‘Low-Dose’ Cannabidiol: An Emerging Area of Clinical Practice

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Statement of Originality

This is to certify that to the best of my knowledge; the content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

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Authorship Attribution Statement

I, Zeeta Bawa, am the primary author of the work featured in Chapters 2, 4, 5 and 6.

Chapter 2 is published in *BMC Primary Care*
Chapter 4 is published in the *International Journal of Clinical Pharmacy*
Chapter 5 is published in *Scientific Reports*
Chapter 6 is published in *BMJ Open*

For the work featured in Chapters 2 and 4, I took the lead role in the conception and design of the research, data acquisition and analysis, and the writing of manuscripts. For the work featured in Chapter 5, I took the lead role in the conception and design of the research and the writing of the manuscript. For the work featured in Chapter 6, I took the lead role in the conception and design of the research, data acquisition and the writing of the manuscript.

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 has been granted by the corresponding author.

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As primary supervisor for the candidature upon which this thesis is based, I can confirm on behalf of all members of the supervisory team that the authorship attribution statements above are correct.

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Publications and Presentations

Publications

- **Bawa Z.,** Saini B., McCartney D., Bedoya-Pérez M., McLachlan A.J., and McGregor I.S. A cross-sectional survey exploring the knowledge, experiences and attitudes of Australian pharmacists toward medicinal cannabis. *International Journal of Clinical Pharmacy.* 2023; 45(2):375-386. https://doi.org/10.1007/s11096-022-01519-z

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Conference Presentations

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Conference Abstracts

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- Triple J Hack. "Access to CBD oil online" 6 May 2021, interviewed by Hack reporter, Dee Salmin (access here).

- Cannabiz "Medicinal cannabis course for pharmacists to launch at UIC" 17 April 2023, article written by Steve Jones (access here).

- Sydney University Faculty of Medicine and Health News "Survey of pharmacists on medicinal cannabis" 19 May 2021 (access here).

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Other Publications

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List of Abbreviations

11-COOH-THC	11-carboxy-THC
11-OH-THC	11-hydroxy-THC
2-AG	2-arachidonylglycerol
7-COOH-CBD	7-carboxy-CBD
7-OH-CBD	7-hydroxy-CBD
AEs	adverse events
AP	Authorised Prescriber
ARTG	Australian Register of Therapeutic Goods
CAPSTAN	Cannabidiol for Acute Psychosocial Stress and Nausea
CB1	Cannabinoid receptor 1
CB2	Cannabinoid receptor 2
CBD	cannabidiol
CBDA	cannabidiolic acid
CBG	cannabigerol
CBGA	cannabigerolic acid
CBN	cannabinol
CPD	continuing professional development
CUD	Cannabis Use Disorder
CYP 450	Cytochrome P450
ECS	endocannabinoid system
FAAH	fatty acid amide hydrolase
FDA	Food and Drug Administration
GP	general practitioner
MS	Multiple Sclerosis
NS	Not specified
OTC	over-the-counter
PBS	Pharmaceutical Benefits Scheme
PTSD	Post Traumatic Stress Disorder
SAD	Social Anxiety Disorder
SAEs	serious adverse events
SAS	Special Access Scheme
SAS-A	Special Access Scheme Category A
SAS-B	Special Access Scheme Category B
SCRAs	synthetic cannabinoid receptor agonists
TGA	Therapeutic Goods Administration
THC	Δ^9-tetrahydrocannabinol
THCA	Δ^9-tetrahydrocannabinolic acid
VR	virtual reality
vs.	versus
WHO	World Health Organization

Thesis Abstract

Since the legalisation of medicinal cannabis in Australia in 2016, health professionals, particularly general practitioners (GPs) and pharmacists, are at the frontlines of medicinal cannabis access and the care of consumers who use these products. Medicinal cannabis has been trialled across a wide scope of health conditions. However, the evidence around the efficacy of these products is often scarce, reflecting a paucity of high-quality clinical trial evidence. Understandably, this causes difficulties for pharmacists and GPs in the practice of evidence-based medicine.

Cannabidiol (CBD) is a non-intoxicating constituent of the cannabis plant and a common ingredient in medicinal cannabis products. CBD is often consumed at lower doses than those that have been proven to be therapeutic. Nonetheless, the global demand for low-dose CBD products has soared. Furthermore, local restrictions rapidly evolve and determine whether these products are available from health food stores, online, or in pharmacies with or without a prescription. As such, the availability of low-dose CBD can be considered an emerging area of clinical practice.

In this thesis, a series of original investigations were conducted to address two aims. Thesis Aim One was to explore the knowledge, experiences, and attitudes of physicians and pharmacists towards medicinal cannabis products, in particular, low-dose CBD. Thesis Aim Two was to expand the current evidence base around the efficacy of low-dose CBD products by undertaking two clinical trials utilising these products.

Regarding Thesis Aim One, two cross-sectional, online studies were undertaken. The first involved a survey of 217 community pharmacists practicing in Australia, while the second involved a survey of 505 Australian GPs. Findings from these surveys demonstrated that both pharmacists and GPs respondents were regularly queried about medicinal cannabis, including low-dose CBD products, but tended to lack confidence and detailed knowledge in this area. Pharmacist respondents tended to support the availability of low-dose CBD products without a prescription, whereas GP respondents appeared more reserved. Only around a fifth of the GPs surveyed were medicinal cannabis prescribers. A considerable need for further training and education around medicinal cannabis and low-dose CBD was emphasised by both groups of health professionals. Based on the findings of the pharmacist survey, a national medicinal cannabis training program for Australian pharmacists was developed and delivered as a one-

day, continuing professional development (CPD) accredited activity. This training program exemplifies a knowledge translation approach in research and serves as a guide for future educational initiatives around medicinal cannabis for health professionals.

Regarding Thesis Aim Two, two clinical trials were undertaken. The first was an open-label feasibility trial investigating the effects of a four-week treatment with a transdermal, low-dose CBD gel (~30 mg per day) in 15 participants with hand osteoarthritis. This indication was selected based on preliminary evidence suggesting that transdermal CBD preparations have demonstrated some efficacy in treating chronic pain conditions. The trial demonstrated a significant reduction in subjective ratings of hand pain from baseline as well as a significant increase in grip strength over time (measured using a novel smartphone application connected via Bluetooth to a squeeze ball dynamometer). Significant improvements in three subjective quality of life measures (fatigue, stiffness, and anxiety) were also observed from baseline, although subjective sleep was unchanged. CBD and its metabolites were detected in urine samples taken from all participants on the last day of treatment.

The second study was a randomised, double-blind, placebo-controlled trial designed to investigate the acute effects of an oral, low-dose of CBD (150 mg) on anxiety and nausea. This study was based on preliminary evidence that an acute, lower dose of CBD demonstrated some positive effects on anxiety in healthy participants prior to a public-speaking task. Virtual reality (VR) was used to provide a customisable and reproducible test paradigm. Nausea was investigated as there is some preclinical evidence that CBD has anti-emetic properties and the study utilised VR, which is known to induce nausea. As such, three custom-designed VR scenarios were used to investigate psychosocial stress (using a 'Public Speaking' task), situational anxiety (using a 'Walk the Plank' task), and motion sickness (using a 'Rollercoaster Ride' task). Overall, an acute dose of 150 mg CBD reduced self-reported anxiety immediately after the 'Public Speaking' task although there was no significant effect of CBD at speech-delivery. CBD did not affect self-reported nausea during the 'Rollercoaster Ride' task or secondary outcomes. This thesis presents the published protocol for the clinical trial and a manuscript in preparation for publication.

This portfolio of research demonstrates that medicinal cannabis, and in particular, low-dose CBD, is having a considerable impact on the clinical practice of health professionals. Given the legislative distinction of low-dose CBD products from other medicinal cannabis products in Australia, this class of medicine requires its own best practice guidelines and

educational initiatives to support pharmacists and GPs in the quality use of these products. The first clinical trial demonstrated some promise of transdermal CBD in hand OA. However, due to the strong placebo effect often observed in medicinal cannabis pain trials, these preliminary results should be interpreted with caution and evaluated further in larger randomised, placebo-controlled trials. The second clinical trial generated evidence of efficacy in anxiety in healthy participants exposed to a stress-inducing task at a specific timepoint. These results contribute to the broader, complex, and inconclusive body of evidence around the efficacy of low-dose CBD, aiding efforts that will ultimately provide further clarity.

CHAPTER 1. GENERAL INTRODUCTION AND LITERATURE REVIEW

1.1 Prologue

Cannabis sativa is one of the oldest cultivated botanicals in human history. It was first used by humans as early as Neolithic times with domestication likely occurring in Central and Southeast Asia around 4,000 BC [1-3]. The *Cannabis sativa* plant, hereafter referred to as 'cannabis', has exceptional versatility and provided ancient civilisations with a nutritious food source of starch, oil and protein, and a durable fibre that was used for net, rope, and paper (Figure 1) [1, 4]. These uses are typical of 'hemp', a variety of cannabis grown primarily for industrial applications and foodstuffs (e.g., hemp seed and hemp seed oil). Non-hemp varieties of cannabis were also used as a revered mind-altering substance, incorporated into ceremonial practices and widely used as a therapeutic [1, 4, 5]. Emperor Chen Nung, the 'father' of Chinese medicine, included cannabis in his pharmacopeia 5,000 years ago [4]. Ancient texts of Ayurveda similarly identified cannabis as a medicine and Indian myth describes cannabis as a divine agent for mystic inspiration, favoured by the supreme Lord Shiva [5]. The therapeutic use of cannabis proliferated across numerous geographical regions over the millennia with evidence of use by numerous ancient civilisations including those in Egypt, Greece, Rome, and Assyria [4, 6].

Figure 1. *Products made from cannabis plant material (a) rope, (b) textiles, (c) fabric (d) oil extracts, (e) seed and seed meal, and (f) protein powder. See Section 1.13 Image References.*

Despite this rich history of use, the past 200 years have seen notable shifts in the legality and availability of cannabis. Cannabis was prescribed abundantly by Western physicians following its inclusion into the United States Pharmacopoeia in 1850. However, restrictions commenced during the Prohibition Era of the 1930s, perhaps in a bid to control escalating recreational use of the plant for its psychoactive effects [1]. Gradually, social and political influences galvanised to further restrict the availability of cannabis and it was often wrongly connected to racial or ethnic minority groups [7]. Cannabis was removed from the United States Pharmacopoeia in 1941 and internationally criminalised by the United Nations Single Convention on Narcotic Drugs in 1961 [8]. The possession and use of cannabis was punishable by law for many decades.

Over the past 20 years however, there has been a dramatic global 'renaissance' of interest in medicinal cannabis that has led to a shifting international landscape of legal availability. Over 60 countries now permit some form of legal access to cannabis, mostly for medicinal purposes [9].

1.2 Phytocannabinoids

Cannabis plant material contains a wide range of bioactive compounds including phytocannabinoids, terpenoids, alkaloids, and flavonoids [1]. More than 140 different phytocannabinoids have been characterised to date and these share a standard chemical scaffold (Figure 2). Phytocannabinoids have been sourced almost exclusively from the cannabis plant species [10, 11] and can be found in both the male and female plants but are more abundant in the latter [12]. Their biosynthesis (Figure 3) and accumulation mainly occurs in the trichomes of the cannabis plant. Here, olivetolic acid, and geranyl diphosphate are paired to form cannabigerolic acid (CBGA) [12]. Enzymatic processing of CBGA results in the production and accumulation of acidic cannabinoids such as Δ^9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) [12]. When post-harvested plant material is heated, these acidic precursors undergo non-enzymatic decarboxylation to form phytocannabinoids such as Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Female cannabis plants are used for medicinal purposes and advances in plant sciences have permitted the cultivation of cannabis strains containing specific ratios of phytocannabinoids such as THC and CBD [3].

It should be noted that the term 'cannabinoid' broadly describes a family of compounds that includes 'phytocannabinoids' (i.e., plant-derived cannabinoids), synthetic cannabinoids, and endocannabinoids (i.e., cannabinoids naturally occurring in the human body) [10]. Furthermore, synthetic cannabinoids (e.g., synthetic THC or CBD) should not be confused with synthetic cannabinoid receptor agonists (SCRAs, e.g., JWH-018, MDMB-FUBINACA and ADB-BUTINACA) which are full and potent agonists of the CB1 receptor [13]. SCRAs are often illicitly manufactured for recreational purposes and sold as herbal blends termed "Spice", "Kronik" and "Black Mamba." These pose serious health risks to users, including death [13].

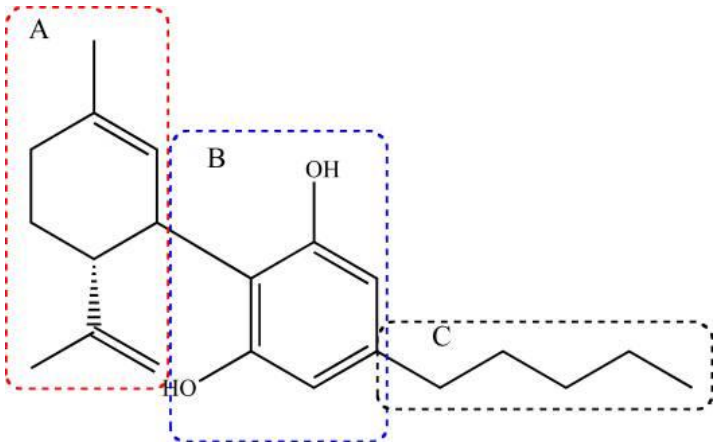

Figure 2. *General structure of a phytocannabinoid scaffold with 21-carbon atoms and three variable structural fragments: The isopropenyl residue at the terpenoids moiety (A), the resorcinol nucleus (B), and the alkyl side chain (C). Reproduced from Dos Reis Rosa Franco et al., (2021) [10].*

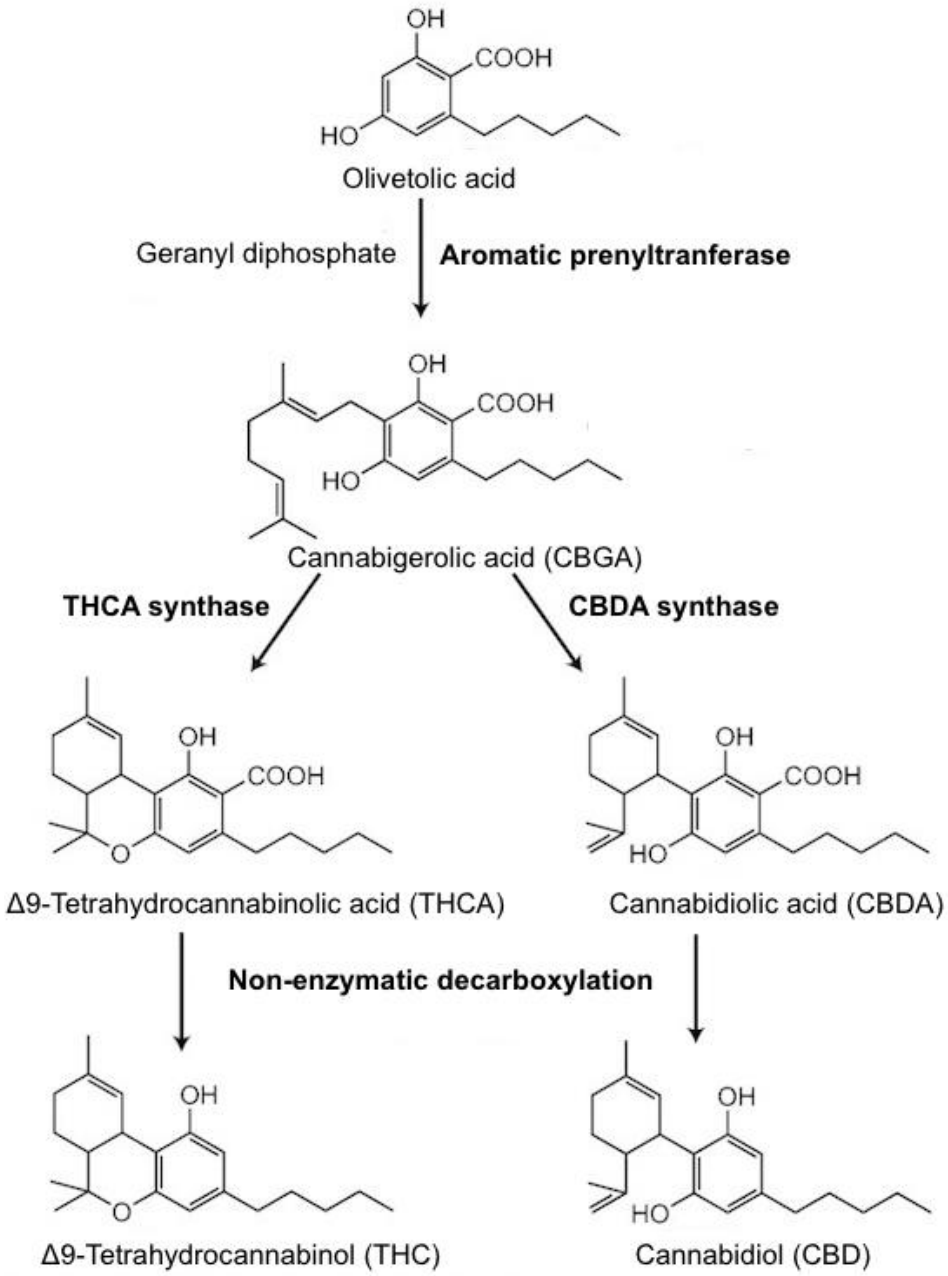

Figure 3. *Biosynthesis of the phytocannabinoids, Δ^9-tetrahydrocannabinol and cannabidiol. Adapted from Gagne et al., (2012) [14].*

1.2.1 Introduction to THC and CBD

Of the many phytocannabinoids present in the cannabis plant, the two most studied are THC and CBD. These phytocannabinoids have a similar structure (Figure 4) and an identical molecular weight [15]. THC is the major intoxicating ingredient of cannabis plant and is recognised by its distinctive psychotropic effects. CBD is non-intoxicating and has demonstrated therapeutic value [16-18]. These phytocannabinoids will be discussed in further detail below.

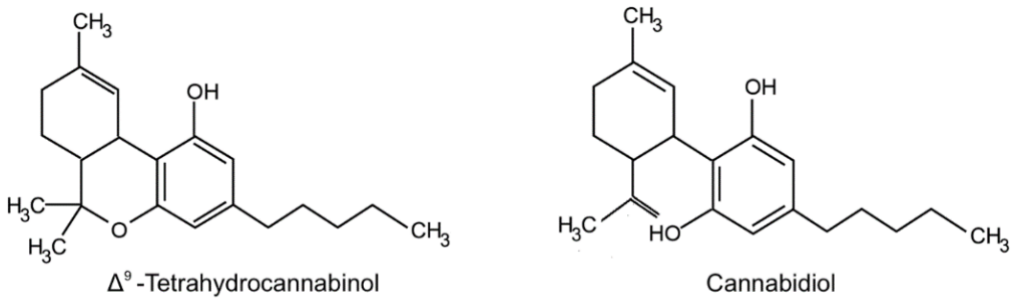

Figure 4. *The chemical structures of Δ^9-tetrahydrocannabinol and cannabidiol. Adapted from Mazzetti, Carlo et al., (2020) [19].*

1.3 Pharmacology of Phytocannabinoids

Phytocannabinoids have been reported to interact with a wide range of pharmacological targets in the human body. The most notable of these is the endocannabinoid system (ECS), an intricate neuromodulatory signalling system involved in the homeostatic regulation of many basic physiological processes [17, 18]. The endocannabinoid system is composed of three key features. First, cannabinoid receptor 1 (CB1) and 2 (CB2). CB1 receptors are most abundantly expressed in the central nervous system and peripheral organs [17, 18], whereas CB2 receptors are expressed primarily in the immune system and peripheral tissues [17, 18]. Second, the endogenous ligands for these two receptors, anandamide and 2-arachidonylglycerol (2AG), which are two of many endocannabinoids, the discovery of which marked a major advancement in our understanding of the ECS [20]. Third, the enzymes responsible for deactivating these ligands, including fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [18].

THC acts as a partial agonist at the CB1 and CB2 receptors and its distinctive psychoactive effects are attributed to its activity at the CB1 receptor [21]. CBD is believed to be a negative allosteric modulator at CB1, that is, it does not activate the CB1 receptor itself but affects the binding and intrinsic activity of other ligands [22]. CBD has also demonstrated pharmacological activity across many other targets beyond the ECS such as serotonin receptors (e.g., 5-HT1A), G protein-coupled receptors (e.g., GPR55), peroxisome proliferator-activated receptor gamma (PPARγ) receptors, gamma-amino butyric acid receptor type A ($GABA_A$) receptors, enzymes (e.g., CYP450), and transient receptor potential ion channels (e.g. TRPA1) [23-28]. In fact, a recent review identified more than 65 discrete molecular targets of CBD. Importantly, the molecular targets of CBD are still being established, with many of those identified in in-vitro cellular assays still to be validated as occurring in-vivo [29].

1.4 Consumption and Types of Products

Traditionally, cannabis consumption has primarily involved the smoking of dried cannabis flower. However, in recent years, a wide range of cannabis-based products have been developed including inhalables (for smoking or vaping), oral capsules and oils, oromucosals (e.g., buccals and sublinguals), edibles (e.g., gummies), topicals (e.g., lotions, creams, gels and patches), and rectal suppositories, to name a few [30].

These products typically contain phytocannabinoids sourced from cannabis plant material, although synthetic cannabinoids (e.g., synthetic THC or CBD) may also be used. Most cannabis-based products contain THC and/or CBD in varying concentrations. A product is described as an ‘isolate’ when it contains a single plant-derived or synthetic cannabinoid. On the other hand, ‘full spectrum’ products contain a diversity of constituents from the cannabis plant. These can include major cannabinoids such as THC and CBD, minor cannabinoids such as cannabinol, and other minor constituents such as terpenoids and flavonoids. ‘Broad-spectrum’ products are similar to full-spectrum products, but do not contain THC [31]. Importantly, pharmaceutical-grade medicinal cannabis products are considered to have a more consistent quality than ‘artisanal’ products due to higher regulatory standards imposed during their manufacture [32, 33].

It is worth noting that ‘hemp’ products are generally sourced from cannabis cultivars that contain low levels of THC and are useful for seed and fibre [3].

1.5 Pharmacokinetics and Pharmacodynamics of Phytocannabinoids

Phytocannabinoids have complex pharmacokinetic profiles that are affected by a range of factors, particularly the route of administration, frequency of use, and dose [34, 35]. Inter-subject (e.g., genetics, body composition, and sex) and intra-subject (e.g., food intake and health status) factors can also impact the pharmacokinetic profiles of phytocannabinoids [35]. When THC and CBD are inhaled, there is typically a large and rapid spike in blood concentrations (i.e., within three - 10 minutes), followed by a rapid drop [34, 36]. Inhaled THC and CBD have a bioavailability between 10 and 35% that is subject to variability based on smoking topography [34, 35]. In contrast, when THC and CBD are orally ingested, blood concentrations rise gradually (i.e., over approximately two hours), reach a small peak, and then decline over several hours [34, 37]. Orally ingested THC and CBD have a bioavailability of approximately 6% attributed to extensive first-pass liver metabolism [35, 38].

THC and CBD promptly distribute to highly perfused organs such as the heart, brain and liver, and subsequent distribution occurs in less vascularised tissues [35]. The high lipophilicity of THC and CBD drives storage in adipose tissue and accumulation may occur with chronic use [34, 35]. The resulting slow rediffusion of THC and CBD from adipose and other tissues can cause these phytocannabinoids to persist in the body for many weeks post-administration [34]. THC and CBD are metabolised by hepatic cytochrome P450 (CYP 450) isoenzymes CYP2C9, CYP2C19 and CYP3A4 to their pharmacologically active metabolites 11-hydroxy-THC (11-OH-THC) and 7-hydroxy-CBD (7-OH-CBD), respectively [35, 38]. These hydroxy metabolites are further processed to the inactive metabolites, 11-carboxy-THC (11-COOH-THC) and 7-carboxy-CBD (7-COOH-CBD); further metabolism, including glucuronidation, may occur prior to excretion in the urine and faeces [34, 35]. The metabolites of THC and CBD have their own distinct pharmacokinetic profiles that can differ widely from the parent phytocannabinoid.

It is important to recognise that the pharmacodynamic effects of phytocannabinoids tend not to correlate with their pharmacokinetic parameters [34, 35]. This is most evident when considering the intoxicating effects of THC. For example, following inhalation of THC, blood THC concentrations typically peak between three and 10 minutes and rapidly drop thereafter [34]. However, peak intoxication is typically observed between approximately 20 and 30 minutes [34], with impairment tending to persist for several hours [34, 39]. This

mismatch has been attributed to the complex distribution patterns of THC within the body and the fact that 11-OH-THC, an active metabolite of THC, is also able to activate the CB1 receptor and cause intoxication [34, 35].

1.6 Medical Uses of Cannabis

Research around the medical uses of cannabis (i.e., 'medicinal cannabis') centres largely around THC and CBD. These phytocannabinoids have been trialled across a wide range of health conditions, however, there is an overall lack of robust clinical trials showing consistent efficacy data around many conditions. Nonetheless, this body of evidence continues to evolve and there is reasonable data supporting their utility in select health conditions, as discussed below. The therapeutic potential of lesser-known cannabinoids such as cannabinol (CBN), cannabidiolic acid (CBDA), and cannabigerol (CBG), and other compounds from the cannabis plant such as terpenes and flavonoids, are under investigation, but mostly in preclinical cell-based or animal models that provide little conclusive proof of efficacy in humans [40, 41].

1.6.1 Δ^9-tetrahydrocannabinol (THC)

The clinical efficacy of THC has been reasonably well-established in conditions such as chronic pain, chemotherapy induced nausea and vomiting (CINV), and spasticity associated with multiple sclerosis (MS) [42-45]. Evidence of efficacy in conditions such as Tourette syndrome, neuropsychiatric symptoms in dementia, and palliative care is also emerging [46-48]. Typical therapeutic doses of THC are low, around 2.5 - 20 mg per day, and clinical guidelines recommend starting at a low dose and gradually titrating up until a therapeutic effect is attained, particularly in naïve users [16, 49]. When dosed in this manner, such individualised therapy can be well tolerated and adverse effects such as drowsiness and cognitive impairment minimised [16]. More troublesome adverse effects such as anxiety, paranoia, and psychosis affect a small number of users and these can be lessened by judicious dosing and possibly by combining THC with CBD, although the evidence is conflicting to date [16, 50].

1.6.2 Cannabidiol (CBD)

The clinical efficacy of CBD has been well-established in paediatric epilepsy [51]. Emerging evidence also exists for conditions such as anxiety, psychosis, addiction, and other neurological conditions, whereas the evidence for chronic pain is inconsistent [43, 52, 53]. As noted above, CBD has been suggested to counteract some of the anxiogenic or psychotomimetic effects of THC due to its pharmacological activity as a negative allosteric modulator at the CB1 receptor; however, this has not been extensively researched to date [50].

