.3)	2 (0.4)	3 (0.5)	1 (0.3)	4 (1.8)	2 (2.7)	0	0	0	0	0	0
	Dry eyes	15 (1.1)	4 (0.7)	10 (1.5)	2 (0.7)	2 (0.9)	2 (2.7)	14 (1.9)	3 (1.2)	13 (6.3)	2 (3.9)	4 (5.6)	1 (5.3)
Respiratory thoracic and mediastinal disorders, n (%)	**Total**	**6 (0.5)**	**6 (1.1)**	**5 (0.7)**	**5 (1.7)**	**2 (0.9)**	**2 (2.7)**	**3 (0.4)**	**3 (1.2)**	**1 (0.5)**	**1 (2.0)**	**0**	**0**
	Sore throat	6 (0.5)	6 (1.1)	5 (0.7)	5 (1.7)	2 (0.9)	2 (2.7)	3 (0.4)	3 (1.2)	1 (0.5)	1 (2.0)	0	0
Cardiac disorders, n (%)	**Total**	**5 (0.4)**	**3 (0.5)**	**2 (0.3)**	**2 (0.7)**	**0**	**0**	**2 (0.3)**	**1 (0.4)**	**0**	**0**	**0**	**0**
	Arrhythmia	2 (0.2)	2 (0.4)	2 (0.3)	2 (0.7)	0	0	0	0	0	0	0	0
	Palpitations	3 (0.2)	1 (0.2)	0	0	0	0	3 (0.4)	1 (0.4)	0)	0	0	0
Musculo-skeletal and connective tissue	**Total**	**5 (0.4)**	**4 (0.7)**	**0**	**0**	**0**	**0**	**4 (0.6)**	**3 (1.2)**	**1 (0.5)**	**1 (2.0)**	**0**	**0**
	Muscle twitching	1 (0.1)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Mobility decreased	1 (0.1)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.4)	0	0	0	0

disorders, n (%)	Muscle tension	2 (0.2)	1 (0.2)	0	0	0	0	2 (0.3)	1 (0.4)	0	0	0	0
	Swollen ankles	1 (0.1)	1 (0.2)	0	0	0	0	0	0	1 (0.5)	1 (2.0)	0	0
Ear and labyrinth disorders, n (%)	**Total**	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	0	0	1 (0.1)	1 (0.4)	0	0	0	0
	Tinnitus	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	0	0	1 (0.1)	1 (0.4)	0	0	0	0
Renal and urinary disorders, n (%)	**Total**	**1 (0.1)**	**1 (0.2)**	**0**	**0**	**0**	**0**	**1 (0.1)**	**1 (0.4)**	**0**	**0**	**0**	**0**
	Increased urination	1 (0.1)	1 (0.2)	0	0	0	0	1 (0.1)	1 (0.4)	0	0	0	0
Immune system disorders, n (%)	**Total**	**2 (0.2)**	**1 (0.2)**	**2 (0.3)**	**1 (0.3)**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
	Allergy	2 (0.2)	1 (0.2)	2 (0.3)	1 (0.3)	0	0	0	0	0	0	0	0
Other (undefined), n (%)		18 (1.4)	15 (2.6)	10 (1.5)	7 (2.4)	3 (1.4)	3 (4.0)	11 (1.5)	9 (3.5)	8 (3.7)	6 (11.8)	3 (4.2)	3 (15.8)
Total n		**1314**	**568**	**673**	**297**	**219**	**75**	**727**	**257**	**207**	**51**	**71**	**19**
Number of patients that never reported adverse events, n (%)		227 (40.0)		120 (40.4)		29 (38.7)		89 (34.6)		13 (25.5)		3 (15.8)	

^AE refers to total number of AEs reported.
^^n refers to total number of patients that reported the AE.

A total of 1314 AEs were reported across 568 patients. The maximum number of different AEs reported by a single patient across their total observational period was 13.

There were 227 (40.0%) patients that never reported an AE, and the CBD-only group had the greatest proportion of patients who were in this category (n = 120, 40.4%). The most common type of AE recorded across all formulation types was in the psychiatric class of AEs, with a total of 233 patients (41.0%) reporting a related side event. The most common psychiatric AEs experienced by patients were somnolence (n = 178, 31.3%), anxiety (n = 54, 9.5%), and euphoria (n = 29, 5.1%). Where patients reported anxiety as an AE, it indicated they experienced increased anxiety symptoms since commencing treatment with medicinal cannabis.

Other common AEs included dry mouth (n = 185, 32.6%), fatigue (n = 105, 18.5%), and dizziness (n = 62, 10.9%). A logistic regression established a relationship between THC concentration and gastrointestinal AEs (OR 1.011, p = 0.003); specifically dry mouth (OR = 1.010, p = 0.005) and nausea (OR = 1.008, p = 0.008) (Supplementary Table 9). Anxiety as an AE was also analysed individually in this regression; however, there was no significant association with CBD and/or THC doses.

In patients taking CBD-only formulations, somnolence and dry mouth were the most common AEs, reported by 88 (29.9%) and 87 (29.3%) patients, respectively. Dizziness was most prevalent in patients who took THC dominant (n = 9, 17.6%) and CBD dominant (n = 13, 17.3%) formulations. Patients who took a balanced formulation made up a higher proportion of patients who reported confusion (n = 19, 7.4%) and disorientation (n = 16, 6.2%) compared with patients in the other formulation groups. The THC-only subset had the highest proportion of patients who reported euphoria (n = 3, 15.8%), followed by the THC dominant formulation group (n = 5, 9.8%).

8.5. Discussion

This observational retrospective study of patients using medicinal cannabis for anxiety disorders analysed the effectiveness of medicinal cannabis on different HRQoL outcomes of patients. It has also provided insight into the type and incidence of AEs experienced by patients.

8.5.1. Patient outcomes were similar to that of other studies and provide insight for future medicinal cannabis treatment

The CBD-only and balanced formulations improved patient reported levels of anxiety, depression, fatigue, and ability to participate in social activity in both the full patient sample and the unspecified anxiety subset. In the PTSD patient subset, the CBD-only formulation group at a median (IQR) dose 95 (117.6) mg/day, was the only group that significantly improved the same four patient outcomes. Cannabidiol-only formulations would therefore be considered the most effective medicinal cannabis treatment in patients with PTSD; however, this study only used a small group of PTSD patients so future studies with more patients on other medicinal cannabis formulations are needed. The effectiveness of CBD-only formulations for PTSD was also observed in a case series of 11 patients that were treated with CBD (48.6 mg/day median start dose) as an adjunct to concurrent psychiatric medications (394). A decrease in PTSD symptoms, as measured by the PTSD Checklist for Diagnostic Statistical Manual of Mental Disorders, such was reported in 91% (n = 10) of the patients in in our study; this suggests that lower doses of CBD could be as effective as higher doses (394). It is important to note that concurrent psychiatric medications were reported but not accounted for or analysed in the case series, and not reported in our study.

In our study there were no patient groups that had a significant decrease in their self-reported levels of sleep disturbance. Sleep disturbance, specifically, experiencing regular dreams that patients find distressing (335), is a common symptom of PTSD and experienced by up to 90% of patients (395). The PROMIS-29 questionnaire asks four general questions about sleep quality, feeling refreshed, and difficulty falling or staying asleep, whereas prior studies that looked at the effectiveness of medicinal cannabis for PTSD used more specific measures of PTSD symptoms that asked explicitly about dreams (370). These studies reported that a synthetic derivative of THC, nabilone, clinically improved the incidence of patient reported nightmares in 50% of the sample (370). Future studies could implement measures that are more specific to PTSD, which would therefore give a more accurate indication of effectiveness of medicinal cannabis for decreasing sleep disturbance in these patients.

Patients who took a THC dominant formulation had a significant decrease in their anxiety levels and the highest proportion of patients that were classified as having clinical improvement (61.1%, n = 11), compared with patients who were prescribed other formulation types. This was unexpected as the median THC dose for this patient group was 33.8 mg/day and it has been suggested that doses higher than 30 mg/day could be anxiogenic, and lower doses would be more effective for relieving the symptoms of anxiety (385). A study reported that doses of CBD ranging from 15–60 mg/day could offset the anxiogenic properties of THC, which is reflected in our data; however, with lower doses of CBD (median = 6.0 mg/day CBD) (385). Whilst the THC dominant group had the highest proportion of patients classified as clinically improved, the patient subset was small (n = 18) and was found to be not statistically significant.

Self-reported patient anxiety symptoms significantly improved in patients with unspecified anxiety that used CBD-only, balanced, and THC formulations. In Australia,

the most common types of anxiety disorders are PTSD (6.4%), followed by social anxiety (4.7%) and generalised anxiety disorder (2.7%) (396). Due to the significant prevalence of social anxiety in Australia, it can be assumed that a portion of the patients in the undiagnosed anxiety group had a social anxiety diagnosis. The results from this study can therefore be considered in relation to a study of the effectiveness of CBD for patients with social anxiety (397). Similar to our results in this study, their research found that there were significant improvements to patient anxiety levels when measured by both the Fear of Negative Evaluation Questionnaire and the Liebowitz Social Anxiety Scale measurements (397). Another study that looked at patients with an unspecified anxiety diagnosis who took 25–175 mg/day CBD capsules, reported improved anxiety scores for 79% of the patients (n = 57) (398). These results are not directly comparable to our results for the CBD-only patients, as we reported the number of patients that were classified as clinically improved (n = 38, 49.4%).

There were significant improvements in the depression outcomes for patients taking CBD-only, balanced, and THC dominant formulations. For PTSD patients, CBD-only and balanced formulations were also found to have a significant association with clinically improved depression outcomes. Having a chronic health condition is considered a risk factor for depression, and is a common comorbidity for patients with chronic conditions (399). The effectiveness of medicinal cannabis for depression may therefore have clinical relevance for other chronic conditions that are treated with medicinal cannabis, such as chronic pain (400).

There was no association between the CBD/THC dose and patient improvement in any of the five health outcomes. As such, further studies would need to be conducted to determine the optimal dose for PTSD and other anxiety conditions.

8.5.2. Adverse events were comparable to other studies that reported effects from medicinal cannabis.

In our study, 60% of patients (n = 341) reported at least one AE and 40% (n = 227) reported no AEs. The most common AEs reported in this study were dry mouth (32.6%), somnolence (31.3%), fatigue (18.5%), and dizziness (10.9%). The wide range of AEs of medicinal cannabis in the sample is explained by the significant distribution of the ECS throughout the body (37).

An Australian study that recruited 1302 patients who had been taking medicinal cannabis and reported AEs that they had experienced found that the most common AE was increased appetite, followed by somnolence, ocular irritation, and a lack of energy (401). The incidence of AEs was much higher in this sample; however, the most common AEs were similar to those observed in our study.

A study of 239 medicinal cannabis patients that looked at AEs after six months of treatment found that dizziness was the most common side effect (7.9%, n = 19) (402). This study compared the AEs over the patients' course of treatment and found that there was a significant decrease in side effects experienced by patients six months into treatment when compared with when they started their treatment (402). This has been supported by other studies that report significant decreases in AEs with continued medicinal cannabis use (403).

The AE results from our analysis can be compared to studies looking at side effects for other medications commonly used to treat anxiety such as SSRIs, specifically fluoxetine which is indicated in Australia for obsessive compulsive disorder and PTSD (383). A study that analysed the AEs reported in 14 randomised control trials or fluoxetine compared to other SSRIs found that the incidence of any AEs reported in the two groups were 59.4% and 59.3%, respectively (404). The most

common side effects for those SSRI users were nausea, headache, and dry mouth (404). The incidence of any AEs for SSRI users gives context to the 60% of our sample that reported an AE from medicinal cannabis. Determining whether there is a significant difference in the AEs between medicinal cannabis and SSRIs could be considered in future work, particularly as anxiety patients are often involved in their treatment choice which is based on side effect profiles of indicated medications (382).

8.5.3. Limitations of this study

This study relied on data gathered from surveys that patients completed themselves, and therefore recall bias and misclassification bias were not accounted for. This study cohort may also be subject to potential sample bias as characteristics of patients who chose not to enrol in CACOS are not known. The cohort included may not be representative of the general population. Future studies should attempt to study patients across multiple sites and with diverse characteristics to increase external validity. In addition, potential confounders were also not controlled or accounted for such as other medications the patient was taking nor the duration of their treatment. As this study was observational it can only establish that medicinal cannabis is associated with the identified outcomes and therefore it cannot be concluded it is the cause of these outcomes. The AE analysis did not account for the number of surveys a single patient completed, the severity of effect, or if they were collected less than seven days apart unlike the PROMIS analysis. This study didn't analyse the dose and AEs meaning we were unable to determine whether there was an association between higher doses and greater incidence of AEs. The pharmacology of CBD and THC in anxiety conditions was not discussed within the scope of the paper. Future research should address characteristics that may affect whether patients find CBD and/or THC

effective and at what doses. Different types of oral formulations were included and the differences in outcome between these were not assessed. There was also significant variation in the observational period in both the AE and PROMIS groups. We were unable to specify the anxiety diagnosis of 141 patients, and therefore could not do an in-depth assessment of the effects of medicinal cannabis on each anxiety subset.