The clinical efficacy of CBD is typically demonstrated at doses several orders of magnitude higher than THC (e.g., 300 - 1,500 mg) [16, 43]. However, CBD is also widely used in preparations containing much lower doses (e.g., 5 - 150 mg) despite a scarcity of clinical trials data at these lower dose ranges [33, 49].

CBD has a robust safety and tolerability profile [54, 55] and individuals generally cannot subjectively discriminate between CBD and placebo, even at high doses (e.g., 1,500 mg) [56, 57]. Adverse effects of CBD can include sedation, somnolence, and gastrointestinal upsets [54]. In studies of healthy individuals (i.e., not using other therapies), the only adverse effect that has been consistently observed is diarrhoea, which is commonly associated with the use of CBD oil [54, 58]. CBD can also increase plasma concentrations of liver enzymes such as transaminases alanine transaminase (ALT) and aspartate aminotransferase (AST), which may be indicative of liver stress or toxicity [25, 58]. Importantly, these adverse effects primarily occur when high doses of CBD (i.e., ≥ 1,000 mg per day) are used, particularly concurrently with other therapies (e.g., clobazam and valproate) [25, 58].

An emerging concern with CBD use is its potential to cause drug-drug interactions by slowing the metabolism of co-administered drugs that are metabolised by the CYP2C9, CYP2C19, and CYP3A4 isoenzymes (e.g., tolbutamide, (S)-mephenytoin, and clobazam, respectively); however, the clinical significance of such interactions requires further research in humans [25, 59]. One study found that co-administration of oral CBD (640 mg) and THC (20 mg) led to augmented plasma levels of THC and its metabolites, as well as greater cognitive and psychomotor impairment compared to THC alone (20 mg) or placebo [50]. This suggests the importance of considering drug-drug interactions, including co-administration of CBD with other cannabinoids, particularly when high doses of CBD are used [60].

1.7 Legal Access to Cannabis

1.7.1 A Global Perspective

Legislated use of medicinal cannabis commenced in the early 2000s in countries such as the Netherlands (2000) and Canada (2001), and this shift continued to expand to many other countries such as the United Kingdom (2006), Switzerland (2011), and Italy and France (2013) [61, 62]. In 2014, Uruguay become the first country in the world to legalise cannabis use for both medicinal uses *and* recreational purposes, an approach that was similarly adopted by Canada in 2018 [61]. A pivotal milestone was reached in 2020 when cannabis was removed from Schedule IV of the Single Convention on Narcotic Drugs (1961) by the United Nations General Assembly on the advice of the World Health Organisation (WHO) [63].

Over the last decade, more than 60 countries (and 20 states in America) have introduced some form of legal access to medicinal cannabis [9, 64]. Countries such as the United Kingdom, Norway, Ireland, New Zealand, and Australia permit cannabis for medicinal purposes [61, 63]. Medicinal cannabis is now recognised in many countries as a mainstream medicine and legitimate alternative to more conventional prescription drugs for certain conditions. Indeed, one of the world's most influential medicines regulator, the American Food and Drug Administration (FDA), has approved four medicinal cannabis products. Three include synthetic THC drugs, namely *Cesamet* (nabilone) for CINV, and *Marinol* (dronabinol) and *Syndros* (dronabinol) for CINV and weight loss associated with acquired immunodeficiency syndrome (AIDS). The final drug is a plant-derived CBD product, namely *Epidiolex* for Lennox-Gastaut syndrome and Dravet syndrome [65].

CBD has undergone particular legislative easing across recent years. In 2019, after a careful and detailed review, the WHO Expert Committee on Drug Dependence concluded that CBD preparations should not be subject to international drug controls and that scheduling of CBD products should be eased. This decision was made on the basis that CBD was not intoxicating, had a good tolerability profile, and presented no potential for dependence or abuse [66]. In line with this reasoning, many countries have eased regulations around CBD preparations. This is most evident in the wide availability of CBD products without a prescription in countries such as America, Canada, the United Kingdom, Ireland, and Germany [33]. Typically, these products provide relatively low doses of CBD (e.g., ≤ 50 mg per day) but can contain more than 2,000 mg CBD in total. These products are available online, in health

food stores as a nutraceutical, or in pharmacies [33]. Evidently, the definition of 'low-dose CBD' varies based on the jurisdiction.

The range of CBD products has proliferated considerably and includes oils, tinctures, topical applications, 'gummy' bears, and sports beverages to name a few. While the regulations governing the use and supply of these products vary considerably across jurisdictions, they are nonetheless popular. It is estimated that Americans will spend $20 billion on CBD products during 2024, which is approximately ten times the $1.9 billion spent in 2018 [67].

1.7.2 An Australian Perspective

In 2016, an amendment to the *Narcotic Drugs Act 1967* enabled the cultivation and manufacture of medicinal cannabis using a national licensing and permit scheme. Other legislative changes by the Australian medicines regulator, the Therapeutic Goods Administration (TGA), enabled access to pharmaceutical grade medicinal cannabis products when prescribed by a medical practitioner (i.e., a medical doctor or physician) [16, 68]. Notably, the use of cannabis for non-medicinal purposes remains illegal.

Access was implemented using existing schemes for 'unregistered' therapeutics, that is, medicines that have not been assessed for efficacy (or safety) by the TGA and are, therefore, not listed on the Australian Register of Therapeutic Goods (ARTG). These include the Special Access Schemes (SAS-A or SAS-B) and the Authorised Prescriber (AP) Schemes (Table 1). These schemes require prescribers to notify the TGA (SAS-A) or request approval from the TGA (SAS-B or AP scheme) to prescribe medicinal cannabis products to their patients [16, 69]. Over the first few years of legal access, most prescriptions were approved via the SAS-B scheme; however, the AP scheme has become the leading pathway for accessing medicinal cannabis products [70].

Table 1. *Australian access schemes used for unregistered medicinal cannabis products [71, 72].*

Access Scheme	Description
Special Access Scheme Category A (SAS-A)	• Permits a medical practitioner to prescribe a medicinal cannabis product to a patient who is seriously ill or likely to die • This is a notification pathway. That is, while prior approval from the Therapeutic Goods Administration is not required to prescribe and supply a product, a post-hoc notification is required
Special Access Scheme Category B (SAS-B)	• Permits a registered health practitioner (e.g., medical practitioner, nurse practitioner, dentist) with appropriate qualifications and/or expertise to prescribe a single medicinal cannabis product to an individual patient for a specific medical condition • The intended use of the product must be within the scope of the health practitioner's practice • This is an application pathway. That is, prior approval by the Therapeutic Goods Administration is required to prescribe and supply a product to patient
The Authorised Prescriber (AP) scheme	• Permits a medical practitioner with prior authorisation to prescribe a specific medicinal cannabis product to a group of patients with the same medical condition • Medical practitioners can apply for multiple approvals for different medicinal cannabis products and medical conditions • Individual patient approvals to prescribe and supply are not required, however, six-monthly reports of patients being treated must be submitted to the Therapeutic Goods Administration

Medicinal cannabis requests through these pathways can be completed online and are generally approved by the TGA within 24 - 48 hours. However, further approvals may be required by some state or territory Departments of Health [16, 69]. Applications are submitted based on active ingredient rather than the brand name and prescribers select from one of five categories that are based on the proportion of CBD compared to other cannabinoids present. These medicinal cannabis categories assist physicians and pharmacists in prescribing and supplying medicinal cannabis products, allowing for flexibility in brand substitution when required [73].

All medicines in Australia are categorised by a 'schedule' (Appendix 1), that determines the level of restriction imposed on medicines and chemicals based on their safety to the public [77]. These schedules determine broader aspects of how a therapeutic is packaged, labelled, stored, and supplied - including whether it requires a prescription or can be supplied by pharmacists without a prescription as 'over-the-counter'(OTC) product (i.e., Schedule 2 and 3 medicines) [78]. Medicinal cannabis products that contain greater than 2% THC are considered Schedule 8 *Controlled Drugs* and require far greater oversight compared to products that contain mostly CBD with low THC content (i.e., ≥ 98% CBD and ≤ 1% THC) and are considered Schedule 4 *Prescription Only Medicines* [77]. More recently, certain 'low-dose'

CBD products meeting specific criteria (e.g., containing ≤ 150 mg/day and less than 1% THC) have been down-scheduled to Schedule 3 *Pharmacist Only Medicines*, as described in detail in Section 1.7.2c [77].

Patients using prescribed THC-containing medicines in Australia must be mindful of the fact that they are not exempt from stringent roadside driving or workplace drug testing, except in Tasmania [63]. Unlike many other jurisdictions around the world that offer a medical defence in these situations, Australian patients may incur legal sanctions even if they are not intoxicated [63]. This is an important considerations for many prescribers and patients considering treatment with THC.

1.7.2a Demand for Medicinal Cannabis Products

Since the legalisation of medicinal cannabis in 2016, the TGA has maintained a comprehensive record of medicinal cannabis product approvals under the SAS-B access scheme. This unique repository has been used to track trends in prescribing patterns and provides useful insights into patient demographics, prescriber location, indication, and products prescribed [79]. This resource demonstrates a surge in demand for medicinal cannabis products in the past four years with approximately 130,000 approvals in 2023 compared to 57,000 approvals in 2020 (Figure 5) [80]. Cumulatively, and as of July 2024, Schedule 8 products were the most prescribed product (~285,000 approvals) followed by Schedule 4 products (~66,000 approvals). Across both Schedules 8 and 4, the most common indication that medicinal cannabis was prescribed for was pain, anxiety, and sleep disorders [80]. Medicinal cannabis prescriptions approvals have been granted for approximately 149 distinct indications, classified in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [79]. It should be noted that initially, the SAS-B pathway was the most popular avenue for access to medicinal cannabis, however, the AP scheme is being utilised more frequently in recent years [70]. This indicates that while useful, this data represents a sub-set of the full scope of medicinal cannabis supply in Australia.

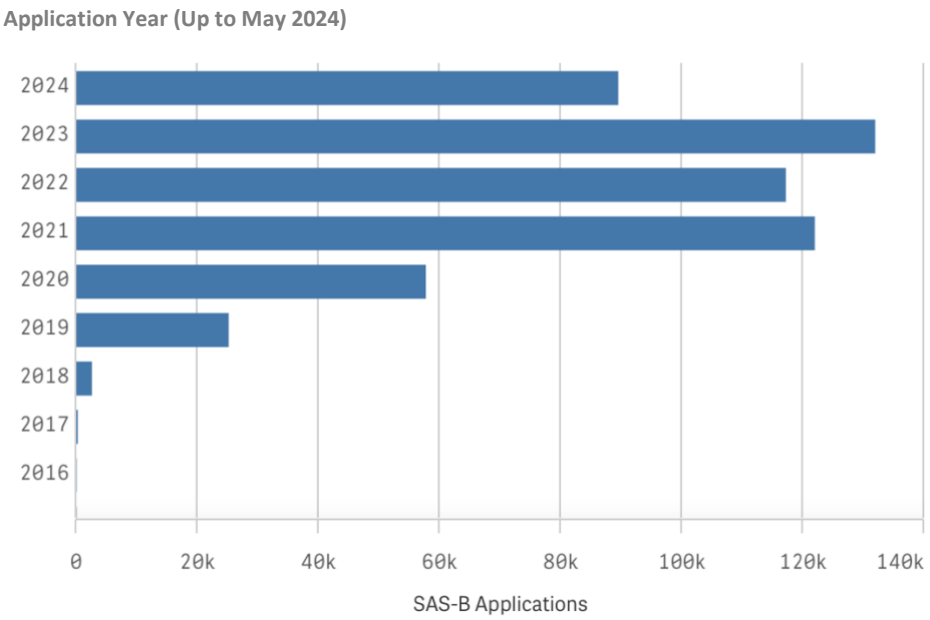

Figure 5. *Special Access Scheme Category B approvals for medicinal cannabis products over time, up to May 2024. Reproduced from the Therapeutic Goods Administration medicinal cannabis Special Access Scheme Category B data dashboard (2024) [80].*

1.7.2b State and Territory Legislation

The regulatory framework for medicinal cannabis in Australia is governed by both federal and state or territory laws. Consequently, there are regional differences around the legality of medicinal cannabis. For an example, Tasmania is the only jurisdiction in Australia that allows patients using prescribed medicinal cannabis products to drive (provided they are not noticeably impaired) [63]. Queensland, Victoria and New South Wales also permit nurse practitioners to prescribe medicinal cannabis products to their patients if clinically appropriate [81].

Relative to the rest of Australia, the Australian Capital Territory (ACT) has been more progressive in its approach to drug policy [82]. In a bid to encourage the public to seek health support around cannabis use and to reduce the number of individuals passing through the justice system, the ACT government implemented the 'Drugs of Dependence (Personal Use of Cannabis) Amendment Bill 2018' in early 2020. This bill decriminalised the personal use (i.e., within individuals' own homes) and possession of small quantities of cannabis (50 g of dried or 150 g of fresh cannabis) as well as the cultivation of ≤ 2 cannabis plants per person or ≤ 4

per household for adults 18 years or older. The sale of cannabis, the use of hydroponic cultivation, and the use of cannabis in public or in proximity to a child remains illegal [83].

1.7.2c Low-dose Cannabidiol

In November 2019, the Australian Federal Senate undertook an inquiry into the barriers of patient access to medicinal cannabis [84]. A number of issues were identified such as complicated state and territory requirements for access, a limited number of medicinal cannabis prescribers, and a lack of education and resources to support prescribers [85]. In response to the inquiry, the TGA undertook a safety review of CBD at lower doses (≤ 60 mg per day). Overall, this enquiry found that CBD had a good safety and tolerability profile and recommended that products providing ≤ 60 mg per day be down-scheduled from Schedule 4 *Prescription Only Medicine* to a Schedule 3 *Pharmacist Only Medicine* [86]. This was suggested to enable consumers to obtain these products without a prescription from pharmacies as an OTC product. It should be noted that *Pharmacist Only Medicines* require a pharmacist's intervention to determine the appropriateness of a therapy and to provide necessary counselling for proper use [87].

On 15 December 2020, following further advice from key stakeholders and experts, the TGA announced its final decision to down-schedule (i.e., from Schedule 4 to Schedule 3) certain low-dose CBD products, specifically, those providing ≤ 150 mg per day (Table 2) and meeting the criteria set out in Table 3 [77, 88]. Notably, these low-dose CBD products would only be available for *Pharmacist Only* supply (i.e. OTC in pharmacies) if product registration on the ARTG was attained.

This landmark decision placed Australia on par with many countries around the world (e.g., America, Canada, and the United Kingdom) that permitted access to lower dose CBD products without a prescription [33]. However, in the four years since this decision, there has yet to be a single low-dose CBD product registered on the ARTG. This is due, in part, to the lengthy nature of registering medicinal products on the ARTG, which requires drug companies to provide comprehensive safety and efficacy data from robust clinical trials. It also reflects the fact that, to date, no clinical trial aiming for product registration has been able to demonstrate a therapeutic benefit of CBD at ≤ 150 mg per day (Table 4). A number of these clinical trials are ongoing and are aimed at indications such as insomnia, anxiety, pain, and

psychological distress. However, it could be many more months or years before Schedule 3 registration on the ARTG is achieved. Until then, CBD products will continue to be accessed exclusively as Schedule 4 (Prescription Only) medicines.

Table 2. *Australian medicine schedules relevant to the supply of medicinal cannabis products. Adapted from the Australian Poisons Standard (June 2024) [77].*

Schedule	Description	Medicinal cannabis constituents
Schedule 3 Pharmacist Only Medicines	Does not require a prescription, supplied at the discretion of a pharmacist	'Low-dose' CBD (≤ 150 mg/day) where: • CBD comprises ≥ 98% of total cannabinoid content • THC comprises 1% of the total cannabinoid content • All other cannabinoids comprise ≤ 2% of total cannabinoid content *Product must be registered on the ARTG
Schedule 4 Prescription Only Medicines	Prescription required, dispensed at a pharmacy	CBD where: • CBD comprises ≥ 98% of the total cannabinoid content • All other cannabinoids comprise ≤ 2% or less of total cannabinoid content *Products that are not registered on the ARTG but otherwise meet the criteria for Schedule 3 low-dose CBD are included in this Schedule
Schedule 8 Controlled Drugs	Prescription required, dispensed at a pharmacy	• Cannabis plant material (e.g., seeds, extracts and resins) • Nabilone, Dronabinol and Nabiximols • THC comprises > 2% of total cannabinoid content
Schedule 9 Prohibited Substances	Only available with approval from the Commonwealth and/or State or Territory Health Authorities (e.g., for research purposes)	Novel or uncommon cannabinoids

Abbreviations - ARTG: Australian Register of Therapeutic Goods, CBD: cannabidiol, THC: Δ^9-tetrahydrocannabinol.

Table 3. *Conditions that must be met for low-dose CBD products ≤ 150 mg/day to be considered a Pharmacist Only Medicine. Reproduced from the Australian Poisons Standard (2024) [77].*

CBD in oral, oromucosal and sublingual preparations included in the Australian Register of Therapeutic Goods (ARTG) when:	
a)	the cannabidiol is either plant derived, or when synthetic, only contains the (-)-CBD enantiomer; and
b)	the cannabidiol comprises 98 % or more of the total cannabinoid content of the preparation; and
c)	any cannabinoids, other than cannabidiol, must be only those naturally found in cannabis and comprise 2% or less of the total cannabinoid content of the preparation and of which tetrahydrocannabinol (THC) can only comprise 1% of the total cannabinoid content; and
d)	the maximum recommended daily dose is 150 mg or less of cannabidiol; and
e)	packed in blister or strip packaging or in a container fitted with a child-resistant closure; and
f)	in packs containing not more than 30 days' supply; and
g)	for adults aged 18 years and over

Table 4. *Clinical trials investigating the efficacy of low-dose CBD (≤ 150 mg) in Australia (unpublished trials as of July 2024).*

Sponsor	Clinical trial registry	Participants	Study design	Inclusion Criteria	Treatment period	CBD Treatment/s	Primary outcome(s)	Objective measures?	Outcome, if known
Swinburne University of Technology	ANZCTR [ACTRN12620000070932]	Insomnia N=30	DB, PC, Parallel	ISI ≥ 15	2 weeks	150 mg, oral	Subjective sleep quality	Yes (actigraphy)	CBD not superior to placebo [89]
Southern Cross University	ANZCTR [ACTRN12621000632897]	Healthy adults with sleep disturbances N= 438	DB, PC, Parallel	ISI ≥ 10	10 weeks	≤150 mg, oral	Subjective sleep quality	No	Completed, yet to be published [90]
BOD Science	Clinicaltrials.gov [NCT05253417]	Insomnia N= ~200	DB, PC, Parallel	ISI = 8 - 21	8 weeks	1: 50 mg, oral 2: 100 mg, oral	Subjective sleep quality	Yes (actigraphy)	Completed, yet to be published [91]
Avecho	Not registered	Insomnia N= ~500	DB, PC, Parallel	ISI ≥ 15	8 weeks	1: 75 mg, oral 2: 150 mg, oral	Subjective sleep quality	Yes (actigraphy)	Recruiting [92]
Cann Group	Not registered	Insomnia N=257	DB, PC, Parallel	Unknown	4 weeks	50-150 mg, oral	Subjective sleep quality	No	CBD not superior to placebo [93]
PharmaCann Pty Ltd	ANZCTR [ACTRN12623000802606]	Sleep disturbances N=80	DB, PC, Parallel	Self-reported sleep disturbances	6 weeks	≤60 mg, oral	Subjective sleep quality	No	Not yet recruiting [94]
PharmaCann Pty Ltd	ANZCTR [ACTRN12623000803695]	Anxiety N=80	DB, PC, Parallel	Self-reported anxiety	6 weeks	≤ 120 mg, oral	Subjective anxiety	Yes (blood cortisol)	Not yet recruiting [95]
Emyria Ltd	ANZCTR [ACTRN12622001319763]	Psychological distress N=300	DB, PC, Parallel	Stress in chronic pain	4 weeks	1: 50 mg, oral 2: 150 mg, oral	Subjective psychological distress	No	Recruitment suspended [96]
Promethean Health Pty Ltd	ANZCTR [ACTRN12623000404628]	Pain N= 172	DB, PC, Parallel	BPI-SF5 = 3-6	4 weeks	150 mg, sublingual	Subjective pain	No	Recruiting [97]
The University of Sydney	ANZCTR [ACTRN12623000593639]	Healthy adults N= 120	DB, PC, Crossover	Healthy adults	Single dose	150 mg, oral	Subjective exercise enjoyment	No	CBD not superior to placebo [56]

Note: One further trial investigating the effects low-dose CBD on stress and sleep in healthy adults was found, however, this was not tabulated due to scare information on this study [98]. **Abbreviations** - BPI-SF: Brief Pain Inventory Short Form, DB: double-blind, ISI: Insomnia Severity Index, PC: placebo-controlled.

1.8 Efficacy of Low-Dose Cannabidiol

While the overall safety of low-dose CBD products has been reasonably well established, we must also consider the efficacy. A narrative review by Arnold et al., (2022) provides a comprehensive evaluation of the clinical trials safety and efficacy data of lower doses of CBD [99]. This review included all interventional studies that investigated the efficacy (i.e., in any health condition) and/or safety and tolerability of oral CBD dosed at ≤ 400 mg per day in adult populations (i.e., ≥ 18 years of age). Studies were excluded if the treatment had a THC content greater than 2%. An upper threshold of 400 mg CBD was used to ensure that all of the relevant clinical trial evidence was captured. Overall, this review found that CBD appeared to be safe even at the maximum dose considered but that further research was required to confirm any therapeutic potential of CBD at lower dose ranges.

Considering the rapid increase in trials of lower doses of CBD since 2022, an updated review was conducted as part of this introductory chapter. All of the interventional studies of efficacy reviewed by Arnold et al., (2022) (n = 60) as well as more recent trials (i.e., from April 5, 2022, up to March 6, 2024) were included. The current review also expanded on the search strategy of Arnold et al., (2022) by including interventional trials of topical CBD (as defined below) up to March 6, 2024. This inclusion was considered important as topical preparations of CBD are sometimes prescribed by Australian doctors as shown by the SAS-B prescribing data published by the TGA [69]. Topical preparations are also popular in countries that permit access to CBD without a prescription [33, 67]. It should be noted that topical preparations of CBD are not currently eligible for categorisation as *Pharmacist Only* low-dose CBD medicines in Australia (see Table 3) - but may become accessible via this pathway in the future.

For oral CBD formulations, a total of 78 eligible publications describing 81 interventional studies were identified. The characteristics and results of these studies are summarised in Table 5. The results of the studies were grouped by eight common 'indications' (*Anxiety, Pain, Substance Use Disorder, Sleep, Neurological Conditions*, *'Other' Mental Health Conditions,* '*Other' Health Conditions, and General Well-Being*) then ordered by daily dose. For topical CBD preparations, a total of nine eligible publications describing nine interventional studies were identified. The characteristics and results of these studies are summarised in Table 6. The results are ordered first by overall outcome (i.e., effect) and then by daily dose, where known.

Henceforth, a ‘lower dose’ of CBD is defined as CBD preparations dosed at ≤ 400 mg per day orally while the term ‘low-dose CBD’ specifically relates to the Australian standard of CBD preparations dosed at ≤ 150 mg per day. Please also note, ‘topical’ refers to the method of application (i.e., CBD that has been applied to the skin), whereas ‘transdermal’ refers to the route of administration (i.e., CBD that has been systemically absorbed through the skin). Studies that have not verified absorption (e.g., by measuring blood and/or urinary cannabinoid concentrations) are considered to be of topical CBD.

Table 5. *Interventional studies investigating the efficacy of oral cannabidiol at lower doses (i.e., ≤ 400 mg/day)*

Citation	Study design	Participant population	CBD dose (mg) / day	Primary outcome(s)	Effect
Anxiety					
Gournay et al., (2023)	DB (PC); BSD	63 (30M); 27.7 ± 9.0 years (CBD); 27.0 ± 7.3 years Anxious participants with high trait worry	1: 50 mg; SD 2: 50 mg/day for 2 weeks	Anxiety and worry severity	No effect
Zuardi et al., (2017)	DB (PC); BSD	35 (17 M); ~22 years Healthy participants	100 mg; SD	Anxiety	No effect
Crippa et al., (2022)	DB (PC); BSD	45 M; 18-35 years Healthy participants	150 mg (powder); SD or 150 mg (corn oil); SD	Anxiety and facial emotion recognition	No effect
Leen-Feldner et al., (2022)	DB (PC); BSD	84 (43M); 26.5 ± 9.1 years Healthy participants	150 mg; SD	Fear	No effect
Stanley et al., (2023)	DB (PC); BSD	32 (5M); 21.3 ± 1.0 years (placebo); 20.3 ± 1.2 years (CBD) Healthy participants with high 'test' anxiety	150 mg; SD	Anxiety	No effect
Linares et al., (2019)	DB (PC); BSD	45 M; ~24 years Healthy participants	150 mg; SD	Anxiety	No effect
Kwee et al., (2022)	DB (PC); BSD	80 (48M); 38.3 ±11.3 years (placebo); 34.9 ± 9.3 years (CBD) Treatment refractory SAD or panic disorder with agoraphobia	300 mg; SD once a week for 8 weeks	Fear	No effect
Kwee et al., (2023)	DB (PC); BSD	69 (48M); 34.9 ± 10.2 years (placebo); 32.6 ± 8.2 years (CBD) SAD or panic disorder with agoraphobia	300 mg; SD once a week for 8 weeks	Fear	No effect
Leen-Feldner et al., (2022)	DB (PC); BSD	85 (43M); 26.46 ± 9.07 years Healthy participants	300 mg; SD	Fear and panic	No effect

Citation	Study design	Participant population	CBD dose (mg) / day	Primary outcome(s)	Effect
Gournay et al., (2023)	DB (PC); BSD	63 (30M); 27.7 ± 9.0 years (CBD); 27.0 ± 7.3 years Anxious participants with high trait worry	1: 300 mg; SD 2: 300 mg/day for 2 weeks	Worry severity	No effect
Stanley et al., (2023)	DB (PC); BSD	32 (5M); 21.3 ± 1.0 years (placebo); 21.1 ± 2.9 years (CBD) Healthy participants with high 'test' anxiety	300 mg; SD	Anxiety	No effect
Linares et al., (2019)	DB (PC); BSD	45 M; ~24 years Healthy participants	300 mg; SD	Anxiety	Positive
Zuardi et al., (2017)	DB (PC); BSD	35 (17 M); ~22 years Healthy participants	300 mg; SD	Anxiety	Positive
Zuardi et al., (1993)	DB (PC); BSD	20 (NS) Healthy participants	300 mg; SD	Anxiety	Positive
Masataka (2019)	DB (PC); BSD	37 (26 M); 18-19 years SAD	300 mg/day; 4 weeks	Anxiety	Positive
Crippa et al., (2011)	DB (PC); WSD	10 M; 24 ± 4 years SAD	400 mg; SD	Anxiety	Positive
Crippa et al., (2004)	DB (PC); BSD	10 M; 30 ± 5 years Healthy participants	400 mg; SD	Anxiety	Positive
'Other' Mental Health Conditions					
Pinto et al., (2023)	DB (PC); BSD (pilot)	35 (12M); 45.9 ± 13.0 years (placebo); 42.2 ±13.8 years (CBD) Bipolar disorder with current major depressive episode	150 mg; 8 weeks	Depression ratings	No effect
Bolsoni et al., (2022)	DB (PC); BSD	33 (8 M); ~33 years PTSD	300 mg; SD	VAMS anxiety for PTSD symptoms	No effect

Citation	Study design	Participant population	CBD dose (mg) / day	Primary outcome(s)	Effect
Hallak et al., (2010)	DB (PC); BSD	28 (18 M); NS Schizophrenia	300 mg; SD	Selective attention	No effect
Bolsoni et al., (2022)	DB (PC); BSD	33 (8 M); ~33 years PTSD	300 mg; SD	VAMS anxiety for PTSD symptoms	Positive
Crippa et al., (2021)	Open label (with controls)	118 (39 M); ~33 years Healthy healthcare workers during COVID pandemic	300 mg; 4 weeks	Emotional exhaustion ratings (burnout)	Positive
Pinto et al., (2023)	DB (PC); BSD (pilot)	33 (12M); 45.9 ± 13.0 years (placebo); 42.2 ±13.8 years (CBD) Bipolar disorder with current major depressive episode	300 mg; 8 weeks	Depression ratings	Positive
Pacheco et al., (2021)	Open label (without controls)	13 (6 M); 33 ± 7 years Healthcare workers with burnout during COVID pandemic	330 mg; 4 weeks	'Burnout', depression, anxiety and insomnia	Positive
Substance Use Disorder					
Karoly et al., (2023)	DB (PC); WSD	36 (17M); 26.5 ± 6.8 years Heavy drinkers of alcohol	30 mg; SD	Breath alcohol content and subjective effects of alcohol	No effect
Karoly et al., (2023)	DB (PC); WSD	37 (17M); 26.5 ± 6.8 years Heavy drinkers of alcohol	200 mg; SD	Breath alcohol content and subjective effects of alcohol	No effect
Freeman et al., (2020)	DB (PC); BSD	59 (43 M); ~26 years CUD	200 mg; 4 weeks	Cannabis abstinence	No effect
Solowij et al., (2018)	Open label (without controls)	20 (16 M); ~25 years Regular cannabis users	200 mg; 10 weeks	Symptoms of depression and psychosis	Positive
Meneses-Gaya et al., (2021)	DB (PC); BSD	31 M; ~33 years Crack-cocaine dependence	300 mg; 10 days	Crack-cocaine withdrawal symptoms	No effect
Hua et al., (2023)	DB (PC); BSD	70 (50M); 24.9 ± 7.4 years (placebo); 26.6 ± 6.8 years (CBD 400mg) CUD	400 mg; 4 weeks	Plasma anandamide levels	No effect

Citation	Study design	Participant population	CBD dose (mg) / day	Primary outcome(s)	Effect
Hurd et al., (2019)	DB (PC); WSD	14 (12 M); 52 ± 8 Heroin use disorder	400 mg; 3 days	Opioid craving and anxiety	Positive
Freeman et al., (2020)	DB (PC); BSD	59 (43 M); ~26 years CUD	400 mg; 4 weeks	Cannabis abstinence	Positive
Neurological Disorders					
Chagas et al., (2014)	DB (PC); BSD	21 (15 M); 64 ± 10 years Parkinson's disease	75 mg; 6 weeks	Quality of life and well-being	No effect
de Almeida et al., (2023)	DB (PC), BSD	18 (12M); 58.33 ± 9.24 years (CBD); 60 ±7.8 years (placebo) Parkinson's disease and sleep behaviour disorder	300 mg; 14 weeks	Restless legs rating	No effect
Santos de Alencar et al., (2021)	DB (PC); WSD	19 (10 M); ~63 years Essential tremor	300 mg; SD	Upper limb tremors and motor function	No effect
de Faria et al., (2020)	DB (PC); WSD	24 (22 M); 64 ± 10 years Parkinson's disease	300 mg; SD	Anxiety and tremors	Positive
Chagas et al., (2014)	DB (PC); BSD	21 (15 M); 64 ± 10 years Parkinson's disease	300 mg; 6 weeks	Quality of life and well-being	Positive
Kochen et al., (2023)	Open label (without controls)	55 (11 discontinued); 44 participants included in analysis: (15M), 35 ± 10 years Drug-resistant focal epilepsy	335mg (mean daily dose, range: 250mg-500mg - 85% of participants used a dose < 400mg/day); 6 months as an adjuvant	Seizure frequency from baseline	Positive
Zuardi et al., (2009)	Open label (without controls)	6 (4 M); 59 ± 15 years Parkinson's disease and psychosis	150-400 mg/day; 4-weeks	Psychotic symptoms	Positive
Pain					

Citation	Study design	Participant population	CBD dose (mg) / day	Primary outcome(s)	Effect
Notcutt et al., (2004)	'N-of-1' DB (PC); WSD	34 (11 M); 47 ± 10 years Chronic non-cancer pain	≤15 mg; 1 week	Pain	No effect
Narang et al., (2023)	DB (PC); BSD	90 (55M); 58.1 ± 14.4 years (placebo); 61.3 ± 12.3 years (CBD) Participants undergoing ureteroscopy	20 mg; 3 days	Pain	No effect
Vela et al., (2022)	DB (PC); BSD	136 (48 M); ~62 years hand osteoarthritis or psoriatic arthritis	20 - 30 mg; 12 weeks	Pain	No effect
Hansen et al., (2023)	DB (PC); BSD	134 (35M); 52.2 ± 10.4 years (placebo), 53.0 ± 9.8 years (CBD) MS and SCI	45 mg; 6 weeks	Pain and spasticity	No effect
Zubcevic et al., (2023)	DB (PC); BSD	115 (51); 22-95 years Peripheral neuropathic pain	50 mg; 8 weeks	Pain	No effect
De Vita et al., (2022)	DB (PC); WSD	15 (5M); 20.7 ± 2.60 years Healthy participants	50 mg; SD (sublingual)	Pain	No effect
Alaia et al., (2022)	DB (PC); BSD	99 (61M); 58 ± 8.8 years (CBD) and 57.1 ± 10.1 years (placebo) Patients undergoing rotator-cuff repair surgery	75 mg; 2 weeks (buccally)	Postoperative pain	No effect
Alaia et al., (2022)	DB (PC); BSD	99 (61M); 58 ± 8.8 years (CBD) and 57.1 ± 10.1 years (placebo) Patients undergoing rotator-cuff repair surgery	150 mg; 2 weeks (buccally)	Postoperative pain	No effect overall
Arout et al., (2022)	DB (PC); WSD	17 (8 M); 32 ± 8 years Healthy participants	200 mg; SD	Experimentally induced pain	Improved pain threshold. Worsened painfulness ratings.
Nielsen et al., (2022)	Open label (with control)	54 (17 M); adults ≥ 18 years Participants undergoing chemotherapy	300 mg; 8 days	Pain associated with CIPN	No effect

Citation	Study design	Participant population	CBD dose (mg) / day	Primary outcome(s)	Effect
Arout et al., (2022)	DB (PC); WSD	17 (8 M); 32 ± 8 years Healthy participants	400 mg; SD	Experimentally induced pain	Worsened painfulness ratings
Bebee et al., (2021)	DB (PC); BSD	100 (56 M); ~47 years Lower back pain	400 mg; SD	Pain	No effect
Sleep					
Saleska et al., (2024)	Pre-post within-subject trial	1,793 (771M); 44.7 ± 11.1 years (CBD) Participants with sleep disturbance	15 mg; 4 weeks	Subjective sleep	No effect
Carlini and Cunha (1981)	DB (PC); WSD	15 (NS) Poor sleepers	40 mg; SD	Sleep quality (subjective)	No effect
Carlini and Cunha (1981)	DB (PC); WSD	15 (NS) Poor sleepers	80 mg; SD	Sleep quality (subjective)	No effect
Carlini and Cunha (1981)	DB (PC); WSD	15 (NS) Poor sleepers	160 mg; SD	Sleep quality (subjective)	Positive
Linares et al., (2018)	DB (PC); WSD	26 (12 M); 29 ± 9 years Healthy participants	300 mg; SD	Sleep quality (objective, polysomnography)	No effect
'Other' Health Conditions					
Naftali et al., (2017)	DB (PC); BSD	20 (12 M); 18-50 years Crohn's disease	10 mg; 8 weeks	Crohn's disease symptoms	No effect
Jadoon et al., (2016)	DB (PC); BSD	13 (10 M); 57 ± 10 years Type 2 diabetes	200 mg; 13 weeks	Serum HDL and cholesterol	No effect
Silkiss et al., (2023)	DB (PC); WSD	12 (4 M); 69.8 ± 10.1 years Adult-onset blepharospasm	200 mg; 6 months	Eyelid closure	Positive
Dominiak et al., (2023)	Open-label (with control)	32 (7M); 62.4 ±8.10 years (CBD group); 56.5 ± 8.32 years Chemotherapy patients	300 mg; 8 days	Lean body mass	Positive

Citation	Study design	Participant population	CBD dose (mg) / day	Primary outcome(s)	Effect
Crippa et al., (2022)	DB (PC), BSD	91 (31M); 38.7 ± 11.0 years (CBD); 40.9 ± 10.9 years (placebo) COVID-19 patients	300 mg; 14 days	Deterioration in COVID-19 symptoms	No effect
Dujic et al., (2023)	DB (PC); WSD	70 (40M); 54.8 ± 3.8 years Participants with hypertension	300 mg; 2.5 weeks	Blood pressure	Positive
Yeshurun et al., (2015)	Open label (historical controls)	48 (31 M); ~56 years Patients receiving alloHCT	300 mg; 37 days	Incidence of GVHD	Positive
General Well-Being					
Kisiolek et al., (2023)	DB (PC); BSD	28 (14M); 24.8 ± 5.5 years (CBD), 27.1 ± 6.7 years (placebo) Healthy participants	50 mg; 8 weeks	Mental health outcomes: depression, anxiety, fatigue, and quality of life	No effect
Lopez et al., (2020)	DB (PC); BSD	65 (33 M); 18-55 years Overweight healthy participants	15 mg; 6 weeks	Multiple metabolic, QOL, and sleep-related outcomes	Overall, no effect on multiple measures but increased HDL

Note: Studies in which the only treatment administered was CBD (i.e., no placebo) were considered 'open label' regardless of the design used, as participants were aware that they would be receiving CBD. **Abbreviations**: AEs: adverse events, alloHCT: allogeneic hematopoietic cell transplantation, BSD: between-subjects design, CBD: cannabidiol, CIPN: chemotherapy-induced peripheral neuropathy, COVID: coronavirus disease, CUD: Cannabis use disorder, DB: double-blind, GVHD: Graft versus host disease, HDL: high density lipoproteins, M: male, MS: multiple sclerosis, NS: not specified, PC: placebo-controlled, PTSD: post-traumatic stress disorder, QoL: quality of life, SAEs: serious adverse events, SD: single dose, SAD: Social anxiety disorder, SCI: spinal cord injury, vs.: versus and WSD: within subjects design.

Table 6. *Interventional studies investigating the efficacy of topical cannabidiol preparations.*

Citation	Study design	Participant population	Concentration	Dosage unit	CBD dose/day	Primary outcome(s)	Effect
Xu et al., (2020)	DB (PC); WSD	29 (18M); 68.1 ± 8.9 years, Peripheral neuropathy	250 mg CBD/3 fluid ounce	NS	NS; up to 4 times a day; 4 weeks	Neuropathic pain	Positive
Umpreecha et al., (2023)	DB (PC); BSD	72 (13M); 33.0 ± 10.1 years (placebo); 36.7 ±11.3 years (CBD), Recurrent aphthous ulcers	0.1%	NS	NS; thrice daily for 7 days	Ulcer size and pain	Positive (ulcer size only)
Gao et al., (2022)	DB (PC); BSD	57 (sex NS); 18 - 65 years Atopic dermatitis	NS	NS	NS: CBD with aspartame; twice daily 14 days	Atopic dermatitis	Positive
Heineman et al., (2022)	DB (PC); WSD	18 (5M); 64.2 ± 11.0 years Thumb joint arthritis	6.2 mg/mL	1 mL	12.4 mg; 2 weeks	Pain and functionality	Positive
Hall et al., (2023)	Open-label pilot	20 (14M); 28.7 ± 1.5 years Former elite athletes with chronic pain	5mg/0.5 mL	0.5 mL	20 mg; 6 weeks	Pain and functionality	Positive
Nitecka-Buchta et al., (2019)	DB (PC); BSD	60 (27M); 22.6 ± 1.9 years (placebo); 23.2 ± 1.6 years (CBD) Myofascial pain	20% (2g/10g)	'Size of a pea' (i.e., ~0.25g)	100 mg; 14 days, transdermal	Pain and masseter muscle activity	Positive
Haffar et al., (2022)	DB (PC); BSD	80 (41M), 64.1 ± 6.9 years (CBD), 65.4 ± 7.5 years (placebo) Participants undergoing total knee arthroplasty	120 mg/ ounce i.e., 4.23 mg/ g	NS	NS: CBD alone or CBD with essential oil; thrice daily for 14 days postoperatively	Pain following total knee arthroplasty	No effect
Alpy et al., (2023)	DB (PC); BSD	21 (sex NS); 20.8 ± 1.9 years Healthy adults	1000 mg CBD in 50 mL balm	15 mg/kg	~20 mg, 3 days	DOMS	No effect

Citation	Study design	Participant population	Concentration	Dosage unit	CBD dose/day	Primary outcome(s)	Effect
O'Brien et al., (2022)	DB (PC); BSD (non-inferiority)	188 (85M); 40.3 ±13.4 years (placebo); 37.0 ± 12.6 years (CBD), Adults with drug-resistant focal epilepsy.	NS	~2.6 mg/kg	390 mg; 12 weeks, transdermal (adjunctive to standard treatment)	Seizure frequency	No effect
O'Brien et al., (2022)	DB (PC); BSD (non-inferiority)	189 (85M); 40.3 ±13.4 years (placebo); 40.4 ± 12.3 years (CBD) Adults with drug-resistant focal epilepsy.	NS	~5.3 mg/kg	780 mg; 12 weeks, transdermal (adjunctive to standard treatment)	Seizure frequency	No effect

Note: Studies in which the only treatment administered was CBD (i.e., no placebo) were considered 'open label' regardless of the design used, as participants were aware that they would be receiving CBD. **Abbreviations**: BSD: between-subjects design, CBD: cannabidiol, DB: double-blind, DOMS: delayed onset muscle soreness, M: male, NS: not specified, PC: placebo-controlled, and WSD: within subject design.

1.8.1 Anxiety

This review identified 12 double-blind placebo-controlled trials [100-111] investigating the effects of lower doses of CBD (50 - 400 mg) on subjective (i.e. self-reported) measures of anxiety (Table 5).

Most of these studies were conducted on healthy participants [101, 102, 106, 107, 109-111]. For these studies, an acute dose of CBD was administered prior to a potentially anxiety-inducing task including a public speaking task [107, 110, 111], carbon dioxide breathing challenge [106], statistics exam [109], brain imaging procedure [102], or a facial emotion recognition task [101]. The remainder of the studies involved clinical populations exposed to an anxiety-inducing intervention (i.e., exposure therapy [104], a fear conditioning task [105], or a brain imaging procedure [100]), or to no intervention [100, 103, 108].

Three of the trials conducted on healthy participants administered CBD prior to a public speaking task. All three found that 300 mg CBD significantly reduced anxiety [107, 110, 111]. One of these trials also investigated the effects of 150 mg CBD and found no significant beneficial effects on anxiety [107]. However, 150 mg CBD decreased subjective ratings of anxiety with a moderate effect size (Cohen's *d*=0.70). This suggests that the trial may have not detected a significant effect due an underpowered design with a small sample size [107]. Finally, one of these trials also investigated the effects of 100 mg CBD and found no beneficial effects on anxiety [111].

Of the remaining four trials conducted on healthy participants, the first found significant anxiolytic effects of 400 mg CBD prior to a brain imaging procedure [102]. The three remaining trials did not find significant beneficial effects of 150 mg or 300 mg CBD prior to a statistics exam [10], 150 mg or 300 mg CBD prior to a carbon dioxide breathing challenge [7], or 150 mg CBD prior to a facial emotion recognition task [101].

Regarding the clinical populations that were exposed to an anxiety-inducing intervention, the first found significant beneficial effects of an acute dose of 400 mg CBD prior to a brain imaging procedure in participants with Social Anxiety Disorder (SAD) [100]. The final two studies did not find significant anxiolytic effects; these trials administered 300 mg CBD to participants with SAD or panic disorder once a week for 8 weeks during exposure therapy [104] or a fear conditioning task [105].

In the studies that did not use anxiety-inducing interventions, one found that 300 mg CBD per day for four weeks had significant positive effects in participants with SAD [108]. The second study investigated the effects of CBD when dosed acutely (i.e., 50 or 300 mg) or chronically (i.e., 50 or 300 mg per day for two weeks) on anxious participants with high trait worry; no significant beneficial effects were found [103].

Overall, lower doses of CBD have demonstrated anxiolytic effects in several small-scale clinical trials. These effects were observed at doses between 300 mg and 400 mg CBD. However, studies investigating the efficacy of ≤ 150 mg CBD were few and limited. The anxiolytic effects of CBD were most consistently observed when it was administered prior to a public speaking task or a brain imaging procedure. Furthermore, the anxiolytic effects of CBD were observed in participants who were healthy (and completed an anxiety-inducing intervention), or who had SAD. Hence, future studies investigating the efficacy of lower doses of CBD on anxiety might consider utilising these methodologies and participant populations.

1.8.2 'Other' Mental Health Conditions

This review identified four double-blind placebo-controlled trials [112-115] and two open-label trials [116, 117] investigating the effects of lower dose CBD (5 - 330 mg) on mental health outcomes other than anxiety (Table 5).

Two open-label trials investigated 'burnout' in healthcare workers over four weeks [116, 117]. In one, 330 mg CBD per day had positive effects on measures of burnout, depression, and anxiety [117]. In the other, 300 mg CBD per day had positive effects on ratings of emotional exhaustion [116].

Two double-blind, placebo-controlled trials investigated the acute effects of 300 mg CBD on anxiety during a trauma-recall task in participants with post-traumatic stress disorder (PTSD) [112, 113]. One study found no significant positive effects [112], while the other found that CBD decreased subjective anxiety, specifically in participants with non-sexual trauma [113].

A pilot study of participants with bipolar disorder found that 300 mg CBD per day for eight weeks decreased subjective ratings of depression [115].

A final double-blind placebo-controlled trial in participants with schizophrenia found that an acute dose of 300 mg CBD prior to a 'Stroop Colour Word Test' had no beneficial

effects on selective attention (taken as a measure of schizophrenia-related cognitive impairment) [114].

Overall, lower doses of CBD (~ 300 mg) have demonstrated mixed effects in 'other' mental health conditions. Some beneficial effects have been observed for burnout. However, clear conclusions on other mental health conditions and the efficacy of doses ≤ 150 mg cannot be drawn due to the sparsity of trials

1.8.3 Substance Use Disorder

This review identified four double-blind placebo-controlled trials [118-121] and one open-label trial [122] investigating the effects of lower doses of CBD (40 - 300 mg) on symptoms of substance use disorder (Table 5). Participants were regular users of cannabis [118, 122], alcohol [120], crack-cocaine [121], or heroin [119].

Regarding regular users of cannabis, one double-blind placebo-controlled study found that 400 mg (but not 200 mg) CBD per day for four weeks increased cannabis abstinence [118]. Another open-label trial also found significant positive effects of 200 mg CBD per day for 10 weeks on symptoms of depression and psychosis [122].

Regarding other substance use disorders, one double-blind, placebo-controlled trial in participants with Heroin Use Disorder found that 400 mg CBD per day for three days decreased symptoms of opioid cravings and anxiety [119]. No significant positive effects were found in two other double-blind, placebo-controlled trials on heavy alcohol users (30 or 200 mg CBD) [120] or participants with crack-cocaine dependence (300 mg CBD per day for 10 days) [121].

Overall, lower doses of CBD have demonstrated some beneficial effects in substance use disorders, specifically, Cannabis and Heroin Use Disorders. These beneficial effects have been observed at doses ranging between 200 - 400 mg and involved both subjective outcomes such as depression and anxiety, and objective outcomes such as substance use over time [117]. No studies have investigated the efficacy of ≤ 150 mg CBD in substance use disorders.

1.8.4 Neurological Disorders

This review identified four double-blind placebo-controlled trials [123-126] and two open-label trials [127, 128] investigating the effects of lower doses of CBD (32.5 - 400 mg) on neurological disorders (Table 5).

Four of these studies included participants with Parkinson's disease (PD) [123-125, 128] and the two remaining studies involved participants with essential tremor [126] and drug-resistant focal epilepsy [127].

Regarding PD, three of the four studies found significant beneficial effects [123, 125, 128]. The first double-blind placebo-controlled trial found that 300 mg (but not 75 mg) CBD per day for six weeks had positive effects on quality of life and well-being measures in PD [123]. The second double-blind placebo-controlled trial reported that an acute dose of 300 mg CBD had significant positive effects on both anxiety and tremors [125]. The third open-label trial involving six participants found that 150 mg to a maximum of 400 mg CBD per day for four weeks had positive effects on psychotic symptoms associated with PD [128]. The final double-blind placebo-controlled trial found that 300 mg CBD per day for 14 weeks had no beneficial effect on restless legs ratings in Parkinsonian participants with sleep disorders [124].

Of the remaining trials, one open-label study in patients with drug-resistant focal epilepsy found significant positive effects on seizure frequency; participants received 250 – 500 mg CBD per day (however, 85.0% of participants received < 400 mg per day) over 6 months as an adjuvant [127]. The final double-blind placebo-controlled study involved participants with essential tremor and found that an acute dose of 300 mg CBD had no effect on tremors or motor function [126].

Overall, lower doses of CBD have demonstrated some beneficial effects in neurological disorders. These effects were observed between 300 mg and 400 mg CBD and most consistently found in PD. Symptoms of PD can be characterised as motor (e.g., tremor and bradykinesia) and non-motor (e.g., anxiety, depression, and psychosis) [125], and the efficacy of lower doses of CBD in PD mostly related to non-motor symptoms. Studies investigating the efficacy of ≤ 150 mg CBD were limited.

1.8.5 Pain

This review identified nine double-blind placebo-controlled trials [129-137] and one open-label trial [138] investigating the effects of lower doses of CBD (≤ 400 mg) on outcomes related to pain (Table 5).

Both acute and chronic pain were explored. For acute pain, two studies investigated experimentally-induced pain in healthy participants [130, 132] and four investigated acute pain in clinical populations, including acute lower-back pain [131], post-operative pain [129, 134], and acute and transient chemotherapy-induced neuropathy [138]. For chronic pain, all four studies investigated clinical populations including non-cancer pain [135], hand arthritis [136], multiple sclerosis (MS), and spinal cord injury [133], or neuropathic pain [137].

Only one study found a significant positive effect of CBD on pain [130]. In this double-blind, placebo-controlled trial in healthy participants, an acute dose of 200 mg CBD was found to increased 'pain threshold' (i.e., latency to report of first painful sensation) relative to placebo during a cold pressor task. Interestingly, however, the same dose (and a higher 400 mg dose) was also found to increase (i.e., worsen) subjective ratings of painfulness, suggesting that CBD may not provide better outcomes. None of the remaining studies found beneficial effects at doses ≤ 400 mg CBD, even those that utilised a longer duration of treatment (i.e., up to 12 weeks).

Overall, there is a reasonable number of trials investigating the effects of lower dose CBD (i.e., ≤ 400 mg) on pain and almost all found no effect. However, the types of pain investigated varied considerably. As such, clear conclusions regarding CBD's effect on any particular type of pain are difficult to draw.

1.8.6 Sleep

This review identified two double-blind placebo-controlled trials [139, 140] and one pre-post within-subject trial [141] investigating the effects of lower doses of CBD (15 - 300 mg) on sleep-related outcomes (Table 5).

Only one study conducted in 1981 found a significant positive effects of CBD on sleep [139]. In this double-blind placebo-controlled trial in 'poor sleepers', 160 mg CBD (but not 40 or 80 mg) was found to increase sleep duration compared to placebo.

The final two studies did not find any significant positive effects of CBD on sleep [140, 141]. One administered an acute dose of 300 mg CBD to healthy participants and found no objective improvements on sleep polysomnography [140]. The other administered one of six products containing 15 mg CBD or 5 mg melatonin, alone or in combination with minor cannabinoids, over four weeks and found no difference in self-reported sleep across products [141].

As noted above, a number of Australian-based trials in various stages of completion are investigating the effects of low-dose CBD (≤ 150 mg) on measures of sleep, two of which have reported no evidence of efficacy (Table 4) [89, 93].

Overall, lower doses of CBD have demonstrated little evidence of efficacy on sleep-related outcomes so far. However, ongoing research is expected to provide further clarification in the near future.

1.8.7 'Other' Health Conditions

This review identified five double-blind placebo-controlled trials [101, 142-145] and two open-label trials [146, 147] investigating the effects of lower doses of CBD (10 - 300 mg) on a range of 'other' health conditions (Table 5).

Two trials investigated the effects of CBD on infectious diseases [147, 148]. The first, a double-blind, placebo-controlled trial, reported no effect of 300 mg CBD per day for two weeks on Coronavirus Disease 2019 (COVID-19) symptoms in participants with the infection [148]. The second, an open-label trial, found that 300 mg CBD per day for 37 days significantly decreased the incidence of Graft-versus-host disease in participants receiving allogeneic hematopoietic cell transplantation [147].

There were four other double-blind, placebo-controlled trials with mixed results. One study found that hypertensive participants dosed with 300 mg CBD per day for 2.5 weeks had significantly reduced blood pressure [142]. The second found that participants with adult-onset blepharospasm (uncontrolled blinking) dosed with 200 mg CBD per day for six months as adjunctive therapy with routine botulinum toxin therapy had significant improvements in measures of eyelid closure [145]. Of the remaining double-blind, placebo-controlled trials, one reported that participants with type-2 diabetes who were dosed with 300 mg CBD per day for 13 weeks displayed no significant effects on serum cholesterol [143]. The second study

found that participants with Crohn's disease dosed with 10 mg CBD per day for eight weeks had no improvements in symptoms of Crohn's disease [144].

A final open-label study found that 300 mg CBD per day for eight days increased lean body mass in participants receiving chemotherapy [146].

Overall, further research is required to further clarify the efficacy of CBD in 'other' health condition. Indeed, in most cases, these conditions were only studied in single trials (and at doses >150 mg).