8.6. Conclusions

Medicinal cannabis significantly improved patient-reported outcomes of anxiety, depression, fatigue, and the ability to participate in social activities for patients with anxiety disorders. The only formulation type to improve all four of these patient outcomes in the total patient sample and subsets of unspecified anxiety and PTSD was CBD-only. The most common AEs experienced by patients were dry mouth, somnolence, and fatigue. There were significant associations between the THC dose and gastrointestinal adverse events, dry mouth, and nausea. Further studies into medicinal cannabis should aim to establish the optimal dose and dosage regimen of CBD/THC for patients with anxiety disorders. A more specific analysis should also be undertaken into the effectiveness of medicinal cannabis for other anxiety disorders such as social anxiety and generalised anxiety disorder.

CHAPTER NINE

CONCLUSIONS AND FUTURE WORK

CHAPTER 9: CONCLUSIONS AND FUTURE WORK

In this thesis, the prescribing of medicinal cannabis for chronic pain and anxiety was explored, and protocols for randomised controlled trials developed. One trial has received human research ethics committee approval and has been registered with the federal government.

The limitations of this thesis largely relate to the nature of the data collected as part of the CA Clinics Observational Study (CACOS). As this study was observational, it can only be established that medicinal cannabis therapy was associated with the reported outcomes, and not the cause. The CA Clinics Observational Study relied upon patient-reported outcomes where potential confounders, and recall, misclassification, and confirmation bias were not controlled. The data may be subject to sample bias as the survey response rate and the characteristics of those who did not respond could not be determined. This means the cohorts examined may not be representative of the general population. Future studies should enrol patients across multiple sites and with diverse characteristics to increase external validity. Given the exploratory nature of the studies, data was not corrected for multiplicity so the risk of erroneously rejecting the null hypothesis (type I error rate) may be increased. Key limitations include unknown prior cannabis usage, and varied observational periods, administration routes, CBD and THC dosages, terpene profiles, formulation types, and cohort sizes. Additionally, an increase or decrease in effectiveness over time was not measured. Future study designs should control for these factors which may impact results. Concomitant medication histories were collected from referring medical practitioners which may not be comprehensive, and may have excluded over the counter medicines and dosing information. Further research should ensure accuracy of medication histories by obtaining from multiple sources, including the participant. Relating to safety, the

severity and incidence of adverse events (AEs) were not tracked over time, and it is unknown whether concomitant therapies may have contributed to AE (or effectiveness) outcomes.

The scales selected in the studies in this thesis ensured both unidimensional and multidimensional outcomes were measured. Unidimensional scales (Numerical Rating Scale, Visual Analogue Scale, Global Rating of Change Scale) are one-item scales that measure pain in a quick and easy to administer way. The multidimensional scales (Brief Pain Inventory-Short Form, Patient Reported Outcomes Measurement Information System 29 (PROMIS-29), Western Ontario and McMaster Arthritis Index, Menopause-Specific Quality of Life Scale), are more complex and measure other aspects of pain or chronic illness including participants' physical functioning, or impact on quality of life (405). The PROMIS-29 scale was selected by Applied Cannabis Research as CACOS studied many different chronic health conditions. The PROMIS-29 questionnaire is a generic, validated tool that evaluates physical, mental, and social health and wellbeing in people with any chronic illness. Other scales selected in the protocols described in chapters 4 and 6 were selected after literature review and consultation with the Principal Investigators of each study. Future, controlled research into chronic pain, arthritis, and anxiety conditions would benefit greatly from using disease specific scales.

For chronic pain and anxiety, medicinal cannabis use was associated with improvements in health-related quality of life (HRQoL) outcomes, with results varying between different CBD and THC ratios. Chronic pain patients who took a balanced CBD:THC product reported significantly reduced pain intensity scores. In the arthritis pain-subset, the CBD-only and balanced products aligned with significantly reduced pain intensity. Overall, the balanced products were associated with the highest number

of HRQoL improvements; pain intensity, pain interference, pain impact, sleep disturbance, and social functioning. Chronic pain is associated with high physical, psychological, social, and financial burden. Alternate and effective analgesia options are critical for these patients, particularly due to the high risk for tolerance, dependence and the sedating adverse effects caused by opioids. The promising findings for CBD-only products for arthritic pain provides a foundation for the development of clinical trials. Two forms of arthritic joint pain, osteoarthritis, and aromatase-inhibitor associated arthralgia, are of interest as both need new treatments to address their underlying inflammatory and immunological pathology. For both indications, there are plausible mechanisms of action that CBD could reduce the causative inflammation and potentially improve symptoms. To pilot this, this thesis designed and developed a two-stage study protocol for both CBD and the cannabimimetic PEA for osteoarthritis. The first stage of this pilot study is a dose-finding pharmacokinetic study, and the second stage, a double-blind placebo controlled cross-over efficacy study. Another clinical trial protocol was designed and developed in this thesis to pilot the use of CBD for aromatase-inhibitor associated arthralgias to assess whether CBD could reduce joint pain symptoms, improve HRQoL, and to explore the novel idea that CBD may help with menopausal symptoms. Similar to the second stage of osteoarthritis study, this protocol also follows a double-blind placebo-controlled cross-over design. This clinical trial protocol is currently undergoing human research ethics committee evaluation.

Future clinical trials on inflammatory conditions should also measure objective outcomes before and after treatment, such as circulating cytokines and inflammatory mediators to add to the knowledge of how medicinal cannabis exerts its effect. In addition, the exploration of the endocannabinoid system could also be incorporated

into clinical trials to enhance our understanding of the endocannabinoid system and how exogenous cannabinoid administration may impact its function.

This thesis has shown that polypharmacy occurs in a majority of chronic pain patients taking medicinal cannabis. Possible clinical ramifications were identified where the incidence of AEs such as dizziness, fatigue, and somnolence were associated with concomitant prescribing of gabapentinoids and tricyclic antidepressants. This study into the concomitant medications used in chronic pain medicinal cannabis patients indicates that both pharmacodynamic and pharmacokinetic drug-drug interactions are key concerns, and the clinical impact of these needs to be confirmed. The frequent concomitant use of opioids, benzodiazepines, and adjuvant analgesics necessitates exploration of any medication sparing effects, synergism, or interactions that medicinal cannabis may have. Future studies can distinguish between the effect of a drug interaction or possible synergy between medicinal cannabis and other concomitant treatments by examining the area under the curve in pharmacokinetic studies. Currently under the Special Access Scheme in Australia, cannabis is to be used when other therapies are insufficient or inadequate, meaning cannabis is often used adjunctly to conventional treatments. Knowledge from pharmacokinetic studies will be crucial to inform current prescribers and future guidelines to ensure patient safety and the optimal use of cannabis therapies.

The literature review of medicinal cannabis for anxiety conditions demonstrated promising pharmacological actions; however, robust evidence remains inconclusive. It was concluded that further exploration is needed to determine for which anxiety disorders medicinal cannabis could be effective, and at what dose, and the best CBD:THC concentrations. Analyses of observational data in this thesis showed that

patients with anxiety disorders taking medicinal cannabis reported significantly reduced anxiety scores. In particular, the CBD-only, balanced, and THC dominant products were associated with reduced anxiety scores. In a subset analysis, patients with post-traumatic stress disorder (PTSD) taking a CBD-only product also reported significantly reduced anxiety scores. Overall, CBD-only products were associated with improvements in other HRQoL outcomes, including depression, fatigue, and social functioning. Given the high prevalence and disease burden of anxiety, as well as the limitations of using benzodiazepines and antidepressants, the findings in this thesis indicate medicinal cannabis could be an effective alternative. Further studies need to consider the significant inter-patient variability outlined in this thesis, particularly due to the varied anxiolytic and anxiogenic responses. Another consideration will be assessing whether medicinal cannabis can be used on an intermittent, when required basis, or whether chronic, maintenance dosing is superior. Anxiety specific scales will be imperative to determine efficacy in future studies, including for PTSD, and other conditions worth exploring such as social anxiety disorder and generalised anxiety disorder.

Both analyses into chronic pain and anxiety suggests that more than 50% of patients experience at least one adverse event (AE) whilst taking medicinal cannabis, with the most common being dry mouth, somnolence, and fatigue. These findings align with the wider literature, providing consistency and adding to real word insights. Conventional treatment options for both anxiety and chronic pain have been shown to have differing AE profiles, at similar or higher rates. For example, opioids and constipation, and serotonin re-uptake inhibitors and headache. Medicinal cannabis may be useful as another option for patients with anxiety and chronic pain who do not tolerate conventional treatment.

Despite the benefits of observing real-world prescribing practices described in this thesis, this type of data comes with limitations, many of which can only be addressed in future, controlled studies as outlined. Significant complexities and variations exist when it comes to medicinal cannabis therapy, not only in the numerous product formulations, but in how people respond, adding to the complexity of conducting large scale rigorous controlled trials. Substantial inter-patient variability means patients experience medicinal cannabis therapy differently with regard to both efficacy outcomes and AEs. In addition, patients that are naive to cannabis may respond to treatment and experience AEs differently compared to previous users. These are all important concepts that need to be further explored and addressed in future works. In spite of these challenges, randomised controlled and blinded studies are imperative to establish clinical efficacy, and will by their nature, address the important limitations found in this thesis that future work should focus on. The results in this thesis show observed improvements in both chronic pain and anxiety whilst taking CBD-only and balanced products, and the efficacy of these products should be established in future, randomised, placebo-controlled studies. Importantly, the sample sizes between those prescribed different ratios of CBD:THC varied, which is an inherent issue in observing standard practice. Further comparisons are needed to determine if the ratios identified in this thesis are indeed superior. In addition, evaluation and control of the minor cannabinoids and terpenes present in cannabis products is needed due to the aforementioned possible synergistic entourage effects. An optimal dose and route of administration of cannabis in chronic pain and anxiety is also yet to be identified and warrants further exploration. Having an established dose regimen is complicated by the heterogeneous response that individuals have to

cannabis, but will be critical for successful clinical trials and eventual registration of cannabis products on the Australian Register of Therapeutic Goods.

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SUPPLEMENTARY MATERIAL

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Supplementary Table 1. Changes in PROMIS-29 domains over the observational period with different medicinal cannabis products, and the cannabinoid dose at the final survey timepoint.

			Chronic pain (n = 296)					
			All Products (n = 296)	**CBD-only** (n = 174)	**CBD-dominant** (n = 37)	**Balanced** (n = 113)	**THC-dominant** (n = 37)	*MCID*
Dose (mg/day), median (Q1–Q3)[1]	**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)	
Pain Interference								
T score first, mean (SD)			64.5 (7.4)	64.2 (7.8)	66.6 (7.6)	65.4 (7.4)	63.3 (8.1)	
T score final, mean (SD)			63.5 (7.3)	63.4 (7.4)	65.5 (6.7)	63.7 (7.6)	63.4 (8.1)	
p			0.007*	0.114	0.358	0.007*	0.94	
Improved, n (%)			115 (38.9)	64 (36.8)	14 (37.8)	49 (43.4)	13 (35.1)	*2.0 (120)*
Not changed, n (%)			100 (33.8)	60 (34.5)	13 (35.1)	34 (30.1)	12 (32.4)	
Worsened, n (%)			81 (27.4)	50 (28.7)	10 (27)	30 (26.5)	12 (32.4)	
Pain Intensity (1-10)								
Score first, mean (SD)			5.9 (2.1)	5.9 (2.2)	6.2 (1.8)	6.1 (2.1)	5.6 (2.1)	
Score final, mean (SD)			5.6 (2.1)	5.6 (2.2)	6.1 (2)	5.7 (2)	5.7 (2.2)	
p			0.003*	0.055	0.606	0.025*	0.723	
Improved, n (%)			64 (21.6)	37 (21.3)	8 (21.6)	27 (23.9)	5 (13.5)	*2.0 (120)*
Not changed, n (%)			190 (64.2)	108 (62.1)	22 (59.5)	72 (63.7)	26 (70.3)	
Worsened, n (%)			42 (14.2)	29 (16.7)	7 (18.9)	14 (12.4)	6 (16.2)	
Physical Function								
T score first, mean (SD)			37 (7.7)	37.3 (7.5)	35.7 (9)	35.5 (7.1)	38.5 (8.6)	
T score final, mean (SD)			36.9 (6.9)	37.4 (6.7)	35.1 (7.3)	35.8 (6)	37.3 (8.3)	
p			0.792	0.868	0.496	0.536	0.362	
Improved, n (%)			92 (31.1)	57 (32.8)	11 (29.7)	40 (35.4)	12 (32.4)	*1.9 (120, 121)*
Not changed, n (%)			127 (42.9)	71 (40.8)	15 (40.5)	46 (40.7)	13 (35.1)	
Worsened, n (%)			77 (26)	46 (26.4)	11 (29.7)	27 (23.9)	12 (32.4)	
Sleep Disturbance								
T score first, mean (SD)			53.4 (8.5)	53.7 (8.5)	52.1 (9.6)	53.3 (9.1)	54.4 (9)	

T score final, mean (SD)	53 (8.1)	53.6 (7.9)	52.6 (8.4)	52.4 (7.8)	52.4 (9.5)	
P	0.385	0.835	0.599	0.272	0.143	
Improved, n (%)	109 (36.8)	60 (34.5)	11 (29.7)	49 (43.4)	16 (43.2)	
Not changed, n (%)	75 (25.3)	47 (27)	12 (32.4)	24 (21.2)	8 (21.6)	*2.0*[2]
Worsened, n (%)	112 (37.8)	67 (38.5)	14 (37.8)	40 (35.4)	13 (35.1)	
Anxiety						
T score first, mean (SD)	53.4 (10.1)	53.3 (10.2)	54.2 (12.1)	54 (9.8)	56.3 (9.7)	
T score final, mean (SD)	53.8 (10.1)	53.7 (10.2)	54.4 (10.7)	53.6 (9.9)	58.3 (9)	
p	0.381	0.56	0.914	0.661	0.138	
Improved, n (%)	73 (24.7)	44 (25.4)	11 (29.7)	31 (27.4)	7 (18.9)	
Not changed, n (%)	130 (44.1)	78 (45.1)	12 (32.4)	48 (42.5)	15 (40.5)	*2.3 (122)*
Worsened, n (%)	92 (31.2)	51 (29.5)	14 (37.8)	34 (30.1)	15 (40.5)	
Depression						
T score first, mean (SD)	53.6 (10.2)	53.9 (10.2)	54 (11.5)	54.1 (10.8)	55.7 (8.9)	
T score final, mean (SD)	53.8 (9.7)	53.5 (9.7)	55.5 (9.1)	53.5 (10.1)	56.5 (8.8)	
p	0.764	0.456	0.296	0.414	0.509	
Improved, n (%)	86 (29.1)	51 (29.3)	11 (29.7)	37 (32.7)	11 (29.7)	
Not changed, n (%)	133 (44.9)	84 (48.3)	12 (32.4)	49 (43.4)	14 (37.8)	*3.0 (122)*
Worsened, n (%)	77 (26)	39 (22.4)	14 (37.8)	27 (23.9)	12 (32.4)	
Social Functioning						
T score first, mean (SD)	40.8 (9.1)	41.5 (9.3)	38.1 (7.6)	39.1 (8.5)	41.2 (10.4)	
T score final, mean (SD)	41.2 (8.5)	41.9 (8.8)	39.1 (7.4)	39.9 (7.4)	39.7 (8.9)	
P	0.301	0.556	0.283	0.146	0.301	
Improved, n (%)	103 (34.8)	61 (35.1)	14 (37.8)	40 (35.4)	10 (27)	
Not changed, n (%)	129 (43.6)	71 (40.8)	15 (40.5)	50 (44.2)	18 (48.6)	*2.0*[2]
Worsened, n (%)	64 (21.6)	42 (24.1)	8 (21.6)	23 (20.4)	9 (24.3)	
Fatigue						
T score first, mean (SD)	55.9 (10.4)	55.7 (10.5)	58.8 (10.6)	56 (10.5)	57.3 (9.4)	
T score final, mean (SD)	56.1 (10.1)	56.3 (10.3)	57.8 (9.7)	56.3 (9.6)	58 (9.6)	
P	0.699	0.451	0.576	0.718	0.684	
Improved, n (%)	105 (35.6)	56 (32.2)	17 (45.9)	38 (33.9)	14 (37.8)	
Not changed, n (%)	71 (24.1)	43 (24.7)	8 (21.6)	26 (23.2)	9 (24.3)	*2.5 (123)*
Worsened, n (%)	119 (40.3)	75 (43.1)	12 (32.4)	48 (42.9)	14 (37.8)	
Impact Score (Pain)						
Raw score first, mean (SD)	32.2 (9.6)	31.8 (9.7)	34.9 (10.2)	33.9 (9.5)	30.6 (10.5)	
Raw score final, mean (SD)	31.2 (9.3)	30.9 (9.4)	34.1 (9.8)	32.3 (9.2)	31.4 (9.1)	
p	0.02*	0.116	0.515	0.023*	0.63	
Improved, n (%)	121 (40.9)	72 (41.4)	14 (37.8)	47 (41.6)	13 (35.1)	
Not changed, n (%)	94 (31.8)	53 (30.5)	10 (27)	36 (31.9)	11 (29.7)	*3.0 (120)*
Worsened, n (%)	81 (27.4)	49 (28.2)	13 (35.1)	30 (26.5)	13 (35.1)	
Impact shift[3], positive	71 (24)	39 (22.4)	8 (21.6)	28 (24.8)	10 (27)	

No impact shift	181 (61.1)	106 (60.9)	23 (62.2)	71 (62.8)	20 (54.1)	
Impact shift, negative	44 (14.9)	29 (16.7)	6 (16.2)	14 (12.4)	7 (18.9)	

[1] Median dose on last survey.
[2] MCID = 2.0 as default given there is no published MCID value in literature to reference.
* $p < 0.05$ statistical significant in paired t-test.
[3] Impact shift is defined as a change from mild impact (8–27) to moderate impact (28–34) to severe impact (≥ 35) based on impact score cut-offs. A positive impact shift shows patients changed in a positive direction from a detrimental impact level to a lower one (i.e. severe → moderate/moderate → mild)
Patients that changed medicinal cannabis products throughout the survey period were included in both categories for analysis (n = 87).

Supplementary Table 2. Changes in PROMIS-29 domains over the observational period in the arthritis subset with different medicinal cannabis products, and the cannabinoid dose at the final survey timepoint.

			Arthritis subset (n = 92)					
			All products (n = 92)	**CBD-only** (n = 58)	**CBD-dominant** (n = 16)	**Balanced** (n = 28)	**THC-dominant** (n = 9)	*MCID*
Dose (mg/day), median (Q1–Q3)[1]	**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)	
Pain Interference								
T score first, mean (SD)			66.2 (7.6)	65.6 (7.5)	67.7 (9)	69.1 (6.7)	63.4 (11.1)	
T score final, mean (SD)			64.6 (7.5)	63.9 (6.9)	66.2 (6)	65.9 (8.3)	67.3 (10.7)	
p			0.036*	0.066	0.465	0.014*	0.13	
PI improved, n (%)			39 (42.4)	25 (43.1)	6 (37.5)	13 (46.4)	1 (11.1)	*2.0 (120)*
PI not changed, n (%)			30 (32.6)	20 (34.5)	5 (31.3)	10 (35.7)	4 (44.4)	
PI worsened, n (%)			23 (25)	13 (22.4)	5 (31.3)	5 (17.9)	4 (44.4)	
Pain Intensity (1-10)								
Score first, mean (SD)			6.5 (2.2)	6.3 (2.2)	6.7 (1.9)	7.1 (2.2)	5.9 (3)	
Score final, mean (SD)			5.9 (2.2)	5.7 (2.2)	6.3 (1.6)	6 (2.1)	6.6 (2.6)	
p			0.005*	0.018*	0.353	0.005*	0.408	
Improved, n (%)			26 (28.3)	15 (25.9)	4 (25)	12 (42.9)	0 (0)	*2.0 (120)*
Not changed, n (%)			57 (62)	37 (63.8)	10 (62.5)	15 (53.6)	7 (77.8)	
Worsened, n (%)			9 (9.8)	6 (10.3)	2 (12.5)	1 (3.6)	2 (22.2)	
Physical Function								
T score first, mean (SD)			35.5 (8.2)	36.4 (7.6)	32.6 (11)	31.9 (6.5)	40.5 (9.1)	
T score final, mean (SD)			35.3 (6.7)	36.9 (6.4)	32.3 (6.7)	32.5 (6)	33.4 (5.8)	
p			0.743	0.385	0.821	0.406	0.064	
Improved, n (%)			31 (33.7)	23 (39.7)	6 (37.5)	10 (35.7)	1 (11.1)	*1.9 (120, 121)*
Not changed, n (%)			38 (41.3)	22 (37.9)	5 (31.3)	12 (42.9)	3 (33.3)	
Worsened, n (%)			23 (25)	13 (22.4)	5 (31.3)	6 (21.4)	5 (55.6)	
Sleep Disturbance								
T score first, mean (SD)			53.4 (9.5)	53.7 (9)	50.9 (9.5)	53.6 (11.5)	54.5 (11.8)	
T score final, mean (SD)			52.7 (8.6)	54.1 (8.2)	50.9 (5.9)	50.5 (8.9)	53.4 (12)	
P			0.397	0.685	0.97	0.036*	0.764	
Improved, n (%)			38 (41.3)	19 (32.8)	5 (31.3)	16 (57.1)	3 (33.3)	*2.0*[2]
Not changed, n (%)			18 (19.6)	13 (22.4)	6 (37.5)	3 (10.7)	2 (22.2)	
Worsened, n (%)			36 (39.1)	26 (44.8)	5 (31.3)	9 (32.1)	4 (44.4)	

Anxiety						
T score first, mean (SD)	53.2 (10.3)	52.8 (9.9)	53.5 (12.1)	55.7 (10.9)	53.6 (13.1)	
T score final, mean (SD)	53.4 (10.2)	52.8 (9.6)	52 (10.6)	54 (10.6)	60.4 (12)	
p	0.869	0.966	0.637	0.406	0.062	
Improved, n (%)	22 (23.9)	14 (24.1)	5 (31.3)	9 (32.1)	0 (0)	*2.3*
Not changed, n (%)	41 (44.6)	27 (46.6)	7 (43.8)	9 (32.1)	4 (44.4)	*(122)*
Worsened, n (%)	29 (31.5)	17 (29.3)	4 (25)	10 (35.7)	5 (55.6)	
Depression						
T score first, mean (SD)	54.3 (10.7)	54.5 (10)	55.1 (12.7)	57.1 (12.2)	52.9 (12.9)	
T score final, mean (SD)	54.5 (9.1)	53.6 (9.1)	56.5 (7.5)	55.4 (9.3)	58.6 (12)	
p	0.78	0.374	0.597	0.34	0.117	
Improved, n (%)	27 (29.3)	20 (34.5)	6 (37.5)	11 (39.3)	0 (0)	*3.0*
Not changed, n (%)	42 (45.7)	25 (43.1)	5 (31.3)	11 (39.3)	6 (66.7)	*(122)*
Worsened, n (%)	23 (25)	13 (22.4)	5 (31.3)	6 (21.4)	3 (33.3)	
Social Functioning						
T score first, mean (SD)	39.1 (9.5)	40.4 (9.2)	35.9 (8.1)	35 (6.9)	42.6 (13.9)	
T score final, mean (SD)	40 (9.1)	41.8 (9.3)	36.9 (7.6)	37.7 (7.8)	34.6 (6.7)	
P	0.305	0.139	0.563	0.013*	0.138	
Improved, n (%)	40 (43.5)	25 (43.1)	8 (50)	12 (42.9)	3 (33.3)	*2.0*[2]
Not changed, n (%)	34 (37)	22 (37.9)	3 (18.8)	13 (46.4)	2 (22.2)	
Worsened, n (%)	18 (19.6)	11 (19)	5 (31.3)	3 (10.7)	4 (44.4)	
Fatigue						
T score first, mean (SD)	57.7 (10)	56.9 (10.5)	59.6 (11.8)	60.2 (9.4)	58.6 (6.5)	
T score final, mean (SD)	57.9 (9.5)	57 (10.1)	59.7 (8.3)	58.8 (8.3)	63.1 (9.4)	
P	0.864	0.899	0.98	0.372	0.296	
Improved, n (%)	31 (34.1)	18 (31)	5 (31.3)	10 (37)	3 (33.3)	*2.5*
Not changed, n (%)	21 (23.1)	11 (19)	6 (37.5)	9 (33.3)	1 (11.1)	*(123)*
Worsened, n (%)	39 (42.9)	29 (50)	5 (31.3)	8 (29.6)	5 (55.6)	
Impact Score (Pain)						
Raw score first, mean (SD)	34.8 (10.2)	33.6 (10)	38.2 (11.1)	39 (9.3)	30 (13.6)	
Raw score final, mean (SD)	33.1 (9.6)	31.2 (9.6)	36.6 (8.7)	36 (9.5)	37.1 (7.1)	
p	0.058	0.023*	0.404	0.035*	0.084	
Improved, n (%)	43 (46.7)	30 (51.7)	6 (37.5)	14 (50)	1 (11.1)	*3.0*
Not changed, n (%)	28 (30.4)	16 (27.6)	5 (31.3)	8 (28.6)	4 (44.4)	*(120)*
Worsened, n (%)	21 (22.8)	12 (20.7)	5 (31.3)	6 (21.4)	4 (44.4)	
Impact shift[3], positive	22 (23.9)	16 (27.6)	2 (12.5)	6 (21.4)	0 (0)	
No impact shift	59 (64.1)	36 (62.1)	12 (75)	20 (71.4)	6 (66.7)	
Impact shift, negative	11 (12)	6 (10.3)	2 (12.5)	2 (7.1)	3 (33.3)	

[1] Median dose on last survey.
[2] MCID = 2.0 as default given there is no published MCID value in literature to reference.
* $p < 0.05$ statistical significant in paired t-test.
[3] Impact shift is defined as a change from mild impact (8–27) to moderate impact (28–34) to severe impact (≥ 35) based on impact score cut-offs. A positive impact shift shows patients changed in a positive direction from a detrimental impact level to a lower one (i.e. severe → moderate/moderate → mild)

Patients that changed medicinal cannabis products throughout the survey period were included in both categories for analysis (n = 31)

Supplementary Table 3. Patient reported adverse events by medicinal cannabis products during the observational period.