1.8.8 General Well-Being

This review identified two double-blind placebo-controlled trials [149, 150] investigating the effects of lower doses of CBD (50 - 300 mg) on general well-being and functioning in healthy individuals (Table 5).

The first study investigated the effects of 50 mg CBD per day for eight weeks on measures of mental health, sleep quality, and immune function [149], while the second study investigated the effects of 15 mg CBD per day for six weeks on measures related to metabolism, quality of life, and sleep in overweight but otherwise healthy participants [150]. Neither of these trials found a significant beneficial effect.

1.8.9 Topical Cannabidiol

While the effects of orally administered CBD have received considerable scientific attention, relatively few studies have investigated the effects of topical CBD. Topical preparations may offer some advantages over oral administration for certain health conditions (e.g., dermatological or pain conditions). This includes localised application and effect at a specific site and avoidance of first pass metabolism. Topical application also provides an alternative route of administration for those with dysphagia, nausea, or emesis. Possible hazards, however, includes local skin irritation and low or variable skin permeation [151].

This review identified nine double-blind placebo-controlled trials and one open-label trial investigating the therapeutic effects of topical CBD [152-160] (Table 6). Given this

relatively small pool of clinical trials involving topical formulations, a dose limit was not implemented for this review. All studies were published within the last five years (i.e., 2019 or later).

Four trials investigated a dose of ≤ 400 mg CBD per day [152, 155-157], while one trial involved a dose of 390 mg and 780 mg CBD per day [158]. Unfortunately, four trials did not report the dose of the topical CBD preparation being used [153, 154, 159, 160].

Seven out of nine trials investigated the effects of topical CBD in pain-related conditions [152, 154-157, 159, 160]. Of these, five studies explored 'chronic' pain conditions and all reported significant positive effects [155-157, 159, 160]. The two remaining studies explored 'acute' pain conditions with neither finding a significant positive effect [152, 154].

With respect to the chronic pain studies, four were double-blind placebo-controlled trials [156, 157, 159, 160]. These studies involved CBD (daily dose not reported) over four weeks in neuropathic pain [160], 12.2 mg CBD per day for two weeks in thumb joint arthritis [156], 100 mg CBD per day for two weeks in myofascial pain [157], and CBD (daily dose not reported) over two weeks in recurrent mouth ulcers [153]. The final chronic pain study was an open-label trial investigating the effects of 20 mg CBD per day for six weeks on chronic pain consequent to musculoskeletal injury [155]. Regarding the acute pain studies, both were double-blind, placebo-controlled trials; one involved 20 mg CBD per day for three days in healthy participants with delayed onset muscle soreness [152] and the other investigated CBD (daily dose not reported) over two weeks in participants with post-surgery pain [154].

With respect to the other double-blind placebo-controlled trials, one found that CBD (daily dose not reported) over two weeks had significant beneficial effects on disease symptoms in atopic dermatitis [153]. The final study reported that treatment with 390 mg or 780 mg CBD per day for 12 weeks (adjunctive to standard anti-convulsant therapy) had no effect on seizure frequency in adults with drug-resistant focal epilepsy [158].

Overall, topical CBD demonstrated beneficial effects in several clinical trials. These beneficial effects were most consistently observed in 'chronic' pain conditions despite individual pain conditions only being investigated once.

1.8.10 Summary of Findings

This review identified a large number of trials investigating the efficacy of lower doses of CBD across a wide range of indications. Overall, given the diffuse scope of these trials and the highly variable pattern of outcomes, the efficacy of CBD in any specific health conditions was often difficult to determine.

Regarding oral formulations, one of the 'best studied' indications was *Anxiety*. Significant beneficial effects were most consistently observed in healthy participants given an acute dose 300 mg CBD prior to a public speaking task, with a dose of 150 mg CBD having some potential for effect. Some significant beneficial effects were also seen in symptoms of clinical anxiety associated with SAD.

Another well-studied indication was *Neurological Disorders*; significant beneficial effects were consistently observed in symptoms associated with PD at 300 - 400 mg CBD. Some significant positive effects were also evident in *Substance Use Disorder*, *'Other' Mental Health Conditions,* and *'Other' Health Conditions*. Clear conclusions around these indications are difficult to draw given that few trials have investigated any single health condition. Nonetheless, specific health conditions such as Cannabis or Heroin Use Disorders and burnout show some promising outcomes worthy of follow-up studies. There was a general lack of significant beneficial effects in indications such as *Sleep* and *General Well-Being* based on very few clinical trials. Regarding *Pain*, a reasonable number of clinical trials produced little evidence of significant positive effects. There was substantial variability in the type of pain investigated (e.g., experimentally-induced pain or pain associated with a health condition), making clear interpretation of these results difficult.

Regarding topical formulations of CBD, the most consistent significant beneficial effects were found on outcomes relating to chronic pain in conditions such as arthritis and pain associated with musculoskeletal injury.

Overall, the beneficial effects of lower doses of oral CBD were mostly observed between 300 mg and 400 mg. Lower doses of oral CBD showed some promise in participants with SAD and Parkinson's disease, and healthy participants administered an acute dose of CBD prior to an anxiety-inducing task. However, there was an overall lack of clinical trials at the low-dose CBD (i.e., ≤ 150 mg) range. Topical CBD preparations show promise in 'chronic'

pain conditions based on a few clinical trials. Overall, however, the evidence so far does not unambiguously support efficacy for any specific chronic pain condition.

1.9 Demands on Health Professionals

At present, the evidence base around the efficacy of CBD at lower doses (i.e., ≤ 400 mg) is complex and particularly scarce and unfavourable at doses ≤ 150 mg CBD. This makes it difficult for physicians to practice evidence-based medicine in this area. It can also be expected to create challenges for pharmacists who are set to become the new gatekeepers of low-dose CBD products (≤ 150 mg per day) in Australia. It is therefore important to understand how medicinal cannabis is being integrated into current clinical practice. This is crucial given the ever-evolving landscape of legal access to medicinal cannabis, the developing research around its efficacy, and the growing demand for these products [79, 161]

In Australia, only one study of pharmacists and one study of general practitioners (GPs) have been conducted to investigate the knowledge, experience, and attitudes of these health professionals towards medicinal cannabis [162, 163]. Both studies were conducted prior to the expansion of medical cannabis prescribing and dispensing. As such, a detailed review of previous relevant surveys of pharmacists (Appendix 2) and physicians (Appendix 3) around the world was conducted and the main findings presented below. It is noted that while the regulations governing medicinal cannabis supply may vary across jurisdictions, the overarching responsibilities of health professionals are generally similar. These findings provided the background for new, updated studies of Australian pharmacists (Chapter 2) and GPs (Chapter 4) around medicinal cannabis, including low-dose CBD.

1.9.1 Pharmacists and Medicinal Cannabis

Pharmacists are highly accessible and trusted health professionals; they are on the frontline of health care in the community and an essential source of health advice [164, 165]. Pharmacists are a key conduit between prescriber and patient and provide a point of access to therapeutics goods [166, 167]. Pharmacists are known for championing novel health services, for example, harm-minimisation programs and vaccinations clinics [162, 165, 168]. Similarly, pharmacists play a critical role in the access to medicinal cannabis products [167].

In Australia, pharmacists typically procure prescribed medicinal cannabis products for supply to individual patients, conduct health and medication checks, resolve inconsistencies with prescribers, finalise a dispensing record, and provide necessary counselling to the patient [169]. Given their close involvement in medicinal cannabis supply, it is important to examine the knowledge, attitudes, and experiences of pharmacists towards medicinal cannabis.

A review of the scientific literature for the 10 years preceding May 2023 identified 13 studies investigating the knowledge, attitudes, and experiences of approximately 4,000 pharmacists in relation to medicinal cannabis (Appendix 2) [162, 170-181]. Detailed analysis and results of the review are presented in Appendix 2 and a summary of findings are presented here. Eight studies were conducted in the United States of America [171, 172, 175-180], two in Canada [174, 181], and one each in Australia [162], Jordan [170], and Bulgaria [173]. Ten of the studies were published in the last five years and four had a strong CBD-focus. All studies utilised a cross-sectional design including 12 unique survey questionnaires and one semi-structured interview.

Briefly, these surveys demonstrated that pharmacist respondents supported the legalisation of medicinal cannabis, recognised their important role in its supply, and received regular enquires from patients. However, when participants were asked to self-assess their knowledge around medicinal cannabis 'in general', or around specific topics (e.g., product dosing, mechanism of action, and drug interactions), they often reported inadequate knowledge. Nonetheless, respondents performed reasonably well in objectively-assessed knowledge, particularly regarding the regional and regulatory requirements of medicinal cannabis products. Self-assessed knowledge provides some evaluation of knowledge *per se*, but also incorporates personal views and opinions around overall competence [182]. Therefore, these results indicate that while respondents had a good essential knowledge around medicinal cannabis, they did not feel proficient overall.

Notably, respondents indicated a distinct lack of confidence in their knowledge of medicinal cannabis and CBD products. Respondents also expressed a similar lack comfort with counselling patients on medicinal cannabis therapy. Many respondents endorsed the use of CBD for epilepsy and supported the legalisation for medicinal cannabis for this purpose [179]. The greatest concerns for respondents were the lack of research and clinical trials evidence around CBD for many health conditions [175], the safety of medicinal cannabis therapy, and the issue of inconsistency in the quality of medical cannabis products [172]. Interestingly,

respondents noted that the most common medicinal cannabis products sold in the pharmacy were topical creams and lotions [175]. Respondents noted an irregular history of education around medicinal cannabis and CBD, and therefore a strong need for further training in current practice [171, 172, 179, 180].

1.9.2 Physicians and Medicinal Cannabis

In many countries, physicians have a crucial role in managing community access to medicinal cannabis. In Australia, specialist training is not required to prescribe medicinal cannabis and all physicians are permitted to prescribe these products [183]. However, GPs are considered major prescribers due to their large numbers relative to other medical specialties and their high accessibility to the public [163, 184]. Physicians determine patients' eligibility for medicinal cannabis treatment, evaluate the evidence of efficacy, select the most appropriate dose and formulation of product, issue patients with a prescription for a pharmaceutical-grade product, request approval from the TGA and relevant state or territory Departments of Health, and provide ongoing care during treatment [72, 163]. Considerable pressure may be placed on physicians by patients seeking treatment with medicinal cannabis [163, 169]. It is therefore important to understand physicians' knowledge, attitudes, and experiences towards medicinal cannabis.

A review of the scientific literature for the 10 years preceding May 2023 identified 16 studies investigating the knowledge, attitudes, experiences, and training needs of approximately 3,800 primary care physicians (i.e., GPs and physicians of family and internal medicine) regarding medicinal cannabis (Appendix 3) [163, 185-199]. Detailed analysis and results of the review are reported in Appendix 3 and a summary of findings are presented here. Five of the studies were conducted in the United States of America [191, 192, 195, 197, 198], three in Canada [188, 189, 193], two in Ireland [187, 199], two each in Europe [190, 196] and the Middle East [185, 186] and one each in Australia [163] and New Zealand [194]. Five of the studies were published before 2020 and two had a recreational cannabis focus. All of the studies utilised a cross-sectional design including 14 unique survey questionnaires and two semi-structured interviews.

Briefly, this review found that physician respondents regularly received enquiries about medicinal cannabis and believed they had an important role in prescribing. However, many respondents appeared hesitant when queried about their willingness or comfort level with prescribing medicinal cannabis to their patients. Nonetheless, respondents typically demonstrated support for medicinal cannabis therapy in more 'serious' conditions such as chronic pain, cancer, palliative care, and epilepsy. Respondents self-assessed their knowledge of medicinal cannabis 'in general' as low, but high with regard to regional laws and regulatory systems. Objectively-assessed knowledge was largely informed by one study [192], and respondents in this study demonstrated a high level of knowledge, particularly around the risks and harm-reduction strategies associated with medicinal cannabis therapy. Respondents were often concerned about adverse mental health effects associated with medicinal cannabis therapy, particularly with regard to psychosis. Mixed opinions were expressed around the safety of medicinal cannabis compared to other prescription drugs. Respondents believed that there was a lack of clinical trials evidence around medicinal cannabis and that further research was required. Physician respondents generally believed that they had not received adequate training around medicinal cannabis and many were interested in further training in this area.

1.10 Conclusion

The *Cannabis sativa* plant has a long and vibrant history of use by humankind. Over the past decade, there has been a notable worldwide shift in the acceptance of cannabis as a therapeutic agent. As such, many countries have implemented pathways permitting the medicinal use of cannabis. These pathways vary widely according to the jurisdiction with some permitting only the medical uses of cannabis and enforcing rules around how cannabis and its constituents are accessed, and others permitting all uses of cannabis (i.e., 'adult-use'). 'Low-dose' CBD is a class of medicinal cannabis that has undergone dramatic changes to how it is accessed and many countries currently permit OTC access without a prescription. There has been a world-wide surge in interest and uptake of low-dose CBD products.

Health professionals such as physicians and pharmacists are intricately involved in overseeing the safe and judicious use of medicinal cannabis, including low-dose CBD. However, pharmacists (Chapter 1.9.1) and physicians (Chapter 1.9.2) self-assessed their

knowledge as low and lacked confidence around medicinal cannabis. Two important finding around the clinical practice of health professionals regarding medicinal cannabis was a considerable need for further education and clinical trials efficacy data around these products.

A review of the efficacy of lower doses of oral CBD (≤ 400 mg per day) and topical CBD preparations was conducted (Chapter 1.8). Overall, a large number of clinical trials were identified across a broad range of indications, although there was limited evidence of efficacy supporting any specific health condition. Nonetheless, the review found that the beneficial effects of lower doses of oral CBD were most consistently observed at a 300 - 400 mg dose range and that there was an overall lack of evidence at the low-dose (i.e., ≤ 150 mg) CBD range. Lower doses of oral CBD showed some promise in SAD and PD and healthy participants exposed to an anxiety-inducing task. Topical CBD preparations also demonstrated some promise in 'chronic' pain conditions based on a limited pool of recent clinical trials.

Overall, further research is required to evaluate the current impact of medicinal cannabis, including low dose CBD products, on the clinical practice of health professionals. Moreover, efforts to support the clinical practice of health professionals around medicinal cannabis are warranted through training and education initiatives and clinical trials clarifying the efficacy of low-dose CBD products.

1.11 Aims and Overview of Chapters

This thesis investigates low-dose CBD as an emerging area of clinical practice by means of Thesis Aim One and Thesis Aim Two, outlined in Figure 6 below. Thesis Aim One was to investigate the knowledge, experiences, and attitudes of Australian GPs and pharmacists towards medicinal cannabis, including low-dose CBD products, providing valuable insights into the current impact of these products on clinical practice in this region. Given that health professionals are guided by a duty of care to practice within an evidence-based framework, clinical trials clarifying the efficacy of low-dose CBD products can assist these professionals to make evidence-based therapeutic decisions, thereby supporting their clinical practice. Therefore, Thesis Aim Two was to expand the current evidence base around the efficacy of low-dose CBD products by conducting two clinical trials focused on indications that demonstrated some promise (Chapter 1.8). Four studies have been conducted; the specific

aims of each study have been outlined in Figure 6 below. It should be noted that based on findings from Study 1, practical efforts to address the training needs of health professionals around medicinal cannabis products were also implemented (Chapter 3).

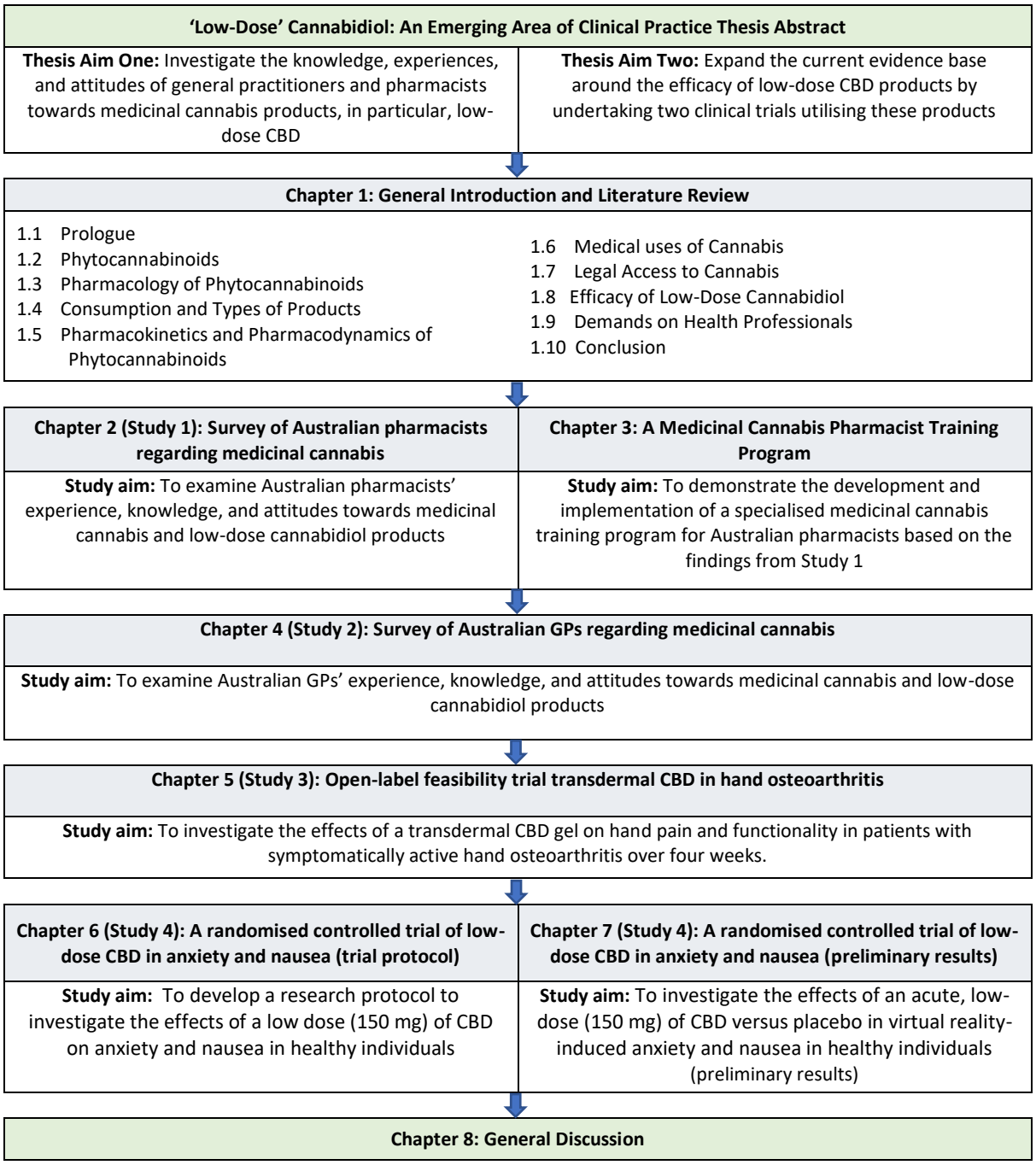

Figure 6. *Thesis aims, study aims, and overview of chapters in this thesis.*

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1.13 Image References

Figure 1. All images sourced from Canva (https://www.canva.com) licensed under a paid subscription:
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CHAPTER 2. A CROSS-SECTIONAL SURVEY EXPLORING THE KNOWLEDGE, EXPERIENCES, AND ATTITUDES OF AUSTRALIAN PHARMACISTS TOWARD MEDICINAL CANNABIS.

Reader's note:

This chapter includes a co-authored publication. The bibliographic details of the co-authored paper, including all authors are as follows:

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The research candidate has made the following contributions to this study:

- Developed the study design
- Completed the human research ethics application
- Conducted all participant recruitment and data acquisition
- Prepared the manuscript for submission to a peer-reviewed journal

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RESEARCH ARTICLE

A cross-sectional survey exploring the knowledge, experiences and attitudes of Australian pharmacists toward medicinal cannabis

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Abstract

Background Australian pharmacists currently dispense a wide range of prescription-only cannabis-based medicines. Recent regulatory changes will expand the role of pharmacists, allowing certain low-dose cannabidiol products to be supplied without a prescription in pharmacies. This harmonises Australia with many other countries where cannabidiol products are readily available to consumers.

Aim To examine Australian pharmacists' experience, knowledge and attitudes towards medicinal cannabis and their preparedness to supply over-the-counter low-dose cannabidiol products.

Method We conducted a cross-sectional study using a 51-item on-line questionnaire that was informed by previous surveys of health professionals and assessed for face validity. Australian pharmacists were recruited to complete the survey between May and December 2021, primarily through professional pharmacy organisations. Pharmacists were included in the final dataset if they completed the demographic characteristics section and at least one additional section of the questionnaire. Data were analysed using descriptive and relational statistical tests.

Results There were 272 attempts to complete this survey and 217 responses included in the final dataset. Over half of the respondents (60.0%, 130/217) had dispensed at least one medicinal cannabis prescription during their career and 58.5% (127/217) had received at least one medicinal cannabis enquiry in the last fortnight. Only around half (53.9%, 117/217) felt comfortable supplying medicinal cannabis products and fewer (39.3%, 79/201) were confident discussing cannabis-related enquiries. More than half of the respondents (58.7%, 118/201) supported the provision of low-dose cannabidiol products through pharmacies. Two-thirds (67.8%, 80/118) of respondents achieved relatively low scores (< 60%) in the knowledge component of the survey. Most respondents (94.2%, 178/189) endorsed a need for further training in this area.

Conclusion Australian pharmacists tended to support medicinal cannabis availability and improved access to low-dose cannabidiol products via pharmacies. However, results highlight a need for improved training and education of pharmacists around cannabis-based medicines.

Keywords Cannabidiol(CBD) · Cannabinoid · Cannabis · Communitypharmacy · Medicinal cannabis · Pharmacists

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Impact statements

- The legalisation of cannabis-based medicines has created an emerging area of pharmacy practice.
- There is a need to provide pharmacists with further training and education around cannabis-based medicines and over-the-counter cannabidiol products.
- Efforts to increase pharmacists' knowledge, confidence and competence in this area have the potential to enhance health outcomes for patients using these products.

Introduction

The term 'medicinal cannabis' (MC) is often used to describe cannabis or cannabis-containing products that are used therapeutically to achieve a curative or remedial effect [1]. Cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) are the two most-studied cannabis constituents [2]. Scientifically, they are termed "cannabinoids", reflecting their distinctive chemotype and their interactions with the human endogenous cannabinoid system [3, 4]. THC is renowned for its intoxicating and euphorigenic effects but has also demonstrated efficacy in treating conditions such as chronic pain, chemotherapy-induced nausea and vomiting, and spasticity in multiple sclerosis [2, 5–10]. CBD is a non-intoxicating cannabinoid with a well-established safety profile at therapeutic doses [11–15]. Clinical trials have demonstrated efficacy of CBD in treating epilepsy, anxiety, and psychosis [16–18].

Access to MC products by Australian patients was legalised in November 2016 via specialised schemes that are overseen by the Australian medicines regulator (the Therapeutic Goods Administration, TGA) [19, 20]. Clinicians must obtain TGA approval to prescribe a specific MC product for an individual patient (Special Access Scheme) or patients with a specific condition (Authorised Prescriber Scheme). The resulting prescription is subsequently dispensed through a pharmacy [21–23]. Over the past five years, there has been a rapid rise in demand for MC products with more than 285,000 approvals issued as of September 2022 [24]. Nonetheless, Australian consumers have voiced concerns that access pathways are difficult to navigate and that available products are too expensive [19, 25].

To further improve access, the TGA announced in December 2020, that low-dose, orally administered CBD products (≤ 150 mg daily dose, containing $< 1\%$ THC) would be down-scheduled to become available without a prescription as *Pharmacist Only Medicines* [26]. This would enable pharmacists to supply these products to consumers over-the-counter for the short-term management of low-risk indications [27]. This development aligns Australia with North America and Europe, where CBD products are readily accessible to consumers without a doctor's prescription [19]. At the time of writing, *Pharmacist Only* CBD products are not yet sold in Australia; no manufacturer has registered a relevant product with the TGA. Registration is a lengthy process that involves presenting the TGA with high-quality product efficacy and safety data from clinical trials. Once *Pharmacist Only* CBD products do become registered, Australian pharmacists will likely be met with significant demand for these products [28] as has been the case internationally [29, 30].

The evolving regulatory landscape of MC access requires pharmacy professionals to have specific expertise around cannabis-based medicines. However, given the complicated MC access pathways and the lag in the registration of *Pharmacist Only* CBD products, it is likely that pharmacy professionals have some uncertainty around low-dose CBD product supply. Indeed, a common theme emerging from preceding surveys of pharmacy practitioners globally is an overall lack of knowledge and confidence in providing non-prescription CBD products [31–33]. An exploratory study of pharmacists' perceptions and experiences around MC found pharmacists had a considerable lack of comfort and preparedness in counselling patients around MC therapy [34]. In Australia, a 2016 semi-structured interview of pharmacists around the role of MC in clinical therapy uncovered a widespread lack of understanding of this drug class [1]. In the six years of legal MC since, there have been no further studies exploring the attitudes, beliefs and knowledge of Australian pharmacists around MC products.

Aim

The present study investigated the preparedness of the pharmacy profession to supply low-dose *Pharmacist Only* CBD products and more generally, the knowledge, experience, attitudes, and education needs of Australian pharmacists concerning cannabis-based medicines.

Ethics approval

Approval was granted by the University of Sydney Human Research Ethics Committee on 16 April 2021 (Ref: 2021/149).

Method

Participant eligibility and recruitment

An on-line cross-sectional survey was conducted between May and December 2021. Participants met the inclusion criteria if they were registered pharmacists working in an Australian community pharmacy. Australian pharmacy organisations (The Pharmacy Guild of Australia and the Pharmaceutical Society of Australia) assisted with participant recruitment by promoting the survey through their professional education events, social media channels and private mailing groups. This study aimed to recruit 250–300 pharmacists, with this number determined both by sample sizes of our teams' earlier surveys of health professionals around MC and resourcing constraints [35–37]. As an incentive to

complete the survey, pharmacists were given the chance to enter a draw to win one of three Apple watches after survey completion.

Survey design

The design of the questionnaire (see Online Resource 1 for a full copy) was informed by previous surveys of health professionals around cannabis-based medicines [1, 32, 33, 35, 36]. The questionnaire also uniquely queried Australian pharmacists' perspectives and knowledge of *Pharmacist Only* CBD products, given the recent legislative changes affecting these products. It contained five sections and a total of 51 items (Table 1) that took ~15-minutes to complete. The questionnaire was administered using a secure, web-based platform (REDCap® 12.0.7, 2022, Vanderbilt University). Pharmacists were required to review the Participant Information Statement and complete an online checkbox to confirm informed consent before commencing the questionnaire. An adaptive algorithm and assortment of query formats were used to reduce respondent fatigue and maximise completion rates, including multiple choice, yes-no-unsure, true-false-unsure and 5-Point Likert Scale (e.g., Strongly Agree, Agree, Neutral, Disagree or Strongly Disagree) formats. An option for open-ended comments was also available at the end of the questionnaire. The survey was specifically developed for this study. The survey underwent three rounds of iterative review by pharmacists and academic researchers to achieve face validity.