MedDRA system organ class			**Chronic pain** (n = 718)									
			All products (n = 718)		**CBD-only** (n = 369)		**CBD-dominant** (n = 64)		**Balanced** (n = 211)		**THC-dominant** (n = 74)	
Dose, mg (median (Q1 – Q3)	**Oral**	n	697		368		62		208		59	
		CBD	**40** (15 – 100)		**80** (40 – 125)		**22.5** (10.5 – 37.8)		**20** (12.5 – 37.5)		**0** (0 – 3)	
		THC	**0** (0 – 15)		**0** (0 – 0)		**8.3** (4.6 – 77.2)		**17.5** (10 – 30)		**44** (22 – 80)	
	Inhaled	n	21		1		2		3		15	
		CBD	**0** (0 – 16)		**198** (198 – 198)		**108** (99 – 117)		**12** (12 – 98)		**0** (0 – 6)	
		THC	**99** (44 – 275)		**0** (0 – 0)		**12** (11 – 13)		**12.6** (9.5 – 77.2)		**198** (65 – 330)	
			AEs[1]	Patients[2]	AEs[1]	Patients[2]	AEs	Patients	AEs	Patients	AEs	Patients
Psychiatric disorders n (%)	**Total**		**423 (34.3)**	**200 (27.9)**	**140 (29.8)**	**76 (20.6)**	**48 (36.6)**	**21 (32.8)**	**173 (37.6)**	**78 (37.0)**	**62 (36.3)**	**25 (33.8)**
	Somnolence		228 (18.5)	153 (21.3)	74 (15.7)	55 (14.9)	27 (20.6)	17 (26.6)	92 (20)	61 (28.9)	35 (20.5)	20 (27)
	Anxiety		59 (4.8)	45 (6.3)	25 (5.3)	18 (4.9)	7 (5.3)	6 (9.4)	20 (4.3)	15 (7.1)	7 (4.1)	6 (8.1)
	Confusion		37 (3.0)	28 (3.9)	9 (1.9)	6 (1.6)	3 (2.3)	2 (3.1)	21 (4.6)	17 (8.1)	4 (2.3)	3 (4.1)
	Disorientation		37 (3.0)	33 (4.6)	9 (1.9)	9 (2.4)	2 (1.5)	2 (3.1)	20 (4.3)	17 (8.1)	6 (3.5)	5 (6.8)
	Depression		26 (2.1)	22 (3.1)	13 (2.8)	11 (3)	3 (2.3)	2 (3.1)	8 (1.7)	7 (3.3)	2 (1.2)	2 (2.7)
	Paranoia		3 (0.2)	3 (0.4)	1 (0.2)	1 (0.3)	-	-	2 (0.4)	2 (0.9)	-	-
	Euphoria		25 (2.0)	20 (2.8)	5 (1.1)	5 (1.4)	6 (4.6)	3 (4.7)	7 (1.5)	7 (3.3)	7 (4.1)	5 (6.8)
	Hallucinations		5 (0.4)	5 (0.7)	2 (0.4)	2 (0.5)	-	-	2 (0.4)	2 (0.9)	1 (0.6)	1 (1.4)
	Insomnia		2 (0.2)	2 (0.3)	1 (0.2)	1 (0.3)	-	-	1 (0.2)	1 (0.5)	-	-
	Psychosis		1 (0.1)	1 (0.1)	1 (0.2)	1 (0.3)	-	-	-	-	-	-
Gastrointestinal disorders n (%)	**Total**		**407 (33.0)**	**231 (32.2)**	**171 (36.4)**	**104 (28.2)**	**41 (31.3)**	**22 (34.4)**	**134 (29.1)**	**74 (35.1)**	**61 (35.7)**	**31 (41.9)**
	Dry mouth		297 (24.1)	28 (3.9)	118 (25.1)	80 (21.7)	30 (22.9)	19 (29.7)	95 (20.7)	62 (29.4)	54 (31.6)	31 (41.9)
	Nausea		83 (6.7)	64 (8.9)	42 (8.9)	35 (9.5)	8 (6.1)	5 (7.8)	30 (6.5)	21 (10.0)	3 (1.8)	3 (4.1)
	Diarrhoea		19 (1.5)	16 (2.2)	7 (1.5)	6 (1.6)	3 (2.3)	2 (3.1)	7 (1.5)	6 (2.8)	2 (1.2)	2 (2.7)

	Gastro-intestinal upset	3 (0.2)	3 (0.4)	1 (0.2)	1 (0.3)	-	-	1 (0.2)	1 (0.5)	1 (0.6)	1 (1.4)
	Vomiting	5 (0.4)	5 (0.7)	3 (0.6)	3 (0.8)	-	-	1 (0.2)	1 (0.5)	1 (0.6)	1 (1.4)
General disorders and administration site conditions n (%)	**Total**	**208 (16.9)**	**131 (18.2)**	**78 (16.6)**	**56 (15.2)**	**19 (14.5)**	**14 (21.9)**	**90 (19.6)**	**49 (23.2)**	**21 (12.3)**	**12 (16.2)**
	Fatigue	144 (11.7)	110 (15.3)	54 (11.5)	46 (12.5)	15 (11.5)	12 (18.8)	61 (13.3)	42 (19.9)	14 (8.2)	10 (13.5)
	Balance problems	64 (5.2)	45 (6.3)	24 (5.1)	20 (5.4)	4 (3.1)	3 (4.7)	29 (6.3)	16 (7.6)	7 (4.1)	6 (8.1)
Nervous system disorders n (%)	**Total**	**95 (7.7)**	**71 (9.9)**	**38 (8.1)**	**31 (8.4)**	**12 (9.2)**	**7 (10.9)**	**39 (8.5)**	**28 (13.3)**	**6 (3.5)**	**5 (6.8)**
	Dizziness	95 (7.7)	71 (9.9)	38 (8.1)	31 (8.4)	12 (9.2)	7 (10.9)	39 (8.5)	28 (13.3)	6 (3.5)	5 (6.8)
Metabolism and nutritional disorders n (%)	**Total**	**9 (0.7)**	**9 (1.3)**	**1 (0.2)**	**1 (0.3)**	**-**	**-**	**4 (0.9)**	**4 (1.9)**	**4 (2.3)**	**4 (5.4)**
	Increased appetite	7 (0.6)	7 (1.0)	-	-	-	-	4 (0.9)	4 (1.9)	3 (1.8)	3 (4.1)
	Decreased appetite	2 (0.2)	2 (0.3)	1 (0.2)	1 (0.3)	-	-	-	-	1 (0.6)	1 (1.4)
Skin and subcutaneous tissue disorders n (%)	**Total**	**1 (0.1)**	**1 (0.1)**	**-**	**-**	**-**	**-**	**1 (0.2)**	**1 (0.5)**	**-**	**-**
	Skin irritation	1 (0.1)	1 (0.1)	-	-	-	-	1 (0.2)	1 (0.5)	-	-
Other (undefined)[3] n (%)	**Total**	**89 (7.2)**	**71 (9.9)**	**42 (8.9)**	**36 (9.8)**	**11 (8.4)**	**9 (14.1)**	**19 (4.1)**	**16 (7.6)**	**17 (9.9)**	**10 (13.5)**
Total		**1232**	**718**	**470**	**369**	**131**	**64**	**460**	**211**	**171**	74 (43.3)
Number of patients who never reported any AEs n (%)		354 (49.3)		209 (56.6)		25 (39.1)		90 (42.7)		29 (39.2)	

[1] AEs: Number of AEs and the relative risk proportion
[2] Patients: Number of patients who reported the AE and the proportion out of the total number of patients
[3] Not extrapolated by patient report and cannot be categorised into a system organ class

Supplementary Table 4. Patient reported adverse events by medicinal cannabis products during the observational period in the arthritis subset.

MedDRA system organ class			**Arthritis subset** (n = 199)									
			All products (n = 199)		**CBD-only** (n = 108)		**CBD-dominant** (n = 20)		**Balanced** (n = 57)		**THC-dominant** (n = 14)	
Dose, mg (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)	
			AEs[1]	Patients[2]	AEs	Patients	AEs	Patients	AEs	Patients	AEs	Patients
Psychiatric disorders n (%)	**Total**		**108 (30.9)**	**54 (27.1)**	**25 (21.2)**	**18 (16.7)**	**20 (41.7)**	**9 (45)**	**51 (34.9)**	**24 (42.1)**	**12 (32.4)**	**3 (21.4)**
	Somnolence		53 (15.2)	37 (18.6)	13 (11)	12 (11.1)	8 (16.7)	6 (30)	29 (19.9)	17 (29.8)	3 (8.1)	2 (14.3)
	Anxiety		15 (4.3)	12 (6.0)	4 (3.4)	3 (2.8)	5 (10.4)	4 (20)	4 (2.7)	3 (5.3)	2 (5.4)	2 (14.3)
	Confusion		9 (2.6)	9 (4.5)	1 (0.8)	1 (0.9)	-	-	6 (4.1)	6 (10.5)	2 (5.4)	2 (14.3)
	Disorientation		13 (3.7)	12 (6.0)	3 (2.5)	3 (2.8)	-	-	8 (5.5)	7 (12.3)	2 (5.4)	2 (14.3)
	Depression		6 (1.7)	5 (2.5)	1 (0.8)	1 (0.9)	3 (6.3)	2 (10)	1 (0.7)	1 (1.8)	1 (2.7)	1 (7.1)
	Paranoia		-	-	-	-	-	-	-	-	-	-
	Euphoria		10 (2.9)	7 (3.5)	3 (2.5)	3 (2.8)	4 (8.3)	1 (5)	2 (1.4)	2 (3.5)	1 (2.7)	1 (7.1)
	Hallucinations		2 (0.6)	2 (1.0)	-	-	-	-	1 (0.7)	1 (1.8)	1 (2.7)	1 (7.1)
	Insomnia		-	-	-	-	-	-	-	-	-	-
	Psychosis		-	-	-	-	-	-	-	-	-	-
Gastrointestinal disorders n (%)	**Total**		**126 (36.1)**	**69 (34.7)**	**43 (36.4)**	**27 (25)**	**18 (37.5)**	**7 (35)**	**54 (37)**	**28 (49.1)**	**11 (29.7)**	**7 (50)**
	Dry mouth		94 (26.9)	58 (29.1)	28 (23.7)	19 (17.6)	15 (31.3)	7 (35)	40 (27.4)	25 (43.9)	11 (29.7)	7 (50)
	Nausea		28 (8.0)	23 (11.6)	14 (11.9)	13 (12)	3 (6.3)	2 (10)	11 (7.5)	8 (14.0)	-	-

	Diarrhoea	3 (0.9)	2 (1.0)	1 (0.8)	1 (0.9)	-	-	2 (1.4)	1 (1.8)	-	-
	Gastro-intestinal upset	-	-	-	-	-	-	-	-	-	-
	Vomiting	1 (0.3)	1 (0.5)	-	-	-	-	1 (0.7)	1 (1.8)	-	-
General disorders and administration site conditions n (%)	**Total**	**59 (16.9)**	**40 (20.1)**	**23 (19.5)**	**16 (14.8)**	**5 (10.4)**	**4 (20)**	**24 (16.4)**	**17 (29.8)**	**7 (18.9)**	**3 (21.4)**
	Fatigue	40 (11.5)	35 (17.6)	16 (13.6)	15 (13.9)	5 (10.4)	4 (20)	14 (9.6)	13 (22.8)	5 (13.5)	3 (21.4)
	Balance problems	19 (5.4)	13 (6.5)	7 (5.9)	4 (3.7)	-	-	10 (6.8)	7 (12.3)	2 (5.4)	2 (14.3)
Nervous system disorders n (%)	**Total**	**28 (8.0)**	**22 (11.1)**	**13 (11)**	**11 (10.2)**	**3 (6.3)**	**2 (10)**	**12 (8.2)**	**9 (15.8)**	**-**	**-**
	Dizziness	28 (8.0)	22 (11.1)	13 (11)	11 (10.2)	3 (6.3)	2 (10)	12 (8.2)	9 (15.8)	-	-
Metabolism and nutritional disorders n (%)	**Total**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
	Increased appetite	-	-	-	-	-	-	-	-	-	-
	Decreased appetite	-	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders n (%)	**Total**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
	Skin irritation	-	-	-	-	-	-	-	-	-	-
Other (undefined)[3] n (%)	**Total**	28 (8.0)	21 (10.6)	14 (11.9)	11 (10.2)	2 (4.2)	2 (10)	5 (3.4)	4 (7.0)	7 (18.9)	4 (28.6)
Total		**349**	**199**	**118**	**20**	**48**	**20**	**146**	**57**	**37**	20 (54.1)
Number of patients who never reported any AEs n (%)		103 (51.8)		69 (63.9)		9 (45)		19 (33.3)		6 (42.9)	

[1] AEs: Number of AEs and the relative risk proportion
[2] Patients: Number of patients who reported the AE and the proportion out of the total number of patients
[3] Not extrapolated by patient report and cannot be categorised into a system organ class

Supplementary Table 5. Comparison of incidence of AEs that occurred before the second clinic visit[1] if (yes/no) patients are co-prescribed opioids, benzodiazepines, and serotonin-noradrenaline reuptake inhibitors.

		Opioids (n = 179)				**Benzodiazepines** (n = 84)				**SNRI** (n = 52)			
MedDRA system organ class		Yes (n =179)	No (n=96)	P[2]	RR[3]	Yes (n=84)	No (n=191)	p	RR	Yes (n=52)	No (n=223)	p	RR
Psychiatric disorders n (%)	Somnolence	30 (16.8)	19 (19.8)	0.531	0.85 (0.50–0.42)	15 (17.9)	64 (33.5)	0.991	1.00 (50.58–1.74)	10 (19.2)	39 (17.5)	0.768	1.10 (0.59–0.06)
	Anxiety	7 (3.9)	3 (3.1)	0.740	1.25 (0.33–4.73)	5 (6.0)	5 (2.6)	0.174	2.27 (0.68–7.64)	0	10 (4.5)	0.120	-
	Confusion	5 (2.8)	3 (3.1)	0.876	0.89 (0.22–3.66)	2 (2.4)	6 (3.1)	0.730	0.76 (0.16–3.68)	0	8 (3.6)	0.166	-
	Disorientation	3 (1.7)	2 (2.1)	0.810	0.80 (0.14–4.73)	3 (3.6)	2 (1.0)	0.149	3.41 (0.58–20.04)	0	5 (2.2)	0.276	-
	Depression	2 (1.1)	4 (4.2)	0.099	0.27 (0.05–1.44)	3 (3.6)	3 (1.6)	0.296	2.27 (0.47–11.04)	1 (1.9)	5 (2.2)	0.887	0.86 (0.10–7.19)
	Paranoia	1 (0.6)	0	0.463	-	0	1 (0.5)	0.506	-	0	1 (0.4)	0.629	-
	Euphoria	3 (1.7)	1 (1.0)	0.675	1.61 (0.17–15.26)	2 (2.4)	2 (1.0)	0.395	2.27 (0.33–15.87)	0	4 (1.8)	0.331	-
	Hallucinations	2 (1.1)	0	0.299	-	0	2 (1.0)	0.347	-	0	2 (0.9)	0.493	-
Gastro-intestinal disorders n (%)	Dry mouth	44 (24.6)	18 (18.8)	0.270	1.13 (0.80–2.14)	16 (19.0)	46 (24.1)	0.357	0.79 (0.48–1.31)	12 (23.1)	50 (22.4)	0.919	1.03 (0.59–1.79)
	Nausea	17 (9.5)	3 (3.1)	0.052	3.04 (0.91–10.11)	5 (6.0)	15 (7.9)	0.576	0.76 (0.29–2.02)	3 (5.8)	17 (7.6)	0.643	0.76 (0.23–2.49)
	Diarrhoea	2 (1.1)	2 (2.1)	0.524	0.54 (0.08–3.75)	2 (2.4)	2 (1.0)	0.395	2.27 (0.33–15.87)	0	4 (1.8)	0.331	-
	Vomiting	1 (0.6)	0	0.464	-	0	1 (0.5)	0.506	-	0	1 (0.4)	0.629	-
General disorders and administration site conditions n (%)	Fatigue	18 (10.1)	9 (9.4)	0.856	1.07 (0.50–2.30)	8 (9.5)	19 (9.9)	0.913	0.96 (0.44–2.10)	5 (9.6)	22 (9.9)	0.956	0.98 (0.39–2.45)
	Balance problems	7 (3.9)	2 (2.1)	0.417	1.88 (0.40–8.86)	2 (2.4)	7 (3.7)	0.581	0.65 (0.14–3.06)	2 (3.8)	7 (3.1)	0.796	1.23 (0.26–5.73)
Nervous system disorders n (%)	Dizziness	14 (7.8)	7 (7.3)	0.875	1.07 (0.45–2.57)	5 (6.0)	16 (8.4)	0.486	0.71 (0.27–1.88)	3 (5.8)	18 (8.1)	0.573	0.72 (0.22–2.34)

Other (undefined)* n (%)	Other	12 (6.7)	7 (7.3)	0.855	0.92(0.37–2.26)	7 (8.3)	12 (6.3)	0.537	1.33 (0.51–3.25)	2 (3.8)	17 (7.6)	0.333	0.51 (0.12–2.12)
None	None	100 (55.9)	56 (58.3)	0.694	0.96 (0.77–1.19)	46 (54.8)	110 (57.6)	0.663	0.95 (0.76–1.20)	31 (59.6)	125 (56.1)	0.641	1.06 (0.83–1.37)

[1]Median (Q1–Q3) observational period from commencement of cannabis until second clinic visit is 25 days (16.0–41.9)
[2] Statistical significance determined using Chi-square test
[3]Relative risk not applicable if n ≤ 1

Supplementary Table 6. Multivariate analyses on the five most common adverse events and univariate outcomes with a significance level > 0.02.

Adverse event	Outcomes with significance > 0.02	p value	Odds ratio (95% confidence interval)
Dry mouth (n = 62; 22.5%)	Age	0.741	1.00 (0.99–1.02)
	Sex	0.580	1.19 (0.65–2.12)
	Cannabis formulation	0.069	0.59 (0.33–1.04)
Somnolence (n = 49; 17.8%)	Age	0.813	1.00 (0.98–1.02)
	Sex	0.134	1.74 (0.85–3.57)
	Gabapentinoids	0.494	1.26 (0.65–2.45)
	Tricyclic antidepressants	0.039*	2.26 (1.04–4.92)
	Cannabis formulation	0.033*	0.38 (0.16–0.93)
	CBD dose	0.401	1.00 (0.99–1.01)
	THC dose	0.625	1.00 (0.98–1.01)
Fatigue (n = 27; 9.8%)	Age	0.968	1.00 (0.97–1.02)
	Sex	0.699	1.20 (0.48–2.99)
	Gabapentinoids	0.670	1.21 (0.50–2.92)
	Cannabis formulation	0.170	0.43 (0.13–1.43)
	CBD dose	0.154	0.99 (0.97–1.00)
	THC dose	0.478	0.99 (0.96–1.01)
	Polypharmacy (>10 medicines)	0.145	0.50 (0.20–1.27)
Dizziness (n = 21; 7.6%)	Age	0.015*	1.04 (1.01–1.08)
	Sex	0.196	2.16 (0.67–6.91)
	Gabapentinoids	0.112	2.17 (0.84–5.64)
	Polypharmacy (>10 medicines)	0.999	1.00 (0.36–2.75)
Nausea (n = 20; 7.3%)	Age	0.871	1.00 (0.97–1.03)
	Sex	0.070	3.24 (0.91–11.56)
	Opioids	0.101	2.95 (0.81–10.77)
	Polypharmacy (>10 medicines)	0.635	0.78 (0.29–2.15)

Supplementary Table 7. PROMIS-29 analysis in patients with a PTSD diagnosis.

PROMIS-29 domain	PTSD patients					
	All formulations (n = 57)	**CBD-only** (n = 35)	**CBD Dominant** (n = 2)	**Balanced** (n = 28)	**THC dominant** (n = 3)	**THC-only** (n = 4)
CBD dose mg/day, median (IQR)	62.5 (80.0)	100.0 (115.0)	51.3 (38.8)	17.5 (52.5)	0.8 (37.5)	0.0 (0.2)
THC dose mg/day, median (IQR)	2.5 (17.5)	0.0 (0.0)	33.1 (26.9)	15.0 (40.0)	75.0 (37.6)	27.5 (27.1)
Anxiety (MCID=4.0)						
Score baseline, mean (SD)	66.4 (8.0)	66.6 (8.0)	44.15 (5.4)	64.9 (8.4)	64.8 (8.0)	68.8 (4.4)
Score final, mean (SD)	61.1 (9.0)	61.5 (9.3)	59.6 (2.6)	60.7 (9.0)	57.0 (4.0)	58.1 (5.1)
p value	<0.001*	<0.001*	0.082	0.064	0.194	0.079
Improved, n (%)	30 (52.6)	18 (51.4)	0 (0.0)	12 (42.9)	2 (66.7)	3 (75.0)
Unchanged, n (%)	20 (35.1)	13 (37.1)	0 (0.0)	11 (39.3)	1 (33.3)	1 (25.0)
Worsened, n (%)	7 (12.3)	4 (11.4)	2 (100.0)	5 (17.9)	0 (0.0)	0 (0.0)
p value[1]	0.555					
Depression (MCID=5.0)						
Score baseline, mean (SD)	63.6 (9.4)	63.1 (9.9)	53.4 (17.5)	63.7 (7.4)	63.0 (8.1)	63.7 (10.6)
Score final, mean (SD)	58.9 (10.9)	60.3 (10.0)	56.5 (10.5)	57.9 (11.3)	55.7 (12.8)	52.0 (12.7)
p value	<0.001*	0.019*	0.641	0.071	0.125	0.271
Improved, n (%)	22 (38.6)	8 (22.9)	0 (0.0)	14 (50.0)	2 (66.7)	3 (75.0)
Unchanged, n (%)	27 (46.4)	24 (68.6)	1 (50.0)	8 (28.6)	1 (33.3)	0 (0.0)
Worsened, n (%)	8 (14.0)	3 (8.6)	1 (50.0)	6 (21.4)	0 (0.0)	1 (25.0)
p value[2]	<0.001*	<0.001*		<0.001*		
Fatigue (MCID=5.0)						
Score baseline, mean (SD)	64.7 (7.9)	65.6 (7.8)	70.2 (7.9)	63.7 (7.4)	57.8 (12.2)	62.4 (9.7)
Score final, mean (SD)	57.6 (10.8)	58.4 (10.1)	63.6 (1.3)	57.2 (10.2)	52.6 (17.8)	48.0 (10.6)
p value	<0.001*	<0.001*	0.500	0.001*	0.673	0.009*
Improved, n (%)	33 (57.9)	19 (54.3)	1 (50.0)	16 (57.1)	2 (66.7)	4 (100.0)
Unchanged, n (%)	19 (33.3)	14 (40.0)	1 (50.0)	9 (32.1)	0 (0.0)	0 (0.0)
Worsened, n (%)	5 (8.8)	2 (5.7)	0 (0.0)	3 (10.7)	1 (33.3)	0 (0.0)
p value[1]	0.575					
Sleep disturbance (MCID=5.0)						
Score baseline, mean (SD)	51.3 (4.9)	52.0 (3.5)	52.4 (2.7)	51.2 (6.0)	42.9 (9.7)	45.9 (9.3)
Score final, mean (SD)	51.7 (3.5)	58.4 (3.4)	54.3 (0)	51.6 (4.0)	51.0 (4.2)	53.8 (1.0)
p value	0.573	0.961	0.500	0.805	0.327	0.151
Improved, n (%)	5 (8.8)	2 (5.7)	0 (0.0)	4 (14.3)	1 (33.3)	0 (0.0)
Unchanged, n (%)	45 (78.9)	29 (82.9)	2 (100.0)	20 (71.4)	1 (33.3)	3 (75.0)
Worsened, n (%)	7 (12.3)	4 (11.4)	0 (0.0)	4 (14.3)	1 (33.3)	1 (25.0)
p value[1]	0.719					
Ability to take part in social roles and activities (MCID=5.0)						
Score baseline, mean (SD)	35.8 (6.0)	35.4 (5.3)	32.4 (6.9)	36.1 (6.1)	35.8 (10.9)	38.2 (7.0)

Score final, mean (SD)	42.0 (9.3)	41.6 (7.7)	37.3 (2.2)	41.3 (10.3)	43.9 (17.9)	57.1 (14.4)
p value	<0.001*	<0.001*	0.385	0.003*	0.180	0.087
Improved, n (%)	29 (50.9)	19 (54.3)	1 (50.0)	11 (39.3)	1 (33.3)	3 (75.0)
Unchanged, n (%)	23 (40.4)	13 (37.1)	1 (50.0)	14 (50.0)	2 (66.7)	1 (25.0)
Worsened, n (%)	5 (8.8)	3 (8.6)	0 (0.0)	3 (10.7)	0 (0.0)	0 (0.0)
p value[1]	0.731					

* p-value is statistically significant ($p < 0.05$)
[1]p-value calculated using Fisher's exact tests including patients from the sample that had been on only one formulation
[2]Further Fishers exact Tests were done on the sample to determine which formulations had significant associations.