Data management and analysis

Data were screened for discrepancies such as non-completions and cleaned data were analysed. Participants were included in the final dataset if they completed the first (i.e., Demographic Characteristics Information) section and at least one additional section of the survey. Results were summarised using descriptive statistics (e.g., proportions, medians, ranges), relational analyses (frequency and percentage of valid responses, IBM SPSS Statistics V.24.0 (IBM, U.S.)), correspondence analyses (R V4.1.2 (R Core Team, 2022 [38], function *CA* from the package 'FactoMineR' [39]) and Asymptotic Linear-by-Linear Association tests (function *lbl_test* from the package 'coin' [40]). Graphs were created using GraphPad Prism V.9.3.1 (350) for Mac (GraphPad Software, La Jolla, California, USA). Open-text comments were grouped by common themes (e.g., perceived benefits and challenges).

Responses to the 5-point Likert scale questions were collapsed into three categories: Agree, Neutral and Disagree. A composite score for knowledge was generated by summing the number of correct responses to the 13 knowledge-based questions. Scores ≥ 60% (≥ eight from a total of 13 questions) were regarded as 'satisfactory' and scores < 60% (< eight from a total of 13 questions) were regarded as 'low.' While there is an inherent arbitrariness to setting scores [41], knowledge scores ≥ 60% were considered acceptable given that pharmacists were yet to manage any over-the-counter CBD products. A higher level of knowledge would be preferable once these products become registered and widely available.

A series of Asymptotic Linear-by-Linear Association tests were performed to determine independence between ordinal response variables (comfort with supply, confidence, need for training and how supportive pharmacists were of low-dose CBD) and predictive variables (age, gender and experience). Due to multiple tests performed per ordinal response variable, Bonferroni correction was used to adjust α (i.e., 0.05/3 = 0.017). Correspondence analyses were then used to visually represent the significant relationships between variables to determine the strength of the associations.

Results

A total of 272 individuals initiated the survey, 55 were considered 'non-completers' and 217 responses from pharmacists were included in the final dataset. The number of respondents who completed each section was as follows: Experience (n = 217, 100%), Attitudes (n = 201, 92.6%), Professional Educational Needs (n = 189, 87.1%) and

Table 1 Survey design

Section	Query type	Number and format of items
Section 1	Demographic information	Multiple choice (10 items)
Section 2	Experience with supply of medicinal cannabis products	Multiple choice & yes-no-unsure (11 items)
Section 3	Knowledge around medicinal cannabis products	True-false-unsure (13 items)
Section 4	Perspectices on the supply of medicinal cannabis products	5-Point likert scale & multiple choice (11 items)
Section 5	Professional education needs	5-Point likert scale; multiple choice; yes-no-unsure & open text (6 items)

Knowledge (n = 118, 54.3%). A technical issue resulted in some respondents (33.4%, 91/272) being unable to complete the Knowledge section of the survey.

Demographic characteristics

Respondents demographics are summarised in Table 2. Many respondents identified as female (67.7%, 147/217). More than half (52.1%, 113/217) of the participating pharmacists worked in pharmacies within major suburban cities. Half of the respondents (51.2%, 111/217) were located in the most populous Australian state of New South Wales (NSW). The most common age range was 25–34 years (29.5%, 64/217).

Table 2 Demographic characteristics of participating pharmacists, n = 217

Characteristics	n = 217	%
Gender identity		
Male	63	29.0
Female	147	67.7
Not provided	7	3.2
Age (years)		
18–24	18	8.3
25–34	64	29.5
35–44	59	27.2
45–54	40	18.4
55–64	28	12.9
65 +	8	3.7
State		
New South Wales	111	51.2
Queensland	40	18.4
Victoria	28	12.9
Western Australia	15	6.9
South Australia	12	5.5
Australian Capital Territory	8	3.7
Tasmania	3	1.4
Northern Territory	0	0
Years of experience		
Less than 1 year	16	7.4
1–5 years	45	20.7
6–10 years	35	16.1
11–15 years	31	14.3
16–19 years	20	9.2
20 or more years	70	32.3
Pharmacy location		
Major metropolitan city centre	39	18.0
Major suburban city centre	113	52.1
Regional town	44	20.3
Rural or remote town	17	7.8
Other	4	1.8

Pharmacists' experiences with the supply of medicinal cannabis products

Over half of the respondents (60.0%, 130/217) had dispensed at least one MC prescription during their careers. During the last two months, 39.2% (85/217) had dispensed at least one MC prescription and of these, many (77.6%, 66/85) had dispensed between one and nine MC prescriptions. A small proportion of pharmacists (4.6%, 10/217) had dispensed ≥ 20 MC prescriptions in the last two months. Over half of the respondents (56.7%, 123/217) felt that MC enquiries had risen over the past three months and had received at least one MC enquiry in the past two weeks (58.5%, 127/217).

Just over half of the respondents (53.9%, 117/217), regardless of whether they had supplied MC, felt 'comfortable supplying MC products and wished to do so in the future.' The remainder (46.1%, 100/217) felt: 'neither comfortable nor uncomfortable' (19.8%, 43/217), 'not comfortable supplying MC products now but interested in doing so in the future' (20.3%, 44/217), or 'not comfortable supplying MC products and not wishing to do so in the future' (6.0%, 13/217). Asymptotic Linear-by-Linear Association Tests and correspondence analyses found a significant association between 'comfort levels' and age, with participating pharmacists aged ≥ 45 years more comfortable supplying MC products ($z = 3.25$, $p = 0.001$). 'Comfort level' was also associated with experience, with participating pharmacists having ≥ 16 years of experience more comfortable supplying MC products ($z = 2.63$, $p = 0.009$). Higher 'confidence' in discussing customers' enquiries about MC products was significantly associated with the male gender ($z = 2.49$, $p = 0.013$). Male gender ($z = 3.166$, $p = 0.002$) and age ≥ 45 years ($z = 2.979$, $p = 0.003$) were significantly associated with more support for low-dose CBD. No other significant associations were detected.

Respondents who had experience dispensing MC products (60.0%, 130/217) were presented with a list of common MC indications and asked what they believed were the three main conditions for which MC is used based on their experience. The top condition was non-cancer pain (55.3%, 120/217), followed by anxiety (29.0%, 63/217), neuropathic pain (26.3%, 57/217), chronic cancer pain (21.2%, 46/217), insomnia (15.2%, 33/217), childhood epilepsy (13.8%, 30/217), spasticity (9.2%, 20/217), 'other' (6.9%), depression (6.5%, 14/217) and 'unsure' (0.5%, 1/217).

Pharmacists' attitudes towards the supply of medicinal cannabis products

Respondents (n = 201) were asked about their attitudes towards the supply of MC and *Pharmacist Only* CBD products (Fig. 1). Overall, many respondents (67.7%, 136/201) 'agreed' that the accessibility of MC products

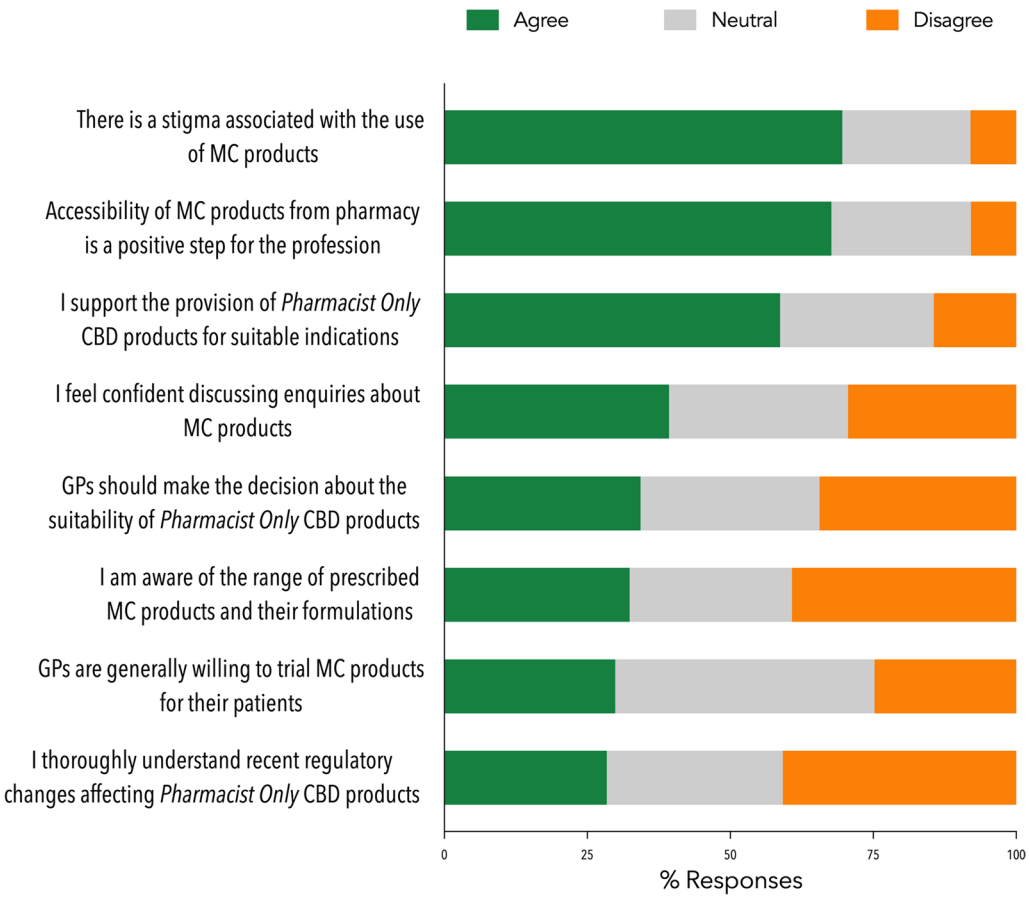

Fig. 1 Pharmacists' responses to statements on various aspects of the supply of medicinal cannabis and *Pharmacist Only* CBD products, n = 201, valid percentage. Abbreviation: MC: medicinal cannabis. Refer to the supplementary materials for a full copy of the survey questions

from community pharmacies was a 'positive' step for the profession, despite 69.6% (140/201) acknowledging an ongoing stigma associated with the use of MC products. Respondents supported the provision of *Pharmacist Only* CBD products for suitable patients (58.7%, 118/201). However, only 39.3% 'agreed' that they felt confident discussing customers' enquiries about MC products.

Few respondents 'agreed' when asked if they had a thorough understanding of the recent scheduling changes affecting *Pharmacist Only* CBD products (28.4%, 57/201), or if they were aware of the current range of MC products and formulations (32.4%, 65/201). Respondents varied in their responses when asked if they thought GPs were willing to prescribe MC products to their patients and whether GPs should decide on the suitability of *Pharmacist Only* CBD products for patients (Fig. 1).

Respondents (n = 217) were presented with a list of potential barriers and asked to select all options that they believed would affect the provision of *Pharmacist Only* CBD products (Fig. 2). The most frequently selected barriers were: (1) a lack of training and resources for pharmacists and staff (61.3%, 133/217), (2) patient safety e.g., potential for misuse, abuse, diversion (53.0%, 115/217) and (3) demand, but lack of an approved *Pharmacist Only* CBD product (52.5%, 114/217).

Respondents were presented with a list of perceived benefits arising from availability of *Pharmacist Only* CBD products and asked to select all options that they agreed with (Fig. 3). The most frequently selected benefits were: (1) improved access to MC products for patients (56.2%, 122/217), (2) continuity of care (47.5%, 103/217) and (3) a reduced burden to the health care system (45.2%, 98/217).

Knowledge around medicinal cannabis products

Due to a technical issue, only 54.4% (118/217) respondents completed the knowledge section of the survey (Fig. 4). Only around one-third of completers (32.2%, 38/118) recorded a 'satisfactory' knowledge score of ≥ 60% (i.e., ≥ 8 correct out of 13 questions). The remainder had 'low' knowledge scores of < 60% with 21.2, 27.1 and 19.5% providing 6–7, 4–5 and 0–3 correct responses, respectively. The questions that were most commonly answered correctly involved the

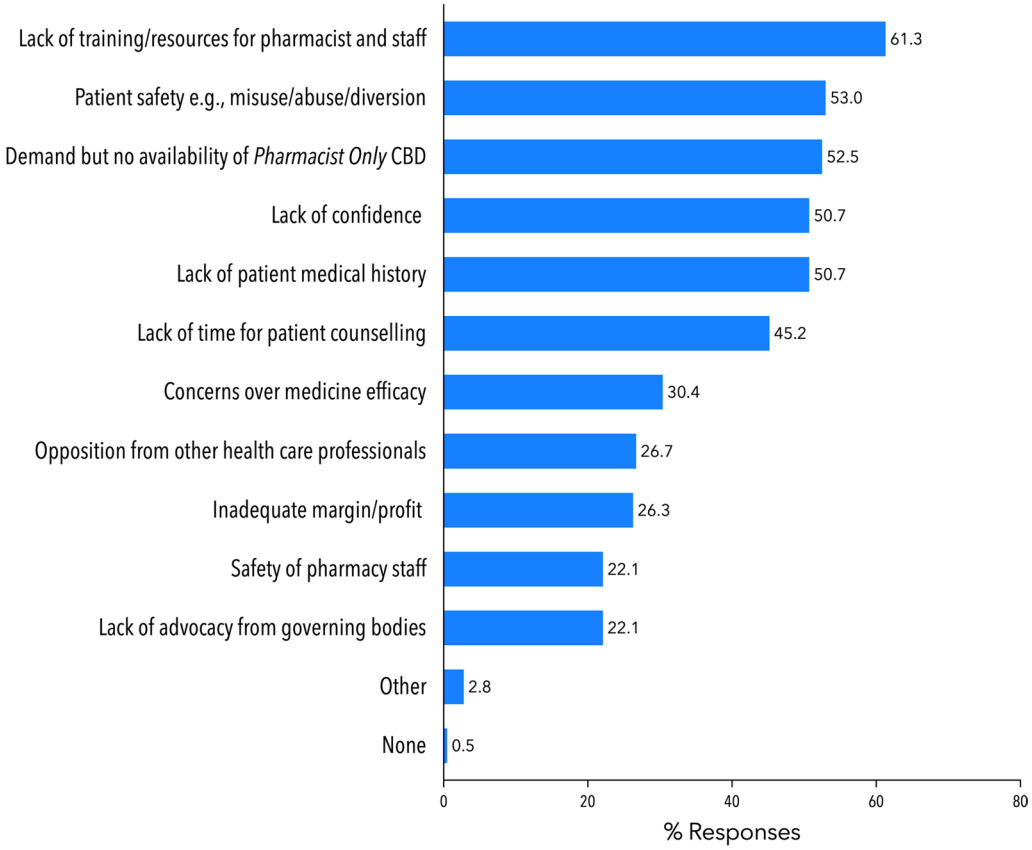

Fig. 2 Pharmacists' perceived barriers around the implementation of *Pharmacist Only* CBD products. Pharmacists (n = 217) were instructed to select all applicable options. Each bar represents % of total respondents (n = 217) who selected this option. Abbreviation: MC: medicinal cannabis. Refer to the supplementary material for a full copy of the survey questions

correct identification of: (1) the access schemes through which MC can be prescribed, (2) the current lack of registered *Pharmacist Only* CBD products and (3) the common active ingredients found in MC (81.9, 78.8 and 73.7%, correct respectively). The questions that were most commonly answered incorrectly involved CBD and adverse effects, potentiating effects with alcohol, and impacts on driving ability (67.8, 41.5 and 38.1%, incorrect respectively).

Pharmacists' professional education needs

Most respondents (94.2%, n = 178/189) 'agreed' that they required training/education on MC and *Pharmacist Only* CBD products. 'Self-learning' was the preferred form of training (69.3%, 131/189), followed by virtual webinars (57.7%, 109/189), pharmacy journals (47.0%, 89/189) and in-person workshops (33.3%, 63/189). Just over half of the respondents (54.5%, 103/189) 'disagreed' that they were provided with adequate support and information on MC and *Pharmacist Only* CBD products from their professional pharmacy organisations.

Discussion

Key findings

Pharmacists generally supported the accessibility of cannabis-based medicines from community pharmacies and an expanded role for pharmacists in supplying *Pharmacist Only* CBD products. Over half of the respondents had dispensed a MC product during their careers and had fielded an enquiry about MC in the past fortnight. However, only around half of the pharmacists were comfortable with supplying MC products and even fewer felt confident managing cannabis-related enquiries, despite such enquiries steadily increasing over time. Most pharmacists did not believe that they had a good understanding of recent regulatory changes affecting *Pharmacist Only* CBD products. The vast majority of participating pharmacists expressed a need for professional educational support.

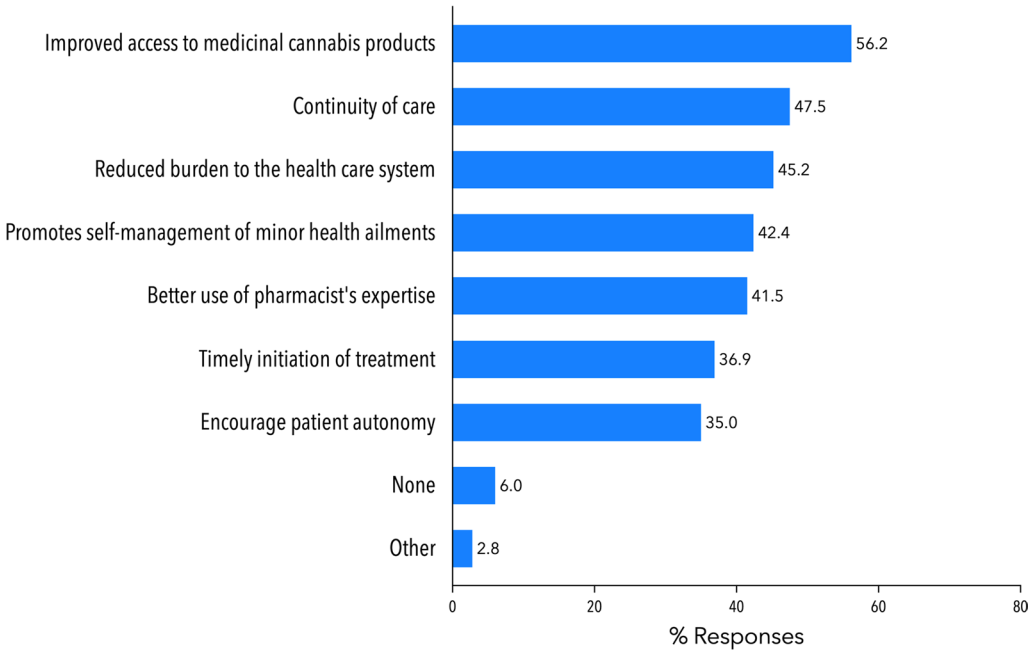

Fig. 3 Pharmacists' perceived benefits around the implementation of *Pharmacist Only* CBD products. Pharmacists (n = 217) were instructed to select all applicable options. Each bar represents % of total respondents (n = 217) who selected this option. Abbreviation: MC: medicinal cannabis. Refer to the supplementary material for a full copy of the survey questions

Strengths and weaknesses

This is the first survey to explore Australian pharmacists' attitudes, beliefs and knowledge around the supply of cannabis-based medicines since legal MC access was introduced into Australia in 2016. The survey is unique in that it was conducted after the Australian Government permitted access to low-dose CBD products without a prescription, but prior to any products being registered for this purpose and therefore available in pharmacies. Since 2016, access to MC products has increased dramatically in the Australian community [42] so the survey provides key insights into the impacts of this improved availability on pharmacists. This survey is also reasonably comprehensive with 51 items scoping numerous MC aspects that are relevant to pharmacy practice. The 217 pharmacists included in this study are a small portion of Australia's population of ~35,000 pharmacists [43]. However, respondents in this survey closely represented the overall demographic profile of Australia's pharmacist workforce of whom more than half identify as female (63.0%) and one-third represent a younger age group (36.2% aged 25–34 years), or work in NSW (29.9%) [43].

This study has some limitations. The COVID-19 pandemic contributed to the difficulty in recruiting pharmacists for this survey. A technical issue with the survey led to some data not being collected for the Knowledge section of the survey. The Knowledge section of the survey was also completed unsupervised. The survey was not psychometrically tested and may be affected by recall bias. There was no way to prevent pharmacists from completing the survey more than once. The recruitment strategies may have biased the results by appealing to pharmacists who were technologically adept and had a strong interest in MC. The generalisability of the findings is limited by the relatively small sample size, meaning that the results may not entirely represent Australian pharmacists.

Interpretation

Australian pharmacists have a key role in facilitating access to novel therapeutics and substantial recent experience with medicines being down-scheduled from *Prescription Only* to *Pharmacist Only* medicines (e.g., melatonin supply for older people with insomnia, morning-after contraceptives) [44–46]. Pharmacists value their involvement in the discourse around MC, given their essential role in supply [1]. Nonetheless, pharmacists in this survey flagged potential barriers to assisting the community with access to MC products. Few respondents felt confident discussing customers' enquiries about MC products despite the rise in such enquiries, and only around half of the respondents felt comfortable supplying MC. Similar findings are observed in many international surveys of pharmacists around MC [1, 31–34, 47]. These results may reflect pharmacists' need to navigate the broad range of clinical applications for cannabis-based medicines [2, 5, 42], only some of which are supported by

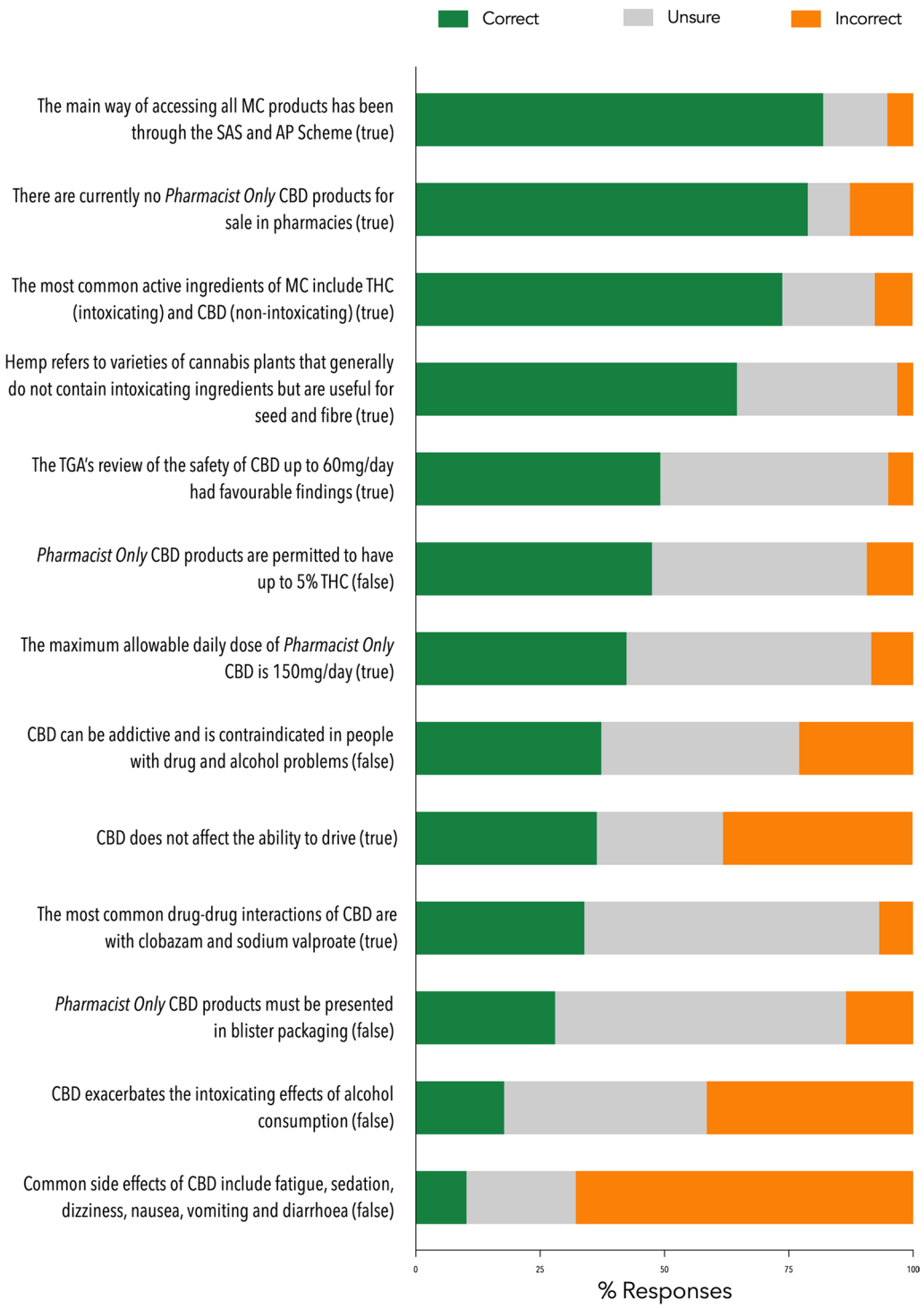

Fig. 4 Knowledge of pharmacists around cannabis-based medicines. Figure shows percentage for each question that were answered correctly, incorrectly or as 'unsure' by pharmacists, n = 118, valid percentage. Correct answers provided after each question. Abbreviations: MC: medicinal cannabis; SAS: Special Access Scheme; AP Scheme: Authorised Prescriber Scheme; THC: tetrahydrocannabinol; CBD: cannabidiol; TGA: Therapeutic Goods Administration. Refer to the supplementary material for a full copy of the survey questions

high-quality evidence [48], and the extensive product range in Australia involving around 240 individual preparations [2, 5]. Participating pharmacists aged ≥ 45 years or with ≥ 16 years of experience were significantly more comfortable with MC supply than other pharmacists. This suggests that

significant expertise in pharmacy practice aided pharmacists when managing MC supply.

Male pharmacists were found to be more supportive of *Pharmacist Only* CBD being available in pharmacies and more confident with managing MC enquiries than female pharmacists. Gender differences were also noted in a Canadian survey of pharmacists and pharmacy students around MC, whereby male pharmacists were more comfortable counselling patients around MC than their female colleagues [47]. Research suggests that women often demonstrate lower confidence than men in various contexts. While this may influence decision-making, self-reported confidence is not necessarily an accurate indicator of ability [49]. These factors must be considered in the interpretation of results.

Lack of pharmacist confidence and comfort with MC supply was underlined by 'low' objective knowledge; two-thirds of pharmacists who completed the Knowledge section of the survey achieved a score of < 60%. While these results may not entirely represent the whole survey cohort, many pharmacists also noted low perceived knowledge around regulatory changes affecting *Pharmacist Only* CBD products. This may reflect the fact that no *Pharmacist Only* CBD products are currently registered or marketed, meaning that pharmacists may not consider competency in this area a priority. The low levels of knowledge observed in this study are consistent with numerous surveys of pharmacists around cannabis-based medicines [31–34, 50, 51]. Indeed, the piecemeal approach to legalising MC has been identified as creating gaps in knowledge [51]. In one review, 58.9–81.9% of pharmacists were predicted to have a low perceived knowledge around MC [34], while only 5% of pharmacists in another survey of Californian pharmacists reported having 'professional level' knowledge around MC [33]. When *Pharmacist Only* CBD products become available, knowledge development in this area will be essential for optimal patient care and to actualise health professionals' roles to their full potential [33, 36], particularly with pharmacists set to become the 'frontline suppliers' of *Pharmacist Only* CBD products.

Almost all survey respondents strongly endorsed the need for further training. This need has been repeatedly highlighted as a priority in surveys of pharmacists around MC [1, 31, 33, 34, 47, 50, 51], at times, in equally high numbers, i.e., ~ 70–90% of pharmacists surveyed [33, 34]. A significant obstacle to pharmacists' education around cannabis-based therapy has been noted as a lack of access to reliable resources and training activities [34, 50, 51]. Currently, an array of MC resources, guidelines, and policies are available from Australian government organisations such as the TGA and pharmacy-specific organisations [4, 48, 52–56]. However, these resources are lengthy and have not been streamlined or tailored to pharmacy practice. Furthermore, resources for pharmacists, specifically around managing *Pharmacist Only* CBD products, are scarce. Indeed, most pharmacists did not believe they were provided adequate support around cannabis-based medicines and *Pharmacist Only* CBD products from professional organisations, indicating that a call to action is required in this space. Educational initiatives have accompanied the down-scheduling of other *Pharmacist Only* products in Australia and resulted in a safe supply of down-scheduled products [44–46, 57].

This survey highlights a number of other concerns that would be beneficial to mitigate. Firstly, the stigma associated with the use of MC was flagged by most pharmacists in this survey, in line with previous surveys [34, 51]. The stigma around MC may arise from the confusion between medicinal and recreational cannabis [34]. Stigma can lead to marginalisation, disempowerment and poor health outcomes for patients utilising these products [51, 58, 59]. Secondly, pharmacists demonstrated concerns about the potential for misuse, abuse, diversion and the effects on driving with *Pharmacist Only* CBD products. These issues have been flagged in surveys of MC and may highlight concerns around THC that some pharmacists also mistakenly attribute to CBD [1, 31, 34]. Indeed, the 2018 World Health Organization Expert Committee on Drug Dependence deemed CBD to have a good safety profile with a low potential for adverse effects [60], reaffirmed by a recent review of low dose CBD safety and efficacy [61]. Thirdly, 6% of pharmacists in this survey noted having no interest in supplying MC products. However, current resources do not provide specific guidance or support for pharmacists who may wish to opt-out of supply [4, 48, 52–56]. These concerns are important to address as patients may be left to navigate the convoluted area of cannabis-based therapy alone, increasing the risk of unsafe practices [51]. Government and professional bodies will play a critical role in the education and support of pharmacists. A clear and strategic pathway to clinical competence is essential before *Pharmacist Only* CBD products become widely available, whether pharmacists decide to be involved with supply or not.

Further research

Further research may involve developing of training and educational resources around MC and *Pharmacist Only* CBD products. The 'pain-points' highlighted in this survey may provide insights into the content of such initiatives, which should be evidence-based, relevant and specific to pharmacy practice [62]. The significant workload-related constraints on pharmacists' time should be carefully considered [62], as should the flexibility and variety of training activities [62, 63]. Indeed, this survey and prior surveys demonstrated that pharmacists had clear preferences

for learning activities [31, 34, 51]. These resources should guide all pharmacists, including those who opt out of MC supply.

Conclusion

This survey explored Australian pharmacists' experience, knowledge and attitudes towards MC and their preparedness to supply low-dose CBD products. This survey was conducted at a time of accelerating demand for MC products in Australia, just before *Pharmacist Only* CBD products become available in pharmacies. Pharmacists generally support their role in the supply of *Pharmacist Only* CBD products and have critical fundamental skills and experience to aid in supply. However, pharmacists require further training to optimise their role to its full potential. This survey provides a unique perspective on the management of MC in Australia and complements prior research in this area. These findings may be relevant to other jurisdictions where improved community access to medicinal cannabis products is being contemplated.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-022-01519-z.

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CHAPTER 3. A MEDICINAL CANNABIS PHARMACIST TRAINING PROGRAM

The current chapter showcases a knowledge translation initiative that was guided by the findings of Study 1, specifically, the fact that pharmacists expressed a desire for further training and education around medicinal cannabis, including low-dose CBD.

Each year, Australia's peak medicinal cannabis advocacy body, United in Compassion (UIC), hosts an annual symposium. This symposium is the primary medicinal cannabis conference in Australia and is attended by professionals from industry, research and health care. For the 2023 symposium, held in Brisbane, QLD, UIC collaborated with the Lambert Initiative for Cannabinoid Therapeutics at the University of Sydney. One of the aims of this collaboration was to develop a training program around medicinal cannabis for pharmacists. This presented a unique opportunity for pharmacist and PhD candidate, Zeeta Bawa, based at the Lambert Initiative, to volunteer and lead the pharmacist training program.

The purpose of this project was not to determine its own research outcomes, but instead, to develop and implement a national, specialised medicinal cannabis training program for Australian pharmacists based on the findings of Study 1. The steps that were taken to design and implement such a program over a six-month period are summarised below.

3.1 Program Outline

Initially, the UIC discussed their interest in developing a series of training programs around medicinal cannabis for physician, pharmacists, and nurses with the Lambert Initiative, with the intent of delivering these programs at the 2023 UIC symposium. Having recently completed Study 1, the Lambert Initiative agreed to lead the pharmacist training program. Subsequently, the UIC specified their requirements for the pharmacist training program. This included an in-person, one-day training event with scheduled breaks. The breaks were necessary for refreshments and food, and to encourage attendees to establish professional connections. It was also recommended to close the training day with a panel discussion so that attendees had one final opportunity to direct their questions and concerns to a selection of experts. The event would welcome all student, intern, community, hospital, and industry

pharmacists residing in Australia. The costs associated with the development and implementation of the training program would be offset by incorporating a one-time attendance fee of $300 that would be subsidised for student and intern pharmacist attendees. The Lambert Initiative also agreed to sponsor up to 20 pharmacy students and interns to attend the event.

3.2 Program Development

Essential competencies relating to medicinal cannabis in pharmacy practice were identified and these served as the basis for seven individual 'training sessions' (Table 1). Important considerations were made around each training session. Firstly, the 'learning objectives' (Table 1) of each training session were charted to guide the learning content. The learning objectives also served as a metric of learning (e.g., by the end of training session x, you should be able to do y). Notably, the findings from Study 1 served as a valuable snap-shot of 'pain-points' that pharmacists experienced with regard to medicinal cannabis, and these were used to identify relevant learning content that required additional attention. For example, pharmacists in Study 1 indicated a considerable lack of knowledge around low-dose CBD product legislation. This was therefore included in the learning content. Secondly, the order and format (i.e., lectures or case-studies) of each training session was carefully considered to maximise attendee engagement, participation, and knowledge retention. As such, information-heavy sessions were placed at the beginning of the day, followed by shorter and more interactive session in the later part of the day.

Table 1. *The competencies and learning objectives of the training sessions included in Pharmacist Training Program and their associated expert presenter(s).*

Training Session	Competencies	Learning Objectives	Expert Speaker(s) and Affiliation
Medicinal Cannabis in Pharmacy: An Overview	Develop an expert knowledge and understanding of medicinal cannabis	• Understand the pharmacological basis for the actions of cannabinoids • Appreciate the complex nature of cannabis-based medicinal products • Appreciate some of the pharmaceutical challenges in delivering cannabinoids • Appreciate the factors that influence response to cannabinoids • Know that evidence to support cannabinoid efficacy and safety varies depending on the extract, formulation and route of administration	Professor Andrew McLachlan, Head of School and Dean of Pharmacy, University of Sydney
Medicinal Cannabis Legislation Refresher	Understand the laws, and regulations underpinning the supply of medicinal cannabis in Australia	• Understand the regulations around Schedule 4 & 8 medicinal cannabis products • Understand the recent regulations around Schedule 3 low-dose CBD products • Understand the five categories of medicinal cannabis products • Understand the Special Access Scheme and Authorised Prescriber pathways • Appreciate the State and Territory Requirements for scripts	Sukanya Lingaratnam, A/g Director - Special Access Section, Therapeutics Goods Administration
Medicinal Cannabis Process for Dispensing	Develop an expert knowledge and skill in medicinal cannabis dispensing that supports the quality use of these medicines	• Recognise the scheduling of medicinal cannabis products • Understand the types of formulations and dosage forms available • Identify the relevant TGA category approval for medicinal cannabis products • Recognise valid medicinal cannabis prescriptions and required legal particulars • Understand the process to order medicinal cannabis products for the pharmacy • Identify the requirements for compounding medicinal cannabis products • Dispense and label medicinal cannabis products appropriately • Recognise the precautions and contraindications of medicinal cannabis use • List the common adverse effects of medicinal cannabis products • Counsel patients on medicinal cannabis oils, flowers and dried herb vaporisers • Identify appropriate resources and references for pharmacists	Lisa Nguyen, Founder &CEO, Astrid Dispensary; and Sarah Rajah, Head Of Education & Stakeholder Engagement, Astrid Dispensary
Medicinal Cannabis Case Studies	Communicate effectively and use interpersonal and problem solving skills when managing medicinal cannabis enquiries	• Recognise common medicinal cannabis queries and how to manage them • Handle patient queries regarding *Pharmacist Only* low-dose CBD products • Provide medication counselling for patients using medicinal cannabis oils and flowers, including relevant device demonstrations • Manage queries around medicinal cannabis use and driving regulations • Counsel on medicinal cannabis use in paediatric populations • Handle instances where a medicinal cannabis product is out of stock • Identify the signs of THC overuse and suggest a treatment plan in collaboration with the prescriber	Lisa Nguyen, Founder &CEO, Astrid Dispensary Sarah Rajah, Head Of Education & Stakeholder Engagement, Astrid Dispensary Jenny and Nick Ravenswood, Pharmacists, Amcal Pharmacy
Current Research: Medicinal Cannabis and Low-Dose CBD	Develop a knowledge and awareness of current research around medicinal cannabis and low-dose CBD	• Understand the scope of research around medicinal cannabis and its constituents • Understand the evidence base supporting therapeutic uses of CBD and THC • Appreciate the common uses of THC and CBD based on the SAS-B trends	Professor Iain McGregor, Academic Director, Lambert Initiative for Cannabinoid Therapeutics

Training Session	Competencies	Learning Objectives	Expert Speaker(s) and Affiliation
		• Address common concerns around medicinal cannabis based on research findings e.g., effects on driving, withdrawal and addiction, safety etc. • Understand the most current evidence around the efficacy of *Pharmacist Only* low-dose CBD • Know how to locate reliable information around medicinal cannabis	
Journey of Medicinal Cannabis Prescribing	Develop and knowledge and understanding of the medicinal cannabis prescribing process	• Understand the journey of patient access to medicinal cannabis from the perspective of a prescriber • Understand the considerations a prescriber must make when deciding on medicinal cannabis therapy • Understand how a SAS-B application or AP notifications are completed • Understand what dosing considerations are made • Understand what counselling must be given and how patients are monitored	Associate Professor Vicki Kotsirilos, General Practitioner, Western Sydney University Dr Nick Giummarra, General Practitioner
Hospital Pharmacy and Medicinal Cannabis	Develop a knowledge and understanding of how medicinal cannabis is managed in hospital pharmacy	• Understand how medicinal cannabis is prescribed, dispensed, stored and delivered within the inpatient and outpatient contexts of a hospital pharmacy • Understand what counselling is provided to patients using medicinal cannabis • Understand the issue around patients' own cannabis being brought into a hospital during admission • Appreciate a community pharmacists' role in assisting patients bringing in their own medicinal cannabis into hospitals	Jeffery Li, Pharmacist, Chris O'Brien Lifehouse

3.3 Specialist Content Creation

Next, leading experts in the field of cannabinoid research and pharmacy practice were invited to participate in the pharmacist training program. Expert volunteers were required to create the learning content for their allocated training session (guided by the pre-mapped learning objectives, Table 1) and to deliver the training session in-person on the day. Further learning content was welcomed if deemed relevant and necessary by the expert. Ten experts (Table 1) were confirmed and each demonstrated a strong support for the project and generously donated their time and expertise to the training program. Following learning content creation, accreditation for each training session was sought from the professional pharmacy organisation, the Australian Pharmacy Council. This enabled the learning content to be formally assessed for educational quality and relevance to pharmacy practice on a national scale. Consequently, pharmacist attendees would be able to earn pre-specified continuing professional development (CPD) points upon completion of the training session, contributing to their mandatory annual requirement set by the Pharmacy Board of Australia.

3.4 Program Delivery

The final one-day pharmacist training program was advertised widely on social medial platforms (see Figure 1) and by universities, pharmacy-specific organisations and news outlets. The training day was held on 12 August 2023 during the annual UIC Australian Medicinal Cannabis Symposium held at the Brisbane Conference and Exhibition Centre from 11-13 August 2023 (Figure 2). Zeeta Bawa co-hosted the event and was a speaker on the expert panel at the close of the event. The event reached maximum capacity with approximately 160 attendees. Most attendees lived in Brisbane. Pharmacists from other states expressed interest in attending but noted that they were limited by busy work schedules and the cost of travel.

A. **B.**

Figure 1. *Advertisement of the one-day pharmacist training program indicating the CPD accreditation status of the event (**panel A**) and the day's schedule (**panel B**).*

3.5 Conclusion

The pharmacist medicinal cannabis training program was welcomed with positivity and a sense of collaboration. This event marked a valuable contribution to the training and education of Australian pharmacists around medicinal cannabis and serves as an exemplar of a knowledge translation initiative. Future endeavours could explore the creation of an annual accredited training program that could be delivered online and at a reduced cost to improve affordability and access. Such an initiative could be used to develop knowledge, build competence, optimise the clinical practice of pharmacists around medicinal cannabis and act as an exemplar for other areas of healthcare.

Figure 2. *Images of the pharmacist training program. Zeeta, co-host and lead of the pharmacist training day standing in front of the event banner (**panel A**). Professor Iain McGregor, expert speaker delivering his 'Research Update' session (**panel B**). Student, intern, community, hospital, and industry pharmacist attendees of the pharmacist training program (**panel C**).*

CHAPTER 4. KNOWLEDGE, EXPERIENCES, AND ATTITUDES OF AUSTRALIAN GENERAL PRACTITIONERS TOWARDS MEDICINAL CANNABIS: A 2021-2022 SURVEY

Reader's note:

This chapter includes a co-authored publication. The bibliographic details of the co-authored paper, including all authors are as follows:

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The research candidate has made the following contributions to this study:

- Developed the study design
- Completed the human research ethics application
- Conducted all participant recruitment and data acquisition
- Conducted analysis of the data
- Prepared the manuscript for submission to a peer-reviewed journal

BMC Primary Care

RESEARCH

Open Access

Knowledge, experiences, and attitudes of Australian General Practitioners towards medicinal cannabis: a 2021–2022 survey

Zeeta Bawa[1,2,3,4], Danielle McCartney[1,2,3], Ramesh Manocha[5] and Iain S. McGregor[1,2,3*]

Abstract

Background: Medicinal cannabis (MC) products have been available on prescription in Australia for around six years. General practitioners (GPs) are at the forefront of MC prescribing and recent years have seen substantial increases in prescription numbers. This study examined the current knowledge, experiences, and attitudes of Australian GPs around MC. We also compared our findings to those of an earlier 2017 investigation.

Method: We conducted a cross-sectional study using a 42-item on-line questionnaire adapted from our earlier 2017 survey. The current survey was completed by GPs attending an on-line, multi-topic educational seminar. Australian GPs ($n = 505$) completed the survey between November 2021 and February 2022. Data were synthesised using descriptive statistics. MC 'prescribers' and 'non-prescribers' responses were compared using Pearson's $\chi 2$ tests.

Results: While most GPs (85.3%) had received patient enquiries about MC during the last three months, only half (52.3%) felt comfortable discussing MC with patients. Around one fifth (21.8%) had prescribed a MC product. GPs strongly supported MC prescribing for palliative care, cancer pain, chemotherapy-induced nausea and vomiting, and epilepsy, more so than in our 2017 survey. Prescribing for mental health conditions (e.g., depression, anxiety) and insomnia received less support. Opioids, benzodiazepines, and chemotherapy drugs were rated as more hazardous than MC. GPs correctly endorsed concerns around Δ^9-tetrahydrocannabinol-related driving impairment and drug-seeking behaviour. However, additional concerns endorsed around cannabidiol causing addiction and driving impairment do not agree with current evidence. Consistent with this, many GPs (66.9%) felt they had inadequate knowledge of MC.

Conclusion: Acceptance of MC as a treatment option has increased among Australian GPs since 2017. However, there is a clear need for improved training and education of GPs around cannabis-based medicines to provide increased numbers of skilled prescribers in the community.

Keywords: Cannabis, Cannabinoid, Medicinal cannabis, General practice, Doctor

Background

The Australian Federal Government legalised medicinal cannabis (MC) in November 2016 [1, 2]. This has enabled patients to be prescribed a wide range of products containing Δ^9-tetrahydrocannabinol (THC) and/or cannabidiol (CBD) [3, 4]. These products are mostly classified

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as 'unregistered medicines' by the Australian drug regulator (the Therapeutic Goods Administration, TGA) and doctors must apply for approval to prescribe such products through the Special Access Schemes (SAS-A or SAS-B) or the Authorised Prescriber (AP) Scheme [2, 3, 5]. The SAS schemes allows doctors to seek approval from the TGA to prescribe MC products to an individual patient, while the AP scheme provides permission to prescribe a MC product to multiple patients suffering from the same condition [6]. Both schemes place the onus of assessing clinical need, justifying MC prescribing, and choosing an appropriate MC product on the prescribing clinician. The subsequent prescription is then dispensed through a pharmacy [2]. The first few years of MC access were characterised by small prescription numbers amidst criticisms that the schemes were too complex, lengthy and restrictive, and products, too expensive [5, 7–9]. The last two years, however, has seen a substantial increase in prescriptions with more than 320,000 SAS-B approvals involving more than 100,000 patients and 4,600 prescribers granted at the time of writing (December 2022) [5, 10, 11].

General practitioners (GPs) are at the forefront of MC prescribing in Australia [12] and handle many patient enquiries [3, 7]. Understanding the experiences of GPs around MC in clinical practice is, therefore, of major interest. Our research team previously surveyed Australian GPs ($n=640$) on their knowledge and attitudes towards MC in 2017, approximately one year following legalisation [7]. Results showed that most GPs were cautiously supportive of MC therapy but often felt 'uncomfortable' handling MC enquiries and felt poorly educated in the area. Similar outcomes have emerged from other surveys of medical practitioners in other countries [13–17].

Since our original survey, the prescribing landscape has changed considerably in Australia. The number of prescribing doctors has increased considerably and prescribing processes have been streamlined by the drug regulator and government [4]. To better understand how these developments have impacted GPs, we have conducted a new and updated survey of Australian GPs. Many of the original questions were retained, allowing us to investigate how attitudes, perceived knowledge, and concerns of GPs may have changed over time.

Method

Survey overview

The current survey consisted of 42-items, 21 of which were retained (or modified subtly) from our earlier 2017 survey [7]. Most of the 21 new questions probed the experiences of current MC prescribers. These were not included in the original 2017 survey as so few GPs (~100 in Australia) were prescribers at that time.

Participant eligibility and recruitment

The on-line, cross-sectional survey was conducted between November 2021 – February 2022. Participants were eligible to complete the survey if they were a registered or registrar GP. All participants were required to review the Participant Information Statement and provide informed consent. Ethics approval was granted by the University of Sydney Human Research Ethics Committee on September 17, 2021 (Ref: 2021/623).

Our original (pre-COVID) GP survey was paper and pen-based and recruited audiences of GPs attending in-person, multi-topic, educational events at major Australian capital cities. These events were hosted by Healthed, an Australian provider of continuing medical education (www.healthed.com) that services a large extended network of Australian GPs [6]. During to the COVID-19 pandemic, Healthed events were moved exclusively to an on-line format meaning that our updated survey could not be conducted in person. The survey, therefore, recruited GPs accessing a 2-h, on-line, multi-topic educational event hosted by Healthed. This event and the survey were promoted to GPs on the Healthed website and through emails to 15,989 GPs from Healthed's network of health professionals. GPs registered to attend the educational event with no cost charged for attendance. This event also included topics on lung disease, the COVID-19 pandemic and iron infusions. GPs completed the survey at their convenience up until February 2022. All participating GPs were eligible to enter a draw to win one of one hundred $100 gift vouchers.

Survey design

The survey (see Supplementary Materials) was developed and administered using a secure, web-based platform (REDCap®12.0.7, 2022, Vanderbilt University). There were six sections and involved a total of 42-items. The survey took approximately 10-minutes to complete. The sections explored participant demographics (nine-items), MC prescribing experiences (12-items), indications for which MC was prescribed or supported (two-items), attitudes and perspectives towards MC (11-items), perceived knowledge (five-items), and concerns around THC and CBD (three-items). Branching logic was used to ensure that only current or previous MC prescribers completed the section around prescribing experience. The demographics and experience sections contained multiple choice and 'yes-no' style questions. Other sections involved responses across a 5-Point Likert Scale (e.g.,

Strongly Agree, Agree, Neutral, Disagree or Strongly Disagree). A text box to allow open-ended comments was provided at the end of the survey.

Data management and analysis

Responses on the 5-point Likert scale questions were collapsed into the following three categories: Agree (Strongly Agree + Agree), Neutral, and Disagree (Strongly Disagree + Disagree). Clean data were synthesised using descriptive statistics (e.g., proportions, medians, ranges). MC 'prescribers' and 'non-prescribers' were compared on certain responses (demographic characteristics and perceived knowledge) using Pearson's $\chi 2$ tests. Analyses was conducted using IBM SPSS Statistics V.24.0 (IBM, U.S.). Figures were created using GraphPad Prism V.9.3.1 (350) for Mac (GraphPad Software, La Jolla, California, USA).

Responses to open-ended questions were grouped by common theme (e.g., perceived benefits and challenges).

Results

A total of 617 GPs initiated the survey. Those who failed to complete all six sections ($n = 112$) were removed from the analysis leaving a total of 505 participants. As the true number of GPs exposed to the advertisement of the educational event and survey through the Healthed website and email-base is unknown, the survey response rate could not be reliably calculated.

Demographic characteristics

Participant demographics ($n = 505$) are summarised in Table 1. Most participants identified as female (59.8%) and the most common age range was ≥ 55 years (51.7%). Participants tended to be located in the state of New South Wales (33.5%), had ≥ 20 years of clinical practice experience (56.9%) and work > 30 h per week (55.2%) in metropolitan areas (64.4%). Only 8.1% of participants ($n = 41$) were registrars.

Prescribing experience

Most GP participants (85.3%, 431/505) had received at least one enquiry about MC in the preceding three months (Supplementary Table 1), with 55.4% (280/505) having received between one and four enquiries during this time. Only around half of all participants (52.3%, 264/505) felt comfortable discussing MC with patients.

Approximately one fifth of the surveyed GPs (21.8%, 110/505) had prescribed MC products during their career and were considered MC 'prescribers.' Of those, more than half (60.0%, 66/110) had written one to nine prescriptions in the preceding three months. Most prescriptions were new (rather than repeats) (60.9%, 67/110) and involved the SAS-B pathway (83.6%, 92/110). Prescribers varied in the number of different MC products they prescribed, from only one (32.7%, 36/110) to more than five (15.4%, 17/110).

Table 1 Demographic characteristics ($n = 505$) of GP participants

Characteristics		$n = 505$	%
Gender	Male	203	40.2
	Female	302	59.8
Age (years)	44 and under	129	25.5
	45–54	115	22.8
	55 and over	261	51.7
State	New South Wales	169	33.5
	Victoria	134	26.5
	Queensland	90	17.8
	Western Australia	50	9.9
	South Australia	38	7.5
	Tasmania	12	2.4
	Australian Capital Territory	10	2.0
	Northern Territory	2	0.4
Years of Practice	9 or less	114	22.6
	10–19	104	20.6
	20 or more	287	56.9
Hours of Practice per Week	≤ 30	226	44.7
	> 30	279	55.2
Area Serviced	Metropolitan Only	318	63.0
	Regional Only	140	27.7
	Remote Only	30	5.94
	Combination of metropolitan, regional and/or remote	17	3.38

The demographic characteristics of prescribers and non-prescribers were compared. Being a prescriber was associated with state of residence ($\chi^2(7) = 16.9$, $p < 0.018$) with over-representation of GPs based in Queensland. Prescribers were also over-represented ($\chi^2(7) = 15.2$, $p < 0.033$) among GPs with 15–29 years of clinical experience. No other significant differences were observed.

GP participants reported prescribing products that mostly contained CBD (71.8%, 79/110) and combined THC and CBD products (70.9%, 78/110). Products that mostly contained THC were less frequently prescribed (27.3%, 30/110). When asked which 'form(s)' of MC they had prescribed (ever), they nominated oil formulations (94.5%, 104/110); flower (also known as flos or plant material) (26.4%, 29/110); and capsules (10.9%, 12/110).

More than half of prescribers believed that cannabis should *only* be legally available for medicinal purposes

(65.5%, 72/110) rather than medicinal and recreational purposes. Prescribers were equally split in their opinions on whether current access pathways were "user friendly" (50%, 55/110).

Indications for Use

Prescribers (21.8%, 110/505) most commonly prescribed MC for chronic non-cancer pain (92.7%, 102/110), anxiety (65.5%, 72/110) and neuropathic pain (61.8%, 68/110) (Supplementary Table 2).

With all GP participants considered ($n=505$), the conditions attracting most support for MC prescribing (Fig. 1) were end of life/palliative care (92.7%, 468/505), chronic cancer pain (91.9%,464/505), chemotherapy-induced nausea and vomiting (86.7%, 438/505) and intractable epilepsy (83.8%, 423/505). Only a minority of GPs endorsed the use of MC to treat anxiety (49.3%, 249/505), insomnia (47.4%, 241/505) and depression (37.2%, 188/505).

Attitudes

More than half of the GP participants ($n=505$) felt the prescribing processes were difficult to navigate (62.0%), and products, too costly (61.4%, Fig. 2). Many also thought GPs should have specific training to prescribe MC (79.0%). Less than half thought that GPs should only prescribe MC with specialist support (42.8%). There was little support for CBD products being made available as over the counter products in pharmacies (23.8%).

Only a minority of GP participants doubted the efficacy of MC (43.8%) while a majority expressed concerns about drug-seeking patients (67.9%) and the effects of MC on driving (65.3%). Few believed the risk of abuse and dependence (27.3%) and risk of side effects (15.6%) were "too high".