Supplementary Table 8. PROMIS-29 analysis in patients with an unspecified anxiety diagnosis.

PROMIS-29 domain	Unspecified anxiety					
	All formulations (n = 141)	**CBD-only** (n = 77)	**CBD Dominant** (n = 18)	**Balanced** (n = 68)	**THC dominant** (n = 15)	**THC-only** (n = 6)
CBD dose mg/day, median (IQR)	43.8 (85.0)	100.0 (100.0)	25.0 (37.0)	22.5 (31.3)	6.0 (11.6)	0.0 (28.1)
THC dose mg/day, median (IQR)	5.0 (24.0)	0.0 (0.0)	6.0 (23.5)	20.0 (30.0)	30.0 (57.0)	60.5 (22.8)
Anxiety (MCID=4.0)						
Score baseline, mean (SD)	63.8 (9.2)	63.7 (9.0)	63.9 (10.0)	63.8 (9.1)	62.7 (8.9)	61.5 (8.8)
Score final, mean (SD)	59.0 (9.0)	59.6 (7.9)	58.9 (7.2)	59.5 (10.0)	58.5 (8.3)	65.3 (8.6)
p value	<0.001*	<0.001*	0.081	<0.001*	0.042*	0.368
Improved, n (%)	74 (52.5)	38 (49.4)	10 (55.6)	34 (50.0)	9 (60.0)	1 (16.7)
Unchanged, n (%)	46 (32.6)	25 (32.5)	5 (27.8)	25 (36.8)	4 (26.7)	2 (33.3)
Worsened, n (%)	21 (14.9)	14 (18.2)	3 (16.7)	9 (13.2)	2 (13.3)	3 (50.0)
p value[1]	0.957					
Depression (MCID=5.0)						
Score baseline, mean (SD)	60.8 (9.9)	60.5 (9.7)	62.6 (8.6)	61.2 (10.8)	57.6 (11.1)	59.4 (10.5)
Score final, mean (SD)	56.9 (9.7)	57.4 (8.5)	58.5 (6.2)	57.9 (11.0)	53.6 (10.3)	64.1 (5.6)
p value	<0.001*	0.002*	0.073	0.006*	0.066	0.343
Improved, n (%)	62 (44.0)	31 (40.3)	8 (44.4)	29 (42.6)	7 (46.7)	1 (16.7)
Unchanged, n (%)	59 (41.8)	35 (45.5)	7 (38.9)	25 (36.8)	6 (40.0)	2 (33.3)
Worsened, n (%)	20 (14.2)	11 (14.3)	3 (16.7)	14 (20.6)	2 (13.3)	3 (50.0)
p value[1]	0.654					
Fatigue (MCID=5.0)						
Score baseline, mean (SD)	62.1 (10.7)	61.8 (9.5)	65.0 (8.6)	63.8 (11.5)	63.1 (12.8)	69.0 (9.1)
Score final, mean (SD)	56.6 (11.0)	56.3 (10.2)	58.1 (8.8)	58.6 (10.4)	56.1 (11.0)	63.7 (12.1)
p value	<0.001*	<0.001*	0.001*	<0.001*	0.034*	0.256
Improved, n (%)	62 (44.0)	33 (42.9)	9 (50.0)	30 (44.1)	8 (53.3)	3 (50.0)
Unchanged, n (%)	66 (46.8)	38 (49.4)	8 (44.4)	32 (47.1)	5 (33.3)	2 (33.3)
Worsened, n (%)	13 (9.2)	6 (7.8)	1 (5.6)	6 (8.8)	2 (13.3)	1 (16.7)
p value[1]	0.514					
Sleep disturbance (MCID=5.0)						
Score baseline, mean (SD)	51.7 (5.5)	51.7 (4.4)	52.7 (3.5)	51.5 (7.0)	53.1 (3.0)	53.0 (3.3)
Score final, mean (SD)	51.5 (4.8)	51.6 (3.6)	51.7 (2.4)	51.6 (6.0)	51.5 (2.6)	51.6 (2.4)
p value	0.746	0.828	0.262	0.877	0.118	0.494
Improved, n (%)	21 (14.9)	9 (11.7)	3 (16.7)	12 (17.6)	3 (20.0)	1 (16.7)
Unchanged, n (%)	105 (74.5)	60 (77.9)	14 (77.8)	47 (69.1)	11 (73.3)	5 (83.3)
Worsened, n (%)	15 (10.6)	8 (10.4)	1 (5.6)	9 (13.2)	1 (6.7)	0 (0.0)
p value[1]	0.701					
Ability to take part in social roles and activities (MCID=5.0)						

Score baseline, mean (SD)	36.8 (7.7)	38.1 (7.6)	36.5 (7.8)	34.4 (7.2)	37.3 (10.2)	32.4 (7.3)
Score final, mean (SD)	41.3 (9.9)	43.4 (9.8)	40.9 (11.9	37.6 (8.7)	40.2 (9.2)	36.4 (12.0)
p value	<0.001*	<0.001*	0.042*	<0.001*	0.228	0.133
Improved, n (%)	62 (44.0)	37 (48.1)	5 (27.8)	26 (38.2)	6 (40.0)	2 (33.3)
Unchanged, n (%)	68 (48.2)	36 (46.8)	12 (66.7)	35 (51.5)	7 (46.7)	4 (66.7)
Worsened, n (%)	11 (7.8)	4 (5.2)	1 (5.6)	7 (10.3)	2 (13.3)	0 (0.0)
p value[1]	0.716					

* p-value is statistically significant ($p < 0.05$)

[1]p-value calculated using Fisher's exact tests including patients from the sample that had been on only one formulation

Supplementary Table 9. Logistic regression analysis of AEs and CBD and THC concentration.

		CBD concentration			THC concentration		
MedDRA classification	**n (%)**	**Dose,** median (IQR)	**OR (95% CI)**	**p value**	**Dose,** median (IQR)	**OR (95% CI)**	**p value**
Gastro – intestinal disorders[1]	220 (38.7)	36.6 (78.0)	1.000 (0.998 – 1.002)	0.741	10.0 (25.3)	1.011 (1.004 – 1.018)	0.003*
Dry mouth	180 (31.7)	31.3 (88.0)	1.000 (0.998 – 1.002)	0.805	10 (25.0)	1.010 (1.003 – 1.017)	0.005*
Nausea	52 (9.2)	40.0 (65.0)	0.998 (0.995 – 1.002)	0.340	10.0 (32.1)	1.008 (1.002 – 1.014)	0.008
Diarrhea	19 (3.3)	37.5 (80.0)	0.999 (0.994 – 1.005)	0.822	12.0 (22.5)	1.003 (0.993 – 1.013)	0.526
GI upset	18 (3.2)	66.3 (75.6)	1.002 (0.999 – 1.006)	0.157	3.1 (23.8)	1.002 (0.993 – 1.011)	0.708
Vomiting	2 (0.4)	142.5 (67.5)	1.004 (0.996 – 1.011)	0.360	30.0 (30.0)	1.003 (0.986 – 1.020)	0.730
Constipation	3 (0.5)	52.5 (48.8)	0.984 (0.958 – 1.011)	0.235	0.0 (0.0)	0.000	0.933
Flatulence	2 (0.4)	87.5 (12.5)	1.001 (0.987 – 0.1014)	0.939	37.5 (37.5)	1.006 (0.989–1.023)	0.505
Psychiatric	233 (41.0)	37.5 (78.0)	1.000 (0.998–1.001)	0.672	6.0 (22.0)	1.005 (0.999 – 1.011)	0.084
Anxiety[2]		55.0 (99.0)	1.001 (0.999–1.003)	0.182	2.25 (14.8)	1.001 (0.996–1.006)	0.628
Nervous System disorders	73 (12.9)	45.0 (87.5)	1.000 (0.998–1.003	0.123	5.0 (20.0)	1.004 (0.999 – 1.010)	0.123
Metabolism disorders	62 (10.9)	25.5 (90.0)	0.999 (0.996 – 1.002)	0.590	10.0 (21.9)	1.004 (0.998 – 1.010)	0.193
Skin disorders	2 (0.4)	38.9 (68.8)	1.000 (0.985 – 1.015)	0.963	12.5 (25.0)	1.004 (0.981 – 1.028)	0.711
General	131 (23.1)	37.5 (66.5)	0.999 (0.996 – 1.001)	0.232	7.5 (23.3)	1.000 (0.994 – 1.006)	0.881
Eye disorders	5 (0.9)	15.0 (62.5)	0.992 (0.975 – 1.009)	0.358	7.5 (53.8)	0.992 (0.995 – 1.024)	0.207
Respiratory thoracic and mediastinal disorders	6 (1.1)	21.9 (61.7)	1.000 (0.991 – 1.009)	0.914	4.4 (19.7)	1.002 (0.984 – 1.021)	0.801
Cardiac disorders	4 (0.7)	48.0 (55.5)	0.995 (0.979 – 1.012)	0.596	5.0 (14.0)	0.980 (0.910 – 1.055)	0.587
Musculo – skeletal and connective tissue disorders	4 (0.7)	9.7 (3.6)	0.925 (0.830 – 1.031)	0.160	12.5 (14.4)	1.001 (0.967 – 1.036)	0.954

Ear and labyrinth disorders	1 (0.2)	0.0 (0.0)	0.999 (0.979 – 1.020)	0.942	90.2 (0.0)	1.014 (0.994 – 1.034)	
Renal and urinary disorders	1 (0.2)	15.0 (0.0)	0.961 (0.852 – 1.085)	0.524	15.0 (0.0)	992 (0.892 – 1.104)	0.888
Immune system disorders	1 (0.2)	40.0 (0.0)	0.971 (0.913 – 1.032)	0.340	0.0 (0.0)	0.000	0.937
Other (undefined)	15 (2.6)	15.0 (40.5)	0.990 (1.002 – 1.020)	0.095	20.0 (41.1)	1.009 (0.998 – 1.020)	0.110
None	227 (40.0)	40.0 (87.8)	1.000 (0.998 – 1.002)	0.915	2.0 (15.0)	0.994 (0.987 – 1.001)	0.080

***** p-value is statistically significant ($p < 0.05$)

[1] Further logistic regressions were run on individual adverse events in the class to determine where the significance was

[2] A logistic regression was performed on the side effect of 'anxiety' as it was particularly relevant to adverse effects in anxiety treatment.

Supplementary Document 1. Copy of the CA Clinics Observational Study Questionnaire

Confidential

PROMIS 29 Quality of life survey

Version 2.0

This is a patient-reported outcomes Survey to a evaluate and monitor physical, mental, and social health of patients living with chronic conditions.

Please complete the survey below.

Are you the patient or completing on behalf of the patient?	◯ I am the patient ◯ Completing on behalf
Full name of individual completing survey on patient's behalf	_____
Relation to Patient	_____

Patient Details

Patient First Name	_____
Patient Last name	_____
D.O.B	_____ (DD-MM-YYYY)

Product Details

Have you been prescribed more than one medicinal cannabis product by CA Clinics? Please note these are products that you are taking at the same time.	◯ No. I have only been prescribed one product. ◯ Yes. I have been prescribed 2 different products. ◯ Yes. I have been prescribed 3 different products.
Have you started taking the medicinal cannabis product/s prescribed by CA Clinics?	◯ Yes ◯ No ((If you have not yet received your initial prescription then select No))

Why have you not started taking the product/s?

- ◯ Have only just sought out treatment
- ◯ Haven't gotten around to it
- ◯ Haven't needed to take it yet
- ◯ Cannot afford the cost of the product
- ◯ Cannot find a pharmacy to fill my prescription
- ◯ Pharmacy is not easy to travel to
- ◯ Am worried about taking it due to possible side effects
- ◯ Need to drive and therefore decided not to take product
- ◯ Was advised by another clinician not to take it
- ◯ Was only seeking to gain TGA approval
- ◯ Have accessed another cannabis product
- ◯ Have changed my mind about trying medicinal cannabis

When did you initially start taking your medicine?