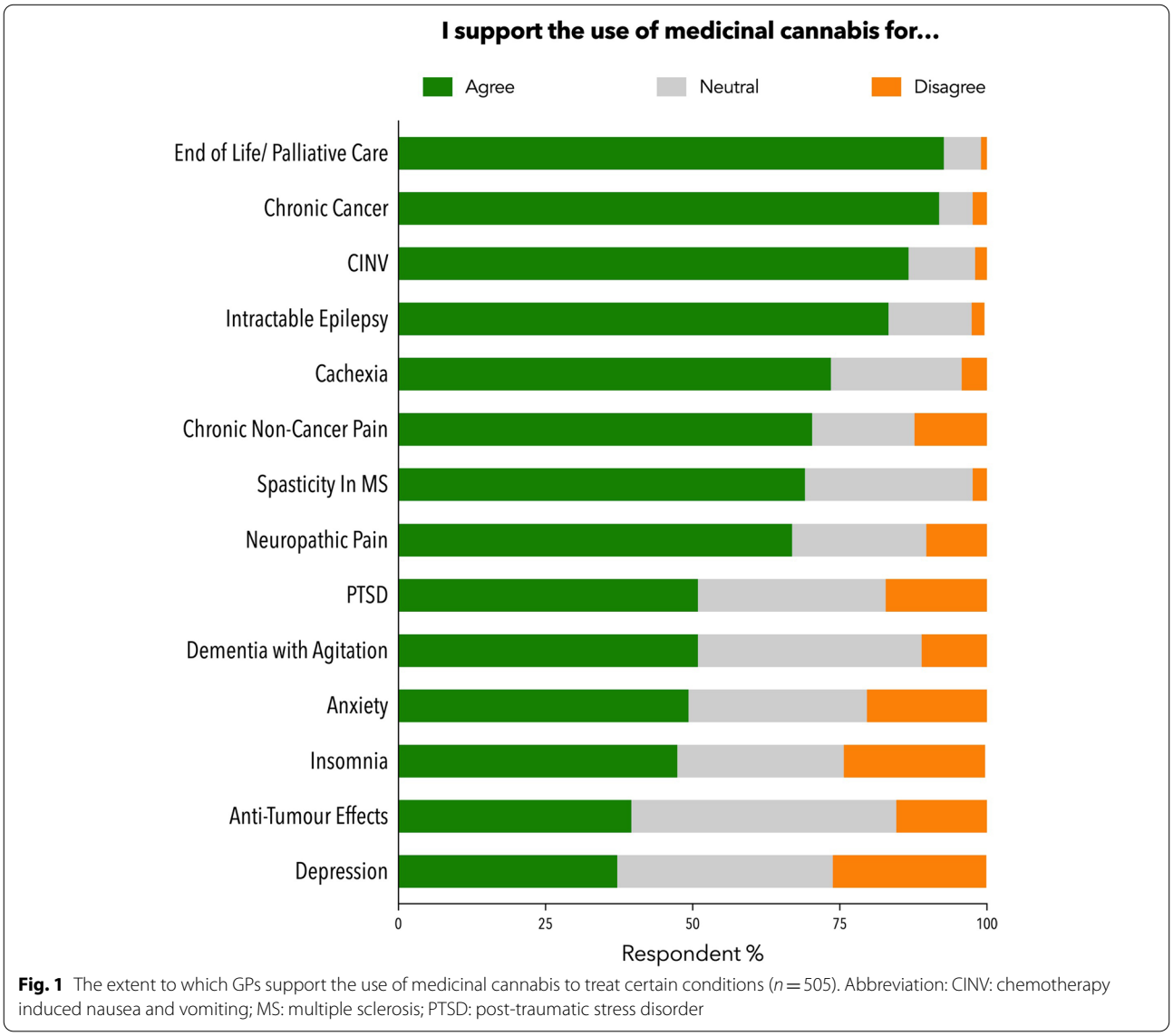

Fig. 1 The extent to which GPs support the use of medicinal cannabis to treat certain conditions ($n=505$). Abbreviation: CINV: chemotherapy induced nausea and vomiting; MS: multiple sclerosis; PTSD: post-traumatic stress disorder

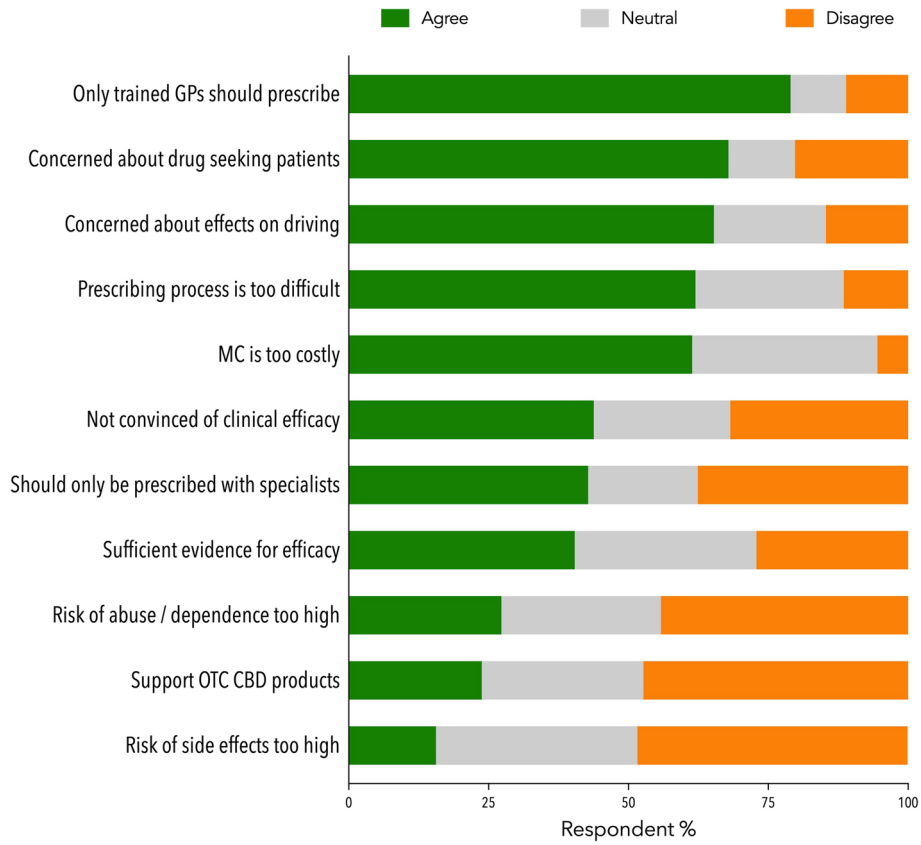

Fig. 2 Attitudes towards,and perceptions of, MC prescribing and use (n=505). Abbreviations: GP: generalpractitioner; MC: medicinal cannabis; CBD: cannabidiol; OTC: over the counter.Refer to the Supplementary Materials for a full copy of the survey questions

Perceived knowledge

Few GP participants ($n=505$) felt they had adequate knowledge about the use of MC in clinical practice (22.6%) (Fig. 3). Only around half knew how to help patients access MC (51.1%) and less than half were aware of the products and formulations available (42.6%). Unsurprisingly, prescribers indicated higher perceived knowledge than non-prescribers (p's <0.001) (Supplementary Table 3). Few GPs were aware of the stated positions of the Australian Medical Association [18] (AMA, 18.0%) and the Royal Australian College of General Practitioners [19] (RACGP, 26.7%) around MC.

Concerns

With regard to THC-containing products (Panel A, Fig. 4), GP participants ($n=505$) endorsed concerns around driving impairment (75.2%), impact on the developing brain (71.1%), cognitive impairment (69.1%), addiction and dependence (64.4%) and psychosis (64.0%). They were largely neutral about the concern of weight gain (56.8% neutral, 28.1% agree, 15.0% disagree).

With respect to CBD products (Panel B, Fig. 4), participants ($n=505$) endorsed concerns about effects on the developing brain (55.4%) and possible interactions with other medications (51.9%). Driving impairment (50.7%) and addiction and dependence (45.1%) were also nominated as significant concerns with CBD even though there is negligible evidence to support such concerns.

Participants ($n=505$) were asked if MC was more hazardous than commonly prescribed medications (Fig. 5). Overall, more than half of participants disagreed that MC was more hazardous than opioids (64.4%), benzodiazepines (63.8%) and chemotherapy drugs (57.0%). Participants also tended to disagree that MC was more hazardous than antipsychotics (47.1%), antidepressants (40.4%) and statins (34.9%) although a sizeable proportion endorsed neutrality around these latter comparisons.

Open ended comments

Open-ended comments provided by participants ($n=86$) commonly centred around the need for knowledge development (29%, 25/86) in this area. Cost issues (14.0%, 12/86), the importance of MC and its availability as a

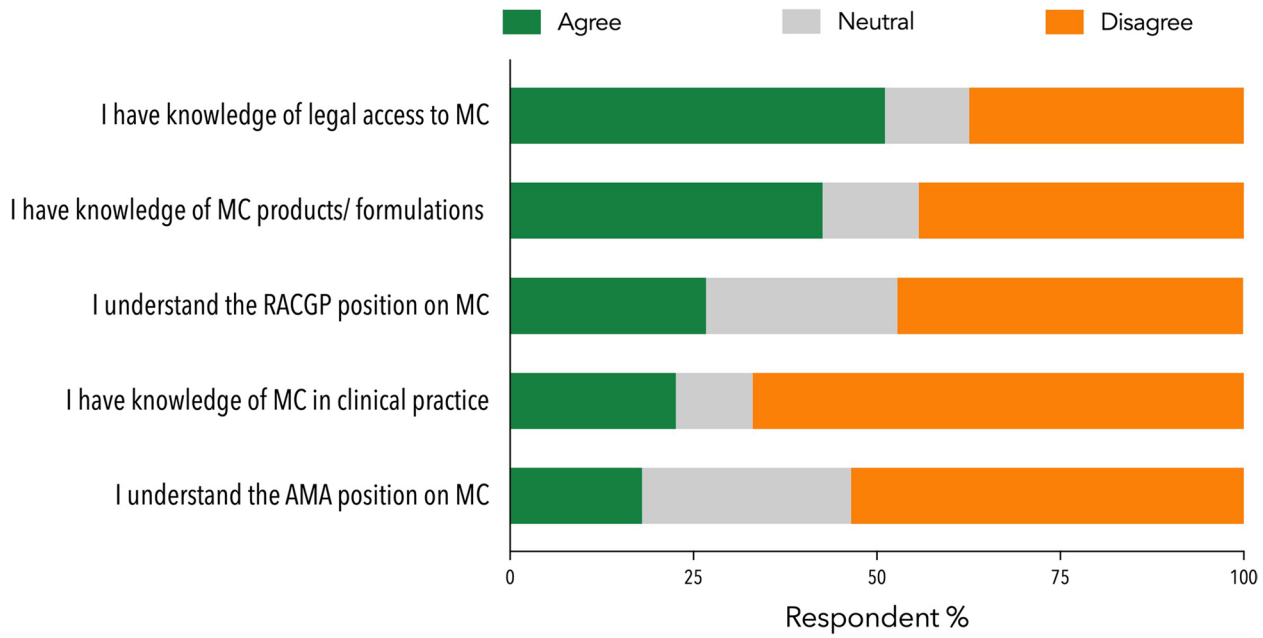

Fig. 3 Perceived knowledgeof MC as expressed by GPs (*n*=505). Abbreviations: AMA: Australian MedicalAssociation; RACGP: Royal Australian College of General Practitioners; MC:medicinal cannabis. Refer to the Supplementary Materials for a full copy of thesurvey questions

treatment option for chronic conditions (11.6%, 10/86), and the difficult or complicated prescribing process (8.1%, 7/86), were also noted by multiple participants.

Discussion

This study explored the current knowledge, experiences, and attitudes of Australian GPs towards MC, and provides key insights into this emerging field subsequent to our original survey of five years ago [7]. This survey is reasonably comprehensive, with 42-items scoping numerous aspects of MC that are relevant and specific to general practice. Overall, most GPs had received MC enquiries from patients. Yet only a minority felt comfortable managing these enquiries. Only around 21% of the cohort were MC 'prescribers', around the same proportion (22%) of the overall cohort reporting adequate self-perceived knowledge around MC in clinical practice. Indeed, many GPs felt they had inadequate knowledge of MC products, MC access pathways and optimal clinical practice. A need for further education in this area was also endorsed in the open-ended comments.

A disproportionate number of MC prescribers resided in Queensland, in agreement with recent government data on prescriber location for SAS-B approvals [5]. Overall, however, GP demographics in the current survey were strikingly similar to our original 2017 survey [7]. More GPs had received recent MC enquiries than in our original survey (85.3% vs. 61.5% respectively in past three months). This observation is consistent with the recent and considerable rise in MC prescribing [2, 10] likely driven by recent initiatives aimed at improving access pathways, as well as the growing acceptance of MC from health professionals [10, 20, 21]. The mental health burden of the COVID-19 pandemic has also been suggested as a contributing factor for the demand for MC products over the past two years [10].

Interestingly, however, GP comfort levels with managing MC enquiries remain low and unchanged since the original survey despite the increase in patient enquiries. Low comfort levels around managing and prescribing cannabis-based therapy are in line with other surveys of physicians [13–17]. Australian GPs currently select from >240 distinct MC products to treat more than 120 distinct medical conditions and often prescribe in the absence of high-quality supporting evidence of efficacy [3, 21, 22]. The specialised prescribing process and costly nature of MC products may also present hurdles in GP discussions with patients [7, 9, 23]. Most GP participants endorsed these two issues as ongoing problems. Formal education around MC has been suggested to improved comfort levels [14, 15, 24].

The greatest support for the use of MC was in terminal and/or often difficult-to-treat medical conditions such as palliative care, chronic cancer pain and CINV, more so than our original survey (Supplementary Table S4) [7] and similar to other international studies [25–27]. MC is often seen as a therapy of last resort, where conventional treatment options have been exhausted [10, 15, 25, 27,

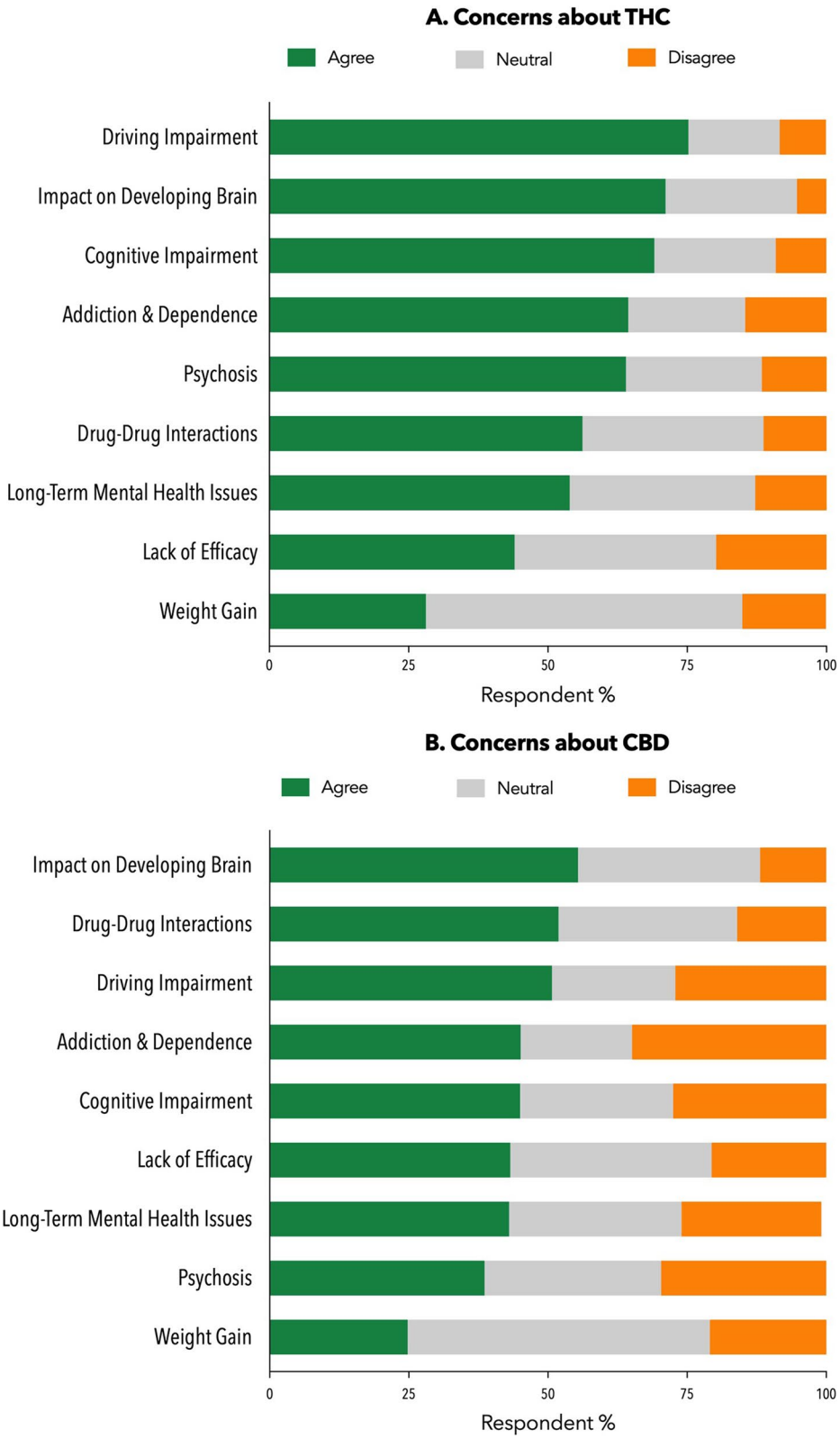

Fig. 4 Concerns around thesafety and efficacy of THC products (Panel **A**, *n*=505).Concerns aroundthe safety and efficacy of CBD products (Panel **B**, *n*=505). Numbers showpercentage of GPs (n=505) endorsing agreement, disagreement, and neutralityaround specific concerns

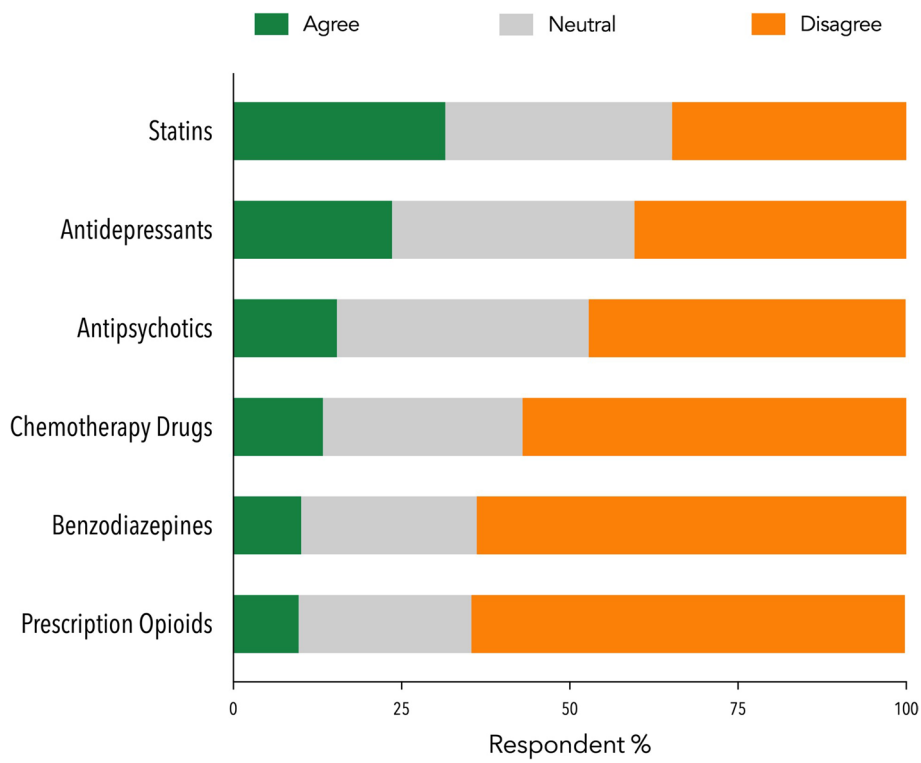

Fig. 5 GPs tended todisagree that MC products were "more hazardous" than commonly prescribedmedications (*n*=505)

28]. Furthermore, the evidence around the use of cannabis-based medicine in these indications has been well-reviewed and summarised in a variety of comprehensive guidance documents by organisations such as the TGA [2, 3, 21].

The extent of participating GPs support for the use of MC in anxiety, depression and insomnia was not well-endorsed relative to other indications, perhaps reflecting the limited evidence for MC efficacy in these conditions [29, 30]. Additional factors here may be the availability of relatively safe and effective conventional therapies for these conditions, as well as concerns around the impact of THC use on mental health [16, 27, 31]. When compared to the original survey however, participating GPs demonstrated increased support for the use of MC in most health conditions compared to the original survey (Supplementary Table 4) [7] and this included mental health conditions such as anxiety and PTSD as well as insomnia and chronic pain. This agrees with TGA data showing chronic pain, anxiety and sleep disturbance as the leading indications for SAS-B approvals [5].

Participating GPs who were MC prescribers had prescribed MC most often for chronic pain and anxiety (Supplementary Table 2). However, prescribing for these indications is supported by relatively sparse evidence [32–35]. Indeed, participating GPs were clearly aware of the limited evidence for clinical efficacy of MC, as has been noted in previous surveys [13, 16, 17, 31]. Widespread prescribing of MC in the absence of evidence suggests a patient-driven rather GP-driven process, or possibly that clinical efficacy is readily apparent to GPs but has yet to be properly captured by published clinical trials.

Concerns endorsed by GPs around THC included driving impairment, addiction and dependence; and are legitimate given current evidence [22, 36]. Some GPs expressed concern around THC causing weight gain; however, regular cannabis users tend to have a leaner phenotype than non-users [37, 38]. Legitimate concerns were expressed around drug-drug interactions with CBD [22]. However, concerns expressed around CBD causing driving and cognitive impairment are unfounded [39, 40]. Similarly, concerns existed around addiction and psychosis, yet CBD has shown some promise as a *treatment* for these conditions [41, 42]. Concerns around MC are therefore not always based on the most current evidence. The lack of endorsement for availability of low dose CBD products in pharmacies may reflect misconceptions around the safety of such products by GPs.

Despite safety concerns, few GPs believed the risk of side effects were "too high" (15.6% in the current survey vs. 19.8% in the original survey). Notably, GPs rated prescription opioids, benzodiazepines, and chemotherapy drugs as more hazardous than MC products, to a greater extent than the original survey [7]. This indicates increasing acknowledgement of the safety of cannabis-based medicines as clinical experience with MC grows.

The low perceived knowledge of GPs around MC, particularly amongst non-prescribers, is perhaps the most striking outcome of the survey and was reiterated in open-ended comments. Notably, most GPs (79%) endorsed the need for compulsory, MC-specific training for prescribers, a belief that has been maintained since the original survey (78.6%). Low knowledge has been highlighted repeatedly in previous surveys of physician around MC [13, 15–17, 26]. It is essential that GPs are supported in developing a sound knowledge around MC, regardless of whether they prescribe MC products or not. Professional organisations will play a leading role in educational initiatives in this area. Knowledge drives optimal patient care [7], and lack thereof may contribute to inadequate provision of support including missed or delayed treatment opportunities [43]. This should be a priority given the ongoing surge in demand for MC therapy.

There are around 4600 MC prescribers in Australia [5] of whom approximately 80% are thought to be GPs (i.e., around 3680) [12]. With a total of 31,000 GPs in Australia [44] MC prescribers were perhaps over-represented in our cohort (21%; 110/505) compared to the overall GP population (12%, 3680/31,000). The 505 GPs included in this study is only a small proportion of the total Australian population of ~31,000 GPs [45] such that issues of sample representativeness are worthy of consideration. Government data show Australian GPs to be 41.0% identifying as female, 40.0% aged ≥ 55 years and 32.1% located in NSW [45] compared to 59.8% identifying as female, 51.7% aged ≥ 55 years and 33.5% located in NSW respectively in the current study. Other limitations include recruitment being limited to GPs participating in continuing education and use of an on-line recruitment strategy due to the COVID-19 pandemic that may have biased the cohort towards more technologically adept GPs.

Conclusion

There is accelerating demand for MC products in Australia, in line with global trends [23]. GPs are well positioned to assist in the safe and efficacious use of cannabis-based medicines in the community. Training around MC is required to address the long-standing concerns of GPs around knowledge and confidence in this area. Findings from this study can be used to develop educational initiatives and promote best practice. Australia has the potential to act as exemplar for other countries in guiding high quality MC prescribing and product utilisation in a government-regulated model. Many countries, such as the United Kingdom, face similar access challenges as those of Australia but are yet to utilise GPs as independent MC prescribers, limiting MC prescribing approvals to specialists only [46, 47].

Abbreviations

MC: Medicinal cannabis; GP: General practitioners; THC: Tetrahydrocannabinol; CBD: Cannabidiol; SAS: Special Access Schemes; AP: Authorised Prescriber.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12875-022-01946-x.

Additional file 1: Table S1. Experiences around Patient Enquiries and Prescribing (*n*=505). **Table S2.** Indications that prescribers have treated with medicinal cannabis (*n*=110, valid percentage). **Table S3.** $\chi 2$ Test Values for each of the Knowledge questions in the GP Survey. **Table S4.** Differences in support for common MC indications between the current survey and the original survey (Karanges et al., 2018).

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Authors' contributions

Zeeta Bawa, Danielle McCartney, Ramesh Manocha and Iain S. McGregor contributed to the conception and design of the research project and/or output. Zeeta Bawa was involved in data acquisition; Zeeta Bawa, Danielle McCartney and Iain S. McGregor contributed to the analysis and interpretation of the research data; and authors all were involved in drafting and critically revising the manuscript and approved the final submitted version.

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Availability of data and materials

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics approval was granted by the University of Sydney Human Research Ethics Committee on September 17, 2021 (Ref: 2021/623) for this cross-sectional survey. All participants provided consent prior to completing the questionnaire. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing Interests

Authors ZB and DM declare they have no financial interests. ISM has received honoraria from Janssen, is currently a consultant to Kinoxis Therapeutics, and has received research funding and fellowship support from the Lambert Initiative, NHMRC and Australian Research Council. He holds a variety of patents for non-cannabinoid therapeutics. This survey was conducted at an online seminar run by Healthed and RM is the CEO of Healthed.