_____

The underlying condition that medicinal cannabis as been prescribed for

- ☐ Epilepsy
- ☐ Cancer associated pain or symptoms
- ☐ Multiple Sclerosis
- ☐ Parkinsons
- ☐ HIV/AIDS associated
- ☐ Inflammatory Bowel Disease (IBD)
- ☐ PTSD
- ☐ Anxiety
- ☐ Sleep disorder
- ☐ Arthritis
- ☐ Chronic pain condition
- ☐ Other

Other conditions - please specify

_____

Please select which chronic pain condition you have

- ◯ Fibromyalgia
- ◯ Neuropathic pain
- ◯ Joint pain
- ◯ Trigeminal neuralgia
- ◯ Arthritis pain
- ◯ Endometriosis
- ◯ Dysmenorrhea
- ◯ Migraine headache
- ◯ Complex regional pain syndrome (CRPS)
- ◯ Musculoskeletal pain - general
- ◯ Tendonitis
- ◯ Other

Symptoms being treated with medicinal cannabis (check all that apply)

- ☐ Pain
- ☐ Nausea
- ☐ Sleep problems
- ☐ Poor appetite
- ☐ Spasticity
- ☐ Seizures
- ☐ Anxiety
- ☐ Depression
- ☐ Other

Other symptom - please specify

Product Name

- ◯ Bediol (6.3% Tetrahydrocannabinol
- ◯ Bedrobinol (13.5% Tetrahydrocannabinol
- ◯ Bedrocan (22% Tetrahydrocannabinol
- ◯ Capilano Cannabis Oil (Tetrahydrocannabinol 10mg/mL: Cannabidiol 12.5mg/mL)
- ◯ Champlain Cannabis Oil (20mg/mL Tetrahydrocannabinol: less than 1mg/mL Cannabidiol)
- ◯ Endoca Hemp Oil 15% (Cannabidiol 150mg/ml)
- ◯ Jasper Cannabis Oil (5mg/mL Tetrahydrocannabinol: 10mg/mL Cannabidiol)
- ◯ Medicabilis (CBD (cannabidiol) extract in MCT oil base.) Each 1mL MediCabilis contains 50mg CBD.
- ◯ Rideau Cannabis Oil (less than 2mg/mL Tetrahydrocannabinol: 25mg/mL Cannabidiol)
- ◯ Satipharm 50mg (Cannabidiol)
- ◯ Tilray Full Spectrum THC10:CBD10 (Tetrahydrocannabinol 10mg/mL: Cannabidiol 10mg/mL)
- ◯ Tilray Full Spectrum THC25:CBD25 (Tetrahydrocannabinol 25mg/mL: Cannabidiol 25mg/mL)
- ◯ Tilray Purified CBD 10 (Cannabidiol 10mg/mL)
- ◯ Tilray Purified CBD 10 (Cannabidiol 10mg/mL) - Oral Solution
- ◯ LGP Classic 10:10 (Tetrahydrocannabinol 10mg/mL:Cannabidiol 10mg/mL) - Oral solution
- ◯ Tilray Full Spectrum THC 2.5: CBD 2.5 (Tetrahydrocannabinol 2.5mg: Cannabidiol 2.5mg) - Capsules
- ◯ Tilray Purified CBD 25 (Cannabidiol 25mg/mL) - Oral Solution
- ◯ Tilray Purified CBD 100 (Cannabidiol 100mg/mL) - Oral Solution
- ◯ Henik (Tetrahydrocannabinol 18% Cannabidiol less than 1%) - Bud
- ◯ Bedrolite (less than 1% Tetrahydrocannabinol
- ◯ Bedrocan (22% Tetrahydrocannabinol
- ◯ Bedrolite (less than 1% Tetrahydrocannabinol
- ◯ LGP Classic 20:5 (Tetrahydrocannabinol 20mg/mL:Cannabidiol 5mg/mL) - Oral solution
- ◯ Sativex Oromucosal Spray 2.7 mg THC/2.5 mg CBD per 100 mcL spray
- ◯ MXP 100 Oil CBD 100 mg/ml: THC < 2 mg/ml
- ◯ Cannepil Oil (Oral Solution) Cannabidiol 100mg/ml: Tetrahydrocannabinol 5mg/ml
- ◯ Spectrum Yellow Oil
- ◯ LGP Classic 1:20
- ◯ Althea CBD 100 Oil 100 mg/ml
- ◯ Bedica Cannabis Flos (Vapourisation) 14% tetrahydrocannabinol, less than 1% cannabidiol
- ◯ MedReleaf Sedamen Dried Cannabis Cannabis Bud 20.4%THC w/w; < 2%CBD w/w 15g
- ◯ Compounded Cannabidiol (CBD) 100mg/ml
- ◯ Green Dispensary CBD 100% Pure 100mg/mL
- ◯ Green Compound Oil 100 % CBD 25mls 100mgm/ml
- ◯ Penrose THC Indica Oil
- ◯ LPG 0:50 (cannabidiol 50mg/ml)
- ◯ Entoura EMC 10:15 (Tetrahydrocannabinol:cannabidiol)
- ◯ Entoura CBD 10 10ml (100mg/ml CBD)
- ◯ Entoura CBD 20 10ml (200mg/ml CBD)

What unit of measure are you using for each dose of your medicinal cannabis product?	◯ millilitres (mL) ◯ drops ◯ milligrams (mg) ◯ capsules or tablets ◯ grams (g) ◯ Other
Morning Dosage (in relevant units you have selected above) e.g. If you taken 1 mL please enter 1 here	_____ (Please enter number)
Night Dosage	_____ (Please enter number)
Extra Dosage	_____ (Please enter number)

Have you been experiencing any side effects from your medicinal cannabis prescribed by CA Clinics? If you have not experienced any side effects then please select 'None'
(Select as applicable)

- ☐ Disorientation
- ☐ Dizziness
- ☐ Euphoria
- ☐ Confusion
- ☐ Drowsiness
- ☐ Dry mouth
- ☐ Somnolence (drowsiness or sleepiness)
- ☐ Balance problems
- ☐ Hallucination
- ☐ Nausea
- ☐ Paranoia
- ☐ Asthenia
- ☐ Fatigue
- ☐ Anxiety
- ☐ Vomiting
- ☐ Diarrhoea
- ☐ Depression
- ☐ Psychosis
- ☐ Insomnia
- ☐ Increase appetite
- ☐ Decreased appetite
- ☐ Skin irritation
- ☐ Gastrointestinal upset
- ☐ Others
- ☐ None

Side Effect severity

For any side effects that you have experienced, please select the severity of that side effect.

Mild = Awareness of sign, symptom or event, but easily tolerated.
Moderate = Discomfort enough to cause interference with usual activity and may warrant intervention
Severe = Incapacitating with inability to do usual activities and warrants intervention

	Mild	Moderate	Severe	I do not experience this side effect
Disorientation	○	○	○	○
Dizziness	○	○	○	○
Euphoria	○	○	○	○
Confusion	○	○	○	○
Dry mouth	○	○	○	○
Somnolence (drowsiness or sleepiness)	○	○	○	○
Balance problems	○	○	○	○
Hallucinations	○	○	○	○
Nausea	○	○	○	○
Paranoia	○	○	○	○
Fatigue/Asthenia	○	○	○	○
Anxiety	○	○	○	○
Vomiting	○	○	○	○
Diarrhoea	○	○	○	○
Depression	○	○	○	○
Psychosis	○	○	○	○
Insomnia	○	○	○	○
Increased appetite	○	○	○	○
Decreased appetite	○	○	○	○
Skin irritation	○	○	○	○
Gastrointestinal upset	○	○	○	○
Others	○	○	○	○

* If you're experiencing any other side effects not listed above then please specify _____

Have you already reported these side effects to CA Clinics? ○ Yes. I have already reported these side effects. ○ No. I have not reported these side effects. ○ N/A

You have indicated you are experiencing side effects from your treatment that you have not discussed with CA Clinics. Please ensure that you notify your doctor of these side effects at your next clinic visit.

Score Physical Function _____

Score Anxiety	_____
Score Depression	_____
Score Fatigue	_____
Score Sleep Disturbance	_____
Score Ability to Participate in Social Roles and Activities	_____
Score Pain Interference	_____
Score Pain Intensity	_____
Total Score	_____

PROMIS 29 (Version 2.0)

These questions are used to evaluate and monitor physical, mental and social health of patients living with chronic conditions.

Please answer all of the following questions, selecting one answer per question. You should choose the answer which best represents how you have felt over the past 7 days. If you have been experiencing varied feelings of both highs and lows then please try and choose an answer which is an average of these feelings.

Physical Function
In the past 7 days...

	Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
1. Are you able to do chores such as vacuuming or yard work?....	○	○	○	○	○
2. Are you able to go up and down stairs at a normal pace?....	○	○	○	○	○
3. Are you able to go for a walk of at least 15 minutes?....	○	○	○	○	○

4. Are you able to run errands and shop?....	○	○	○	○	○

Anxiety **In the past 7 days...**					
	Never	Rarely	Sometimes	Often	Always
5. I felt fearful....	○	○	○	○	○
6. I found it hard to focus on anything other than my anxiety....	○	○	○	○	○
7. My worries overwhelmed me....	○	○	○	○	○
8. I felt uneasy....	○	○	○	○	○

Depression **In the past 7 days...**					
	Never	Rarely	Sometimes	Often	Always
9. I felt worthless....	○	○	○	○	○
10. I felt helpless....	○	○	○	○	○
11. I felt depressed....	○	○	○	○	○
12. I felt hopeless....	○	○	○	○	○

Fatigue **During the past 7 days...**					
	Not at all	A little bit	Somewhat	Quite a bit	Very much
13. I feel fatigued....	○	○	○	○	○
14. I have trouble starting things because I am tired....	○	○	○	○	○
15. How run-down did you feel on average?...	○	○	○	○	○
16. How fatigued were you on average?....	○	○	○	○	○

Sleep Disturbance **In the past 7 days...**					
	Very poor	Poor	Fair	Good	Very good
17. My sleep quality was....	○	○	○	○	○

In the past 7 days...					
	Not at all	A little bit	Somewhat	Quite a bit	Very much
18. My sleep was refreshing....	○	○	○	○	○
19. I had a problem with my sleep....	○	○	○	○	○

20. I had difficulty falling asleep	○	○	○	○	○

Ability to Participate in Social Roles and Activities
In the past 7 days...

	Never	Rarely	Sometimes	Usually	Always
21. I have trouble doing all of my regular leisure activities with others....	○	○	○	○	○
22. I have trouble doing all of the family activities that I want to do....	○	○	○	○	○
23. I have trouble doing all of my usual work (include work at home)....	○	○	○	○	○
24. I have trouble doing all of the activities with friends that I want to do....	○	○	○	○	○

Pain Interference
In the past 7 days...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
25. How much did pain interfere with your day to day activities?....	○	○	○	○	○
26. How much did pain interfere with work around the home?....	○	○	○	○	○
27. How much did pain interfere with your ability to participate in social activities?....	○	○	○	○	○
28. How much did pain interfere with your household chores?....	○	○	○	○	○

Pain Intensity
In the past 7 days...

	No Pain	1	2	3	4	5	6	7	8	9	Worst pain
29. How would you rate your pain on average?....	○	○	○	○	○	○	○	○	○	○	○

Patient Global Impression of Change	
Since beginning my treatment at CA Clinics my health status has:	◯ Very much improved ◯ Much improved ◯ Minimally improved ◯ Not changed ◯ Minimally worsened ◯ Much worsened ◯ Very much worsened
Comments	_____

Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

The SAN Clinical Trials Unit

Title	Randomised, placebo-controlled cross-over trial of cannabidiol extract for aromatase-inhibitor associated musculoskeletal symptoms
Short Title	CAIMSS
Project Sponsor	SAN Clinical Trials Unit
Coordinating Principal Investigator/ Principal Investigator	A/Prof Gavin Marx
Associate Investigator(s)	A/Prof Nial Wheate, Elise Schubert
Location	The SAN Clinical Trials Unit

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this clinical trial. This is because you are experiencing aromatase-inhibitor-associated musculoskeletal symptoms (AIMSS). Aromatase-inhibitors are a class of medications used in the treatment of breast cancer, otherwise known as anastrozole (e.g. Anastrol, Arianna, Arimidex), or letrozole (e.g. Femara, Femolet, Fera, Gynotril). In some people, aromatase inhibitors can cause musculoskeletal symptoms such as joint pains, otherwise referred to as AIMSS.

The clinical trial is testing a new treatment for AIMSS. The new treatment is a medication called cannabidiol broad spectrum extract (CBD extract), which is a type of medicinal cannabis derived from the cannabis sativa plant. Medicinal cannabis can contain many compounds, including cannabinoids, terpenes, and flavonoids. The CBD extract used in this clinical trial will contain a cannabinoid called cannabidiol (CBD), as well as small amounts (< 2%) of other cannabinoids, terpenes, and flavonoids. Cannabidiol is non-psychoactive, meaning it is not intoxicating and will not alter mental processes, perceptions, or behaviours.

This Participant Information Sheet/Consent Form tells you about the clinical trial. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not you wish to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you do not have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the clinical trial, you will be asked to sign the consent section. By signing it you are telling us that you:

- Understand what you have read,
- Consent to taking part in the clinical trial,
- Consent to having the tests and treatments that are described, and
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

The aim of this study is to assess the effects, good and/or bad, of the CBD extract compared to placebo on your joint pain that is associated with taking aromatase inhibitors.

Currently, the only treatment options suggested for people experiencing AIMSS include options such as paracetamol (e.g. Panadol). and ibuprofen (e.g. Nurofen) which may not be effective against the underlying cause of your pain. Research has shown that AIMSS may be caused by an increase in certain inflammatory processes. Cannabidiol has been shown to be effective in reducing these inflammatory processes in other conditions. Therefore, researchers want to examine whether CBD extract is effective at relieving your type of pain. We will also explore the effect of CBD extract on menopausal symptoms that are associated with aromatase inhibitor use.

We hope that this can improve long term outcomes and quality of life for breast cancer patients who are taking aromatase inhibitors by reducing the severity of side effects and improving adherence. Cannabidiol extract is an experimental treatment. This means it is not an approved for AIMSS in Australia.

The research will be analysed by the University of Sydney, and results will be used by Elise Schubert in the process of obtaining a Doctor of Philosophy degree. This research has been initiated by your medical doctor, Associate Professor Gavin Marx.

3 What does participation in this research involve?

Before you begin the study…

You will need to have the following exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of your regular cancer care and may be done even if you do not join the study. If you have had some of these tests recently, they may not need to be repeated for this research. This will be up to your doctor.

- Medical history and physical exam,
- Blood test to check your liver and kidney function, and
- Blood test to check your menopause status (if necessary).

You will also complete a questionnaire to collect information about joint pain that you are currently having. This is not part of routine cancer care but will help us determine if you are eligible to take part in this study.

During the study…

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then this section describes what is involved in taking part in the study.

You will be participating in a randomised controlled clinical trial. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try and make sure the groups are the same, each participant is put into a group by chance (random). In this study, we will be comparing CBD

extract to placebo treatment. A placebo is a medication with no active ingredients; it looks like the real thing, but it is not. There will be a total of two groups, and you will have a 50% chance of being assigned to either group.

This study has a “cross-over” design which means both groups will have each treatment in turn; that is, you will receive two treatments, one after the other. There will be a three week break between treatments so that the first drug is cleared from your body before the second drug is started. This means you will receive both CBD extract (the study drug) and placebo (which contains no drug) at some time during this study. One group will receive CBD extract for the first study period, and then placebo for the second study period, while the other group will receive placebo for the first study period, and CBD extract for the second study period. This study is a double-blind study. This means that neither you nor your medical doctor will know which treatment you are receiving. However, in certain circumstances your doctor can find out which treatment you are receiving.

You will be asked to complete a total of four questionnaires during this study, which will be at the beginning and the end of each of the two study periods. These questionnaires will collect information about how you are feeling physically and how you are performing your daily activities. You will also be asked questions about other symptoms you may be having, including hot flushes, sleep difficulties, and mood changes. If any of the questions make you uncomfortable you may skip those questions and not give an answer. Your personal information will remain private. These questionnaires are not part of your routine cancer care and will only be done as part of this research study.

You will be supplied with the study drug at the start of each of the two study periods. You will need to take one capsule orally twice a day immediately after food for four (4) weeks of the first study drug, followed a three (3) week break, after which you will then take one capsule orally twice a day immediately after food for four (4) weeks of the second study drug. You and your doctor will not know if you are receiving the CBD extract or placebo in either study period. We will compare your outcomes of each study period to see whether the CBD extract was better, worse, or the same as the placebo.

At the first visit…
You will be given your first study drug with directions to take one capsule twice a day for the next four (4) weeks.

Our medical team or staff will record:

- Aromatase inhibitor use;
- Any pain treatments you are taking; and
- A questionnaire.

At the four week visit…
Our medical team or staff will record:

- Any side effects you may be experiencing;
- Aromatase inhibitor use;
- Any pain treatments you are taking;
- Number of capsules remaining in your container; and
- A questionnaire.

At the seven week visit…
You will be given your second study drug with directions to take one capsule twice a day for the next four (4) weeks.

Our medical team or staff will record:

- Any side effects you may be having;
- Aromatase inhibitor use;
- Any pain treatments you are taking; and
- A questionnaire.

At the eleven week visit…
Our medical team or staff will record:

- Any side effects you may be having;
- Number of capsules remaining in your container;
- Aromatase inhibitor use;
- Any pain treatments you are taking; and
- A questionnaire.

How long will I be in the study?
You will be asked to participate in the study for a total of eleven (11) weeks. During the study, you will be taking CBD extract for a total of four (4) weeks, and the placebo for a total of four (4) weeks, with a three (3) week break in between.

The research will be monitored on site at the SAN Clinical Trials Unit and by researchers from the University of Sydney. This clinical trial has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

4 Costs
There are no additional costs associated with participating in this clinical trial, nor will you be paid. All medication, tests, and medical care required as part of the clinical trial will be provided to you free of charge.

5 What do I have to do?
To participate in this study, you will be asked to undertake the research processes outlined in Section 3, which are attending the study visits, taking the study drug as directed, answering questionnaires. It will be your responsibility to ensure you commit to taking the study drug in accordance with the instructions provided. You will not be required to restrict or change any of your usual lifestyle or dietary behaviours. You may continue taking your usual medications. The medical team will ask you what pain medications you are taking at the visits.

6 Other relevant information about the clinical trial
There will be about 20 people participating in this study, with about 10 people assigned to each group.
This study is taking place at one site; the SAN Clinical Trials Unit. The project involves researchers from the University of Sydney.

7 Do I have to take part in this clinical trial?
Participation in any clinical trial is voluntary. If you do not wish to take part, you do not have to. If you decide that you want to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether you can take part or not take part, or take part and then be withdrawn, will not affect your routine treatment, or your relationship with those treating you, or your relationship with The SAN Clinical Trials Unit.

8 What are the alternatives to participation?

You do not have to take part in this clinical trial to receive treatment at this hospital. Other options are:

- Getting other treatments to manage your symptoms without participating in a study,
- Taking part in another study for this condition, and
- Getting no treatment for your symptoms.

Your study doctor will discuss these options with you before you decide whether or not you can take part in this clinical trial. You can also discuss the options with your local doctor.

9 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any health benefits from this research. We hope that the information from this study will help doctors learn whether CBD extract reduces joint pain in patients receiving aromatase inhibitors. This information could help future patients taking aromatase inhibitors to manage the side effects and improve their adherence to the medicine.

10 What are the possible risks and disadvantages of taking part?

Medical treatments, such as the CBD extract used in this study can have side effects. You may have none, some, or all of the effects listed below, and they may be mild, moderate, or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect, or do not know about, and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting, or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

Overall, CBD extract is generally considered well tolerated and is rarely associated with serious side effects. The Australian Therapeutic Goods Administration has listed commonly reported side effects of cannabidiol from clinical trials. These are:

- Tiredness
- Diarrhoea
- Changes in appetite/weight
- Abnormalities of liver tests
- Sedation (sleepiness)
- Sleep disturbances
- Infections
- Anaemia (low red blood cell count)

In order to be included in this study, you will be post-menopausal; therefore, not required to undergo a pregnancy test or use additional contraception for the duration of this trial. The effects of cannabidiol on an unborn child and on a newborn baby are not known. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support. Any counselling or support will be provided by qualified staff who are not members of the clinical trial team. This counselling will be provided free of charge.

11 What if new information arises during this clinical trial?

Sometimes during the course of a clinical trial, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the clinical trial. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the clinical trial, you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the clinical trial. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this clinical trial?

While you are participating in this clinical trial, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture, or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the clinical trial. Your study doctor will also explain to you which treatments or medications need to be stopped for the time you are involved in the clinical trial. It is important for your doctor to know about your other treatments so we can accurately determine the effect the CBD extract may be having.

13 What if I withdraw from this clinical trial?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the clinical trial, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the clinical trial can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the clinical trial results. If you do not want them to do this, you must tell them before you join the clinical trial.

14 Could this clinical trial be stopped unexpectedly?

This clinical trial may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects,
- The drug being shown not to be effective,
- The drug being shown to work and not need further testing, and/or
- Decisions made in by local regulatory/health authorities.

15 What happens when the clinical trial ends?

Once the clinical trial is complete CBD extract will not be readily available for you to continue using. If you wish to continue taking CBD extract after the study is finished, you may speak with your study doctor or local doctor about whether obtaining a CBD extract through the Special Access Scheme is appropriate for you. To manage your symptoms after the trial is complete, you should speak with your doctor about what options are right for you.

Your study doctor will inform you on whether the clinical trial is a success. In the months after the trial is concluded, you will be emailed a summary of the results.

Part 2 How is the clinical trial being conducted?

16 What will happen to information about me?

The data collected in this study will be re-identifiable. Participants will be assigned a number at the beginning of the trial. Data collected from questionnaires will be entered into Research Electronic Data Capture (REDCap) along with the participant codes. Other data, including the participants' date of birth, gender, medical history, and medication history will be obtained from the participants medical records on site and entered into REDCap. Trial related information trial will be stored for a minimum of 15 years. The data collected in this study will be used for this analysis and may be used for extended related research. This clinical trial does not involve the establishment of a databank.

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the clinical trial. Any information obtained in connection with this clinical trial that can identify you will remain confidential. The data collected will be re-identifiable and participants will be provided with a participant identification number. Your information will only be used for the purpose of this clinical trial and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this clinical trial.

Your health records and any information obtained during the clinical trial are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities the institution relevant to this Participant Information Sheet, The SAN Clinical Trials Unit, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

It is anticipated that the results of this clinical trial will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Data presented will be qualitative analysis of the overall cohort and will not include any individual patient identifying characteristics.

Information about your participation in this clinical trial may be recorded in your health records.

In accordance with relevant Australian and New South Wales privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you

disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Any information obtained for the purpose of this clinical trial that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you wish to make a complaint about your treatment by members of staff, or if you have any concerns regarding the conduct of the clinical trial you may speak with The Research Office at the Sydney Adventist Hospital on 9480 9604.

If you are experiencing a serious side effect, or you suffer any injuries or complications as a result of this clinical trial, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This clinical trial is being conducted by The SAN Clinical Trials Unit in collaboration with the University of Sydney.

The medicinal cannabis company supplying this trial may benefit financially from this clinical trial if, for example, the project assists them to obtain approval for a new drug from the Australian Therapeutic Goods Administration.

In addition, if knowledge acquired through this research leads to discoveries that are of commercial value to the medicinal cannabis company, or the study doctors or their institutions, there will be no financial benefit to you or your family from these discoveries.

No member of the research team will receive a personal financial benefit from your involvement in this clinical trial (other than their ordinary wages).

Declarations of interests:

Elise Schubert is funded by scholarship from the University of Sydney and Canngea Pty Ltd. Nial Wheate is the science director of Canngea Pty Ltd. Canngea Pty Ltd. is an Australian medicinal cannabis company.

19 Who has reviewed the clinical trial?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this clinical trial have been approved by the HREC of The SAN Clinical Trials Unit.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor, A/Prof Gavin Marx on 9056 1100 on or any of the following people:

Clinical contact person

Name	A/Prof Gavin Marx
Position	Medical Oncologist and Clinical Director SAN Integrated Cancer Centre
Telephone	9056 1100
Email	gmarx@nhog.com.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Name	The Research Office, Sydney Adventist Hospital
Telephone	9480 9604
Email	research@sah.org.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Local HREC Office contact:

Reviewing HREC name	Adventist HealthCare Limited Human Research Ethics Committee
HREC Research Officer	Shari Emerton
Telephone	9480 9604
Email	research@sah.org.au

Consent Form - *Adult providing own consent*

Title	Randomised, placebo-controlled cross-over trial of cannabidiol extract for aromatase-inhibitor associated musculoskeletal symptoms
Short Title	CAIMSS
Protocol Number	XXXXXX
Project Sponsor	SAN Clinical Trials Unit
Coordinating Principal Investigator/ Principal Investigator	A/Prof Gavin Marx
Associate Investigator(s)	A/Prof Nial Wheate, Elise Schubert
Location	The SAN Clinical Trials Unit

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals, or laboratories outside this hospital to release information to The University of Sydney concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this clinical trial as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the clinical trial, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the clinical trial.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	Randomised, placebo-controlled cross-over trial of cannabidiol extract for aromatase-inhibitor associated musculoskeletal symptoms
Short Title	CAIMSS
Protocol Number	XXXXXX
Project Sponsor	SAN Clinical Trials Unit
Coordinating Principal Investigator/ Principal Investigator	A/Prof Gavin Marx
Associate Investigator(s)	A/Prof Nial Wheate, Elise Schubert
Location	The SAN Clinical Trials Unit

Declaration by Participant

I wish to withdraw from participation in the above clinical trial and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with The University of Sydney.

Name of Participant (please print) _____

Signature _____ Date _____

For Study Doctor/Senior Researcher only: Description of the circumstances for withdrawal

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the clinical trial and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the clinical trial.

Note: All parties signing the consent section must date their own signature.