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Publisher's Note

CHAPTER 5. AN OPEN-LABEL FEASIBILITY TRIAL OF TRANSDERMAL CANNABIDIOL FOR HAND OSTEOARTHRITIS

Reader's note:

This chapter includes a co-authored publication. The bibliographic details of the co-authored paper, including all authors are as follows:

Bawa Z., Lewis D., Gavin P.D., Libinaki R., Joubran L., El-Tamimy M., Taylor G., Meltzer R., Bedoya-Pérez M., Kevin R.C., and McGregor I.S. An open-label feasibility trial of transdermal cannabidiol for hand osteoarthritis. *Scientific Reports*, 2024; 14(1):11792. https://doi.org/10.1038/s41598-024-62428-x

The research candidate has made the following contributions to this study:

- Developed the study design
- Prepared the clinical trial protocol
- Completed the human research ethics application
- Prepared the manuscript for submission to a peer-reviewed journal

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An open-label feasibility trial of transdermal cannabidiol for hand osteoarthritis

Zeeta Bawa[1,3], Daniel Lewis[4], Paul D. Gavin[5], Roksan Libinaki[5], Lida Joubran[5], Mahmoud El-Tamimy[5], Greg Taylor[6], Ryan Meltzer[6], Miguel Bedoya-Pérez[1,2], Richard C. Kevin[1,3] & Iain S. McGregor[1,2]✉

Hand osteoarthritis (OA) is an irreversible degenerative condition causing chronic pain and impaired functionality. Existing treatment options are often inadequate. Cannabidiol (CBD) has demonstrated analgesic and anti-inflammatory effects in preclinical models of arthritis. In this open-label feasibility trial, participants with symptomatically active hand OA applied a novel transdermal CBD gel (4% w/w) three times a day for four weeks to their most painful hand. Changes in daily self-reported pain scores were measured on a 0–10 Numeric Pain Rating Scale (NPRS). Hand functionality was determined via daily grip strength measures using a Bluetooth equipped squeeze ball and self-report questionnaire. Quality of life (QoL) ratings around sleep, anxiety, stiffness and fatigue were also measured. All self-report measures and grip strength data were gathered via smartphone application. Urinalysis was conducted at trial end to determine systemic absorption of CBD. Eighteen participants were consented and 15 completed the trial. Pain ratings were significantly reduced over time from pre-treatment baseline including current pain (− 1.91 ± 0.35, $p < 0.0001$), average pain (− 1.92 ± 0.35, $p < 0.0001$) and maximum pain (− 1.97 ± 0.34, $p < 0.0001$) (data represent mean reduction on a 0–10 NPRS scale ± standard error of the mean (SEM)). A significant increase in grip strength in the treated hand ($p < 0.0001$) was observed although self-reported functionality did not improve. There were significant ($p < 0.005$) improvements in three QoL measures: fatigue, stiffness and anxiety. CBD and its metabolites were detected at low concentrations in all urine samples. Measured reductions in pain and increases in grip strength seen during treatment reverted back towards baseline during the washout phase. In summary, pain, grip strength and QoL measures, using smartphone technology, was shown to improve over time following transdermal CBD application suggesting feasibility of this intervention in relieving osteoarthritic hand pain. Proof of efficacy, however, requires further confirmation in a placebo-controlled randomised trial.

Trial registration: ANZCTR public trials registry (ACTRN12621001512819, 05/11/2021).

Keywords Medicinal cannabis, Cannabidiol (CBD), Osteoarthritic pain, Chronic pain, Transdermal

Osteoarthritis (OA) is a common, heterogeneous disease of synovial joint cartilage, with inflammatory, biomechanical and genetic factors contributing to its aetiology[1,2]. Hand OA can significantly impact the quality of life (QoL), functionality and economic security of those affected[3]. The Framingham Community cohort study established lifetime prevalence rates of ~ 44% in women and ~ 38% in men[1]. Hand OA can be characterised into erosive hand OA, nodal hand OA and thumb base OA, each with its own phenotypes and risk factors[4,5]. Nonetheless, active hand OA symptoms are similar and include pain, stiffness, a reduction in grip and/or pinch strength, inflammation and bony enlargements known as *nodes*[4,6].

There are no disease modifying treatments for OA[5] and therapy focuses on symptom relief and preservation of function[5,7]. As such, the first-line therapy for symptomatically active hand OA involves topical non-steroidal anti-inflammatory drugs (NSAIDs). These are recommended for their superior safety profile compared to oral

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analgesics[5,8], but are limited in their ability to provide pain relief[9]. Oral analgesics are prescribed when there is insufficient relief of symptoms with topical medications. However, oral NSAIDs can lead to troublesome gastrointestinal, cardiovascular, renal adverse effects that are amplified in the elderly population[5,8]. Given the narrow range of treatment options for symptomatically active hand OA, there is an urgent need for the development of novel and efficacious treatment options, yet progress in this area has been slow, if not stationary[7].

Cannabidiol (CBD) is a non-intoxicating constituent of cannabis that has shown efficacy in the treatment of epilepsy, anxiety and psychosis[10–12]. Reviews of the literature suggest only limited available data around the efficacy of CBD in OA, chronic pain[13–15] and inflammation[16,17]. A 12-week randomised, double-blind, placebo-controlled trial of oral CBD (20–30 mg/day) as an add-on therapy in 136 patients with hand OA or psoriatic arthritis found no significant difference to placebo in the primary outcome measure of pain intensity during the past 24 h[18]. It should be noted, however, that 20–30 mg is a very low oral CBD dose[13]. In a trial of transdermal CBD for OA, adults with knee pain due to OA were treated with Zygel™, a transdermal synthetic CBD gel that was massaged onto the upper arm twice daily for 12 weeks[19]. While the primary endpoint was not reached in this trial (change in the 24-h average worst pain score at Week 12), the secondary endpoints (≥ 30 percent reduction in worst average daily pain scores and a ≥ 20 percent improvement in physical function scores) were met[19]. In a recent trial, the effects of six weeks of topical CBD (10 mg) applied twice a day to the legs were explored in 20 retired elite athletes who experienced chronic pain from acute lower extremity injuries. Self-reported pain was significantly improved including aspects of pain-related disability[20]. Finally, in two recent clinical studies involving COVID-19 and cancer patients respectively, CBD failed to demonstrate anti-inflammatory effects[16,17]. Preclinical studies, however, have demonstrated analgesic and anti-inflammatory effects of CBD in OA and other conditions[21–30]. For example, transdermal CBD gel applied four times daily significantly reduced pain-related behaviours and inflammation in rats with induced arthritic joints without any notable adverse effects[31]. Given this preliminary evidence, further exploration of the feasibility of using transdermal CBD as an intervention in OA is warranted.

Transdermal application has advantages for conditions that only require a localised action of CBD[32]. This route bypasses first-pass metabolism in the liver and gastrointestinal tract[32–34] and minimises adverse effects and drug-drug interactions associated with oral CBD doses[32], possibly promoting greater treatment adherence[32,35]. Transdermal treatments generally provide a superior safety profile compared to the oral analgesics used in the management of hand OA[5,36]. Indeed, the first-line therapy for symptomatic hand OA is topical non-steroidal anti-inflammatory drugs (NSAIDs)[5,8,36], although the reported effectiveness of these products has been less than ideal[9].

It is important to note that CBD is a highly lipophilic molecule[37]. While it penetrates the upper layers of the stratum corneum with ease, permeation into the deeper, relatively aqueous layers of the dermis is relatively low[34,37]. Consequently, various transdermal permeation enhancers have been trialled to increase CBD bioavailability[34,37–41]. The current study utilised a novel transdermal CBD gel preparation containing a mixture of two forms of phosphorylated vitamin E (i.e., a tocopheryl phosphate mixture (TPM)) as a permeation enhancer. Effects of this CBD formulation on hand pain and functionality in patients with symptomatically active hand OA were examined over a four-week intervention phase. It was hypothesised that treatment with transdermal CBD gel would decrease measures of pain and improve hand functionality.

Ethics approval

This study was approved by the Bellberry Ethics Committee on 1 February 2022 (Ref: 2021-07-787-A-1) and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki (1983). All participants provided written informed consent prior to enrolment into the study. This study was registered on the ANZCTR public trials registry (ACTRN12621001512819, 05/11/2021).

Method

Study design

This was a single-centre, interventional, feasibility trial. An overview of the study design is summarised in the Study Flowchart (Fig. 1). All participants completed the study at the same time. The study involved a one-week run-in phase which included a 4-day "Pre-baseline practise" phase where participants practised data acquisition procedures including use of the device for measuring grip strength. This was followed by a 3-day "Baseline" phase which provided the baseline comparator data for the intervention. During a four-week "Treatment" phase, participants were instructed to apply 0.25 mL of a transdermal 4% w/w CBD gel three times per day (~ 30 mg CBD per day) to the same hand (their most painful hand, that is, the "treated hand") while leaving the other hand untreated (the "untreated hand"). This is because hand OA does not always present bilaterally[42], precluding the uniform use of the untreated hand as a control. Participants were advised to base their self-reported outcome measures on the treated hand. At the end of the 4 week Treatment phase, participants underwent a one-week "Washout" phase during which the CBD transdermal gel was ceased while measurement of outcomes continued.

Participant population

The COVID-19 pandemic and the exploratory nature of the study limited recruitment to up to 20 participants. This sample size was chosen based on the number of long-term patients under the care of the trial physician who would likely meet the eligibility criteria for the trial. Participants met the inclusion criteria if they had painful symptomatic distal interphalangeal (DIP) nodal hand OA affecting at least three joints of the fingers and thumb, where at least one DIP node had 1) a pain severity of at least three on a 0–10 Numeric Pain Rating Scale (NPRS), and 2) pain on most days of the month for at least one month in the last year.

Exclusion criteria were as follows: (1) a history of or current inflammatory arthritis (examples: gout, psoriatic arthritis, and rheumatoid arthritis); (2) medications and/or medical conditions likely to change over the six-week

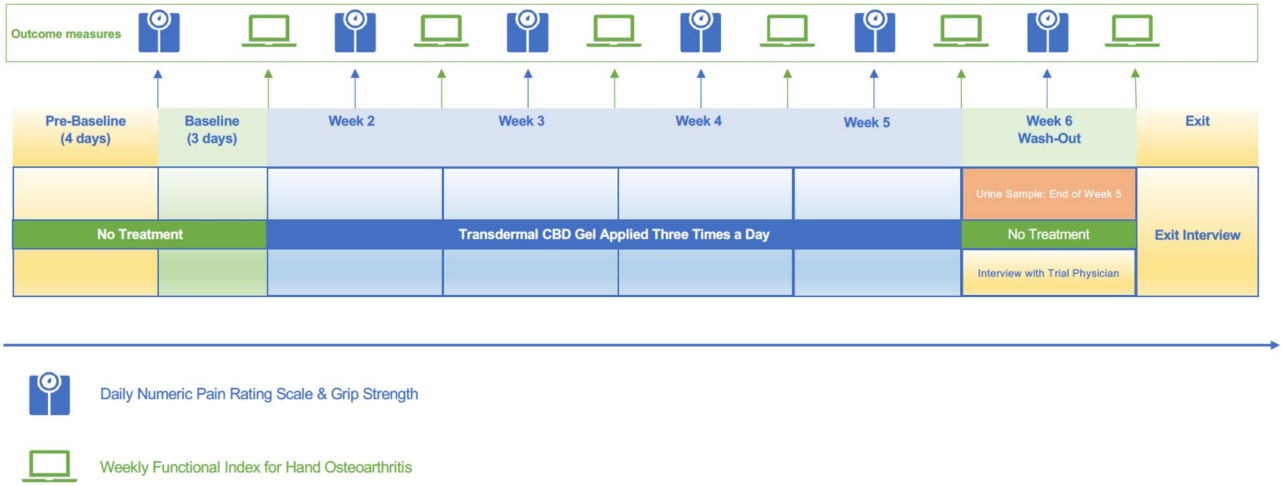

Figure 1. Study flowchart illustrating pre-baseline practise, baseline, treatment and washout phases of the trial.

trial phase; (3) prior surgery on the DIP joint(s); (4) pregnancy or lactation; (5) dermatological conditions of the hand; (6) use of cannabis, or cannabis-based products during the last three months; and (7) known allergies or hypersensitivity to cannabis-based products.

Recruitment, screening and enrolment

Participants with symptomatic hand OA were recruited from an outpatient rheumatology clinic in Victoria, Australia between February to March 2022. The trial physician conducted a thorough medical history of all volunteers and excluded those who noted recent use of cannabis or cannabis-derived products, including CBD. Volunteers were screened on-site and informed of the study risks. Volunteers reviewed the participant information sheet prior to providing written informed consent. Subsequently, the trial physician conducted a mandatory physical examination and medical history check prior to enrolling participants to the study. The trial physician also assisted participants to determine which of their hands would be treated and which would remain untreated. Participants attended a single group training session detailing the study procedures prior to commencing the trial.

Study treatment

The investigational product was a novel transdermal 4% w/w CBD gel containing tocopheryl phosphate mixture (TPM) that is used as a transdermal permeation enhancer[43]. TPM self-assembles into nanostructures in the presence of water, forming elastic vesicles able to encapsulate lipophilic molecules at high efficiency to increase their solubility in aqueous environments[43–45]. As reported for other highly elastic vesicle systems such as ethosomes[46] and transfersomes[47–49], TPM increases the dermal absorption of a variety of drug molecules[43]. Currently, two topical anti-inflammatory gels formulated with TPM (Voveran TPM® and Aquadol TPM Gel®) are marketed in India for the treatment of pain associated with OA[50,51].

As this was an early phase clinical trial, a compounding pharmacy in Victoria, Australia was used to prepare, package and label the investigational product. As permitted by Australian standards, the extemporaneous preparation of medicines by pharmacists is considered exempt from good manufacturing practice (GMP) licensing[52]. Furthermore, the compounding pharmacy had no role in the design or analysis of the study. Participants were provided with a single 30 mL pump pack and instructed to apply 0.25 mL three times per day (~ 30 mg CBD per day) to the treatment hand during the four-week Treatment phase.

Data collection

Participants were provided with free access to the "10tiv®" smartphone application (Fig. 2, the NTF group, v1.1.6, 2023 Australia) and a squeeze ball dynamometer (Fig. 3, Smart Stress Ball, 2019 China) which connected via Bluetooth to the 10tiv smartphone application. All outcome data submitted by participants were collected through the 10tiv smart phone application and stored in the 10tiv database, located in a secure Australian Amazon Web Services cloud server. No personally identifiable information was stored in the 10tiv database. Access to this database was limited to Australia and the research team using a username and password with two-factor authentication.

At 07:00 pm each day, participants received an automated mobile "push notification" to complete the day's outcome measures and further automated notifications were sent to participants in the event of missed submissions. The research team actively monitored participant response rates using the 10tiv data dashboard with real-time visibility of data capture and followed up repeated non-completions with a phone call from the trial coordinator. Throughout the trial, participants received weekly phone calls from the trial coordinator during which adverse event reports were collected.

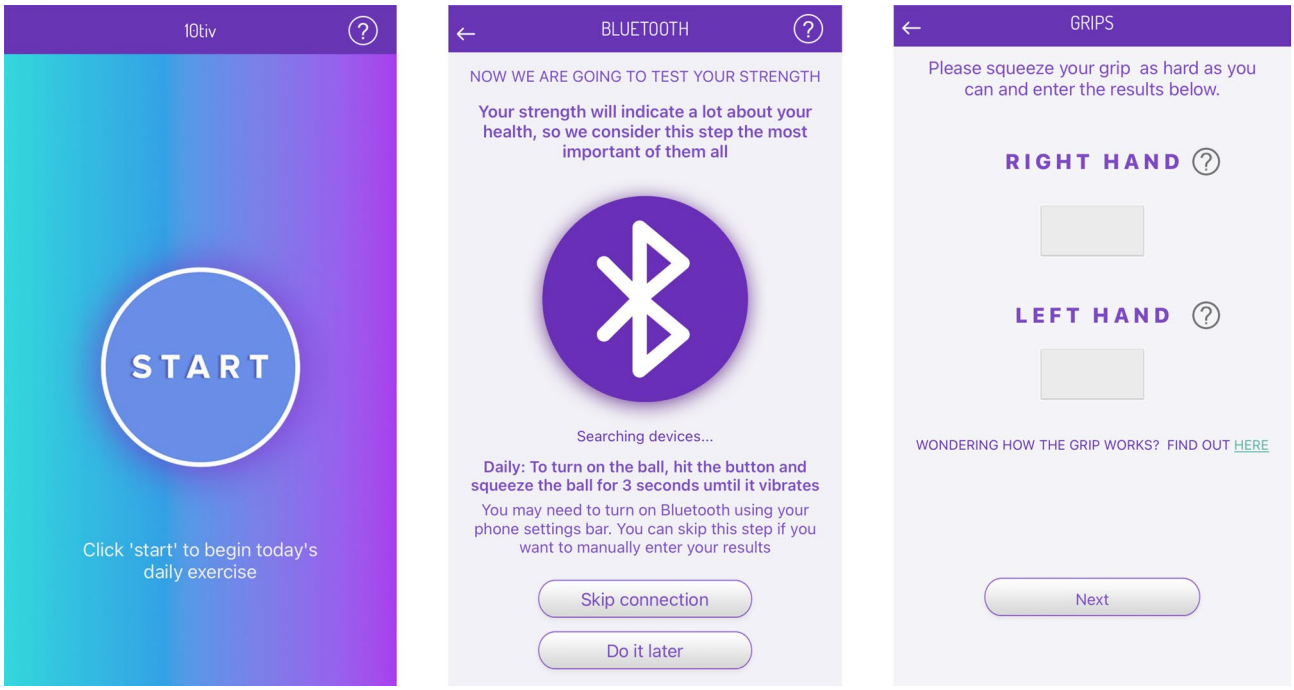

Figure 2. Screenshots of the 10tiv smartphone application displaying the grip strength questionnaire using the squeeze ball dynamometer.

Figure 3. Squeeze ball dynamometer (Smart Stress Ball, 2019 China) used by participants to record daily grip strength to their smartphones via Bluetooth.

Experimental procedure

Seven days were allocated to the trial's run-in phase as participants familiarised themselves with the 10tiv smartphone application and squeeze ball dynamometer. The first four days of the run-in were used as a Pre-baseline practise phase. The final three days of the run-in were used as a Baseline phase, with reported outcome measures across the three days averaged to calculate the Baseline scores against which the intervention was compared (see Fig. 1).

Participants submitted their outcome measures every evening during the trial's one-week run in, four-week intervention phase and one-week washout. On the first day of the Treatment phase (Day 8), participants commenced application of the transdermal CBD gel three times per day at approximately 08:00 am, 02:00 pm and 08:00 pm. This dose regimen was maintained throughout the Treatment phase (Weeks 2–5).

Participants were instructed to wash their hands prior to each application, thoroughly dry their hands, apply a single pump (0.25 mL) of the transdermal CBD gel to the back of the treatment hand and massage the gel into the skin surrounding the joints until dry. They were also instructed to refrain from washing the treated hand for at least 30-min after application. With regard to the untreated hand, participants were instructed not to apply any CBD gel to this hand and to rinse it thoroughly after each application of CBD gel to the treated hand. It is

expected that transdermal absorption of the CBD gel through the palm or fingertips of the untreated hand would be minimal due to the action of rinsing the hand immediately after application.

At the end of the four-week Treatment phase (i.e., on Day 35), participants collected and stored a single urine sample in a freezer until their final, in-person visit with the trial physician. The research team then batched and stored all participant samples at − 20 °C for ~ 3 days until they were transported using dry ice for analysis at the Lambert Initiative for Cannabinoid Therapeutics analytical chemistry laboratories. This aimed to determine whether CBD and its metabolites, 7-hydroxy-cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOH-CBD) could be detected and provided an indication of whether transdermal CBD application led to systemic absorption of CBD.

On the first day of the Washout phase (Day 36, Fig. 1), participants ceased transdermal CBD gel application but continued with the 10tiv-based submission of their outcome measures. At the conclusion of the trial, the trial coordinator completed a follow-up phone call with all participants to discuss their transition out of the trial.

Outcome measures

Primary outcome measure

Hand Pain. Subjective measures of hand pain were submitted daily using the Numeric Pain Rating Scale (NPRS), a validated diagnostic tool that measures pain intensity on a 11-point scale (0 (no pain) to 10 (extreme pain))[53,54]. Participants were asked three questions relating to hand pain (1) 'In your affected joints, how strong is your CURRENT pain?' (Current pain), (2) 'In your affected joints, how strong was your AVERAGE pain today?' (Average pain) and (3) 'In your affected joints, how strong was your WORST pain today?' (Maximum pain).

Secondary outcome measures

Grip Strength. Grip strength is defined as they amount of static force that a hand can generate through the motion of squeezing and provides an indication of functional integrity of the hand[55,56]. A squeeze ball dynamometer (Fig. 2) connected via Bluetooth to the 10tiv smartphone application was used to measure grip strength daily. For patients identifying their thumb as the most painful digit, pinch strength, that is, the use of only the index finger and thumb, was used as an alternative. The 10tiv smartphone application guided participants through a standardised process to capture grip or pinch strength data for both the treated and untreated hands.

FIHOA. The Functional Index for Hand OA is a validated questionnaire consisting of ten questions scored on a four-grade scale, allowing for the categorisation of functional impairment from 0 (no functional impairment) to 30 (maximal impairment). This outcome has been used in previous studies of OA[57–59]. In the current study, the FIHOA score was measured weekly throughout the study run-in, intervention phase and washout using the 10tiv smartphone application, allowing for the consideration of the change in hand functionality pre-/post-treatment.

Exploratory outcome measures

Subjective QoL measures. Subjective QoL Numeric Rating Scales (NRSs), delivered through the 10tiv smartphone application, were measured daily and included fatigue from 0 ('no unusual fatigue') to 10 ('significant unusual fatigue'), stiffness from 0 ('no stiffness') to 10 ('very stiff'), anxiety from 0 ('not anxious') to 10 ('very anxious') and sleep quality from 0 ('very disturbed') to 10 ('very improved'). These measures were not derived from a validated questionnaire, but rather included to provide simple numerical self-report of subjective troublesome symptoms of hand OA[36].

Urinary Cannabinoid Concentrations. The samples collected from participants on Day 35 were analysed by the Lambert Initiative for Cannabinoid Therapeutics analytical chemistry laboratory to determine urinary CBD, THC and metabolite concentrations (7-COOH-CBD, 7-OH-CBD, 11-OH-THC and 11-COOH-THC) using liquid chromatography-tandem mass spectrometry (LC-MS/MS) applying previous published methods[60,61]. Briefly, urine samples were hydrolysed with β-glucuronidase and analytes subsequently extracted using supported liquid extraction prior to quantification using a Shimadzu LCMS-8040 (Shimadzu Corp., Kyoto, Japan). All samples were analysed in triplicate and quantified against a seven-point standard curve, using deuterated forms of each analyte as internal standards.

Statistical methods

All data processing and statistical analyses were performed in R v 4.2.3[62]. All analyses included "participant" as the only random factor to account for the repeated measures design. Due to a skewness towards female participants (n = 11/15), gender was not included in any of the analyses to avoid overfitting. All graphs were created using GraphPad Prism v 9.5.1 for Windows (GraphPad Software LLC).

Ordinal variables, namely, Hand Pain NPRS, FIHOA and Subjective QoL NRSs, were analysed by Cumulative Link Mixed Models (CLMM) fitted with the Laplace approximation by the function *clmm* from the package "ordinal"[63]. *P*-values were generated by the type III Wald chi-square test using the function *Anova.clmm* from the package "RVAideMemoire"[64]. Each of these tests initially included Phase (Baseline, Treatment and Washout), time point (day for NPRS and NRS, and week for FIHOA), and their interaction as fixed factors. The models were further refined by removing fixed factors based on the corrected Akaike information criterion (AICc) calculated with the AICc from the package "MuMIn"[65]. We calculated Δm between models and excluded models with $\Delta m > 2$ as having substantially less support[66].

Grip Strength for the treated and untreated hands was analysed separately by two Generalised Linear Mixed Models (GLMM) by the function *glmer* from the package "lme4" version 1.1–30[67]. Residual plots, Shapiro–Wilk test of normality and Pearson's dispersion test were used to identify the best distribution (Gaussian, Gamma, or Inverse Gaussian) and link (Identity, Inverse, Log or Square root) for each model[68]. *P*-values were generated by the type III Wald chi-square test using the function *Anova* from the package "car"[69].

For all CLMMs and GLMMs, pairwise comparisons by Phase were performed using Dunn-Šidák corrections through the functions *emmeans*, with a time point covariate reduction, and "emtrends" from the package "emmeans"[70]. The threshold for statistical significance was set at $\alpha = 0.05$.

Consent for publication

Consent for the images used in Figs. 2 and 3 of this publication have been sought. The persons providing consent have been shown the article contents to be published. All other images are the property of the authors of this article.

Results

Eighteen participants were consented to the trial but three females were withdrawn by the trial physician prior to the collection of outcome measures due to no longer meeting the eligibility criteria (i.e., ongoing or a history of cannabis-based therapy during the last three months (n = 2) and rheumatoid arthritis diagnosis (n = 1)). A total of 15 participants were included in the final data analysis.

As this is an open label trial with a single treatment arm, an intention to treat analysis (ITT) was not used as there were no data to analyse for the withdrawn participants. ITT analyses are typically used in randomised controlled trails with more than one treatment arm.

On average, the daily participation in submission of outcome measures was 96% with only one participant failing to complete outcome submissions at a level of 90% or above.

Demographic characteristics

Participant (n = 15) demographic characteristics are summarised in Table 1. The most common characteristics were Australian ethnicity (66.7%), female gender (73.3%), an age between 60 and 69 years old, having a Bachelor's degree (53.3%), a retired employment status (66.7%) and a managerial (33.3%) or professional (33.3%) occupation.

Characteristic	N = 15	%
Gender identity		
Male	4	26.7%
Female	11	73.3%
Age		
50–59	1	6.7%
60–69	8	53.3%
70–79	4	26.7%
> 80	1	6.7%
Ethnicity		
Australian	10	66.7%
European	5	33.3%
Grip strength		
Hand[a]	13	86.7%
Thumb[b]	2	13.3%
Education		
Bachelor's degree	8	53.3%
High school	5	33.3%
Master's degree	2	13.3%
Employment status		
Retired	10	66.7%
Self-employed	2	13.3%
Part-time employment	1	6.7%
Full-time employment	2	13.3%
Occupation		
Manager	5	33.3%
Clerical and administrative work	2	13.3%
Professionals	5	33.3%
Community and personal services workers	3	20.0%

Table 1. Demographic characteristics of participants in this study (n = 15). [a]Participants identifying a finger other than the thumb as the most painful digit; these participants used the whole hand to measure grip strength. [b]Participants identifying their thumb as the most painful digit; these participants used only the index finger and thumb to measure "pinch" strength (that is, an alternative to grip strength).

Hand pain

Current hand pain scores were affected by Phase (Baseline, Treatment and Washout) ($X^2_2 = 6.169$, $p = 0.046$) and by the interaction between Phase and Day ($X^2_3 = 68.320$, $p < 0.0001$). Average daily hand pain scores were affected only by the interaction between Phase and Day ($X^2_3 = 61.870$, $p < 0.0001$) and Phase trended towards a significant effect ($X^2_2 = 5.697$, $p = 0.058$). Maximum daily hand pain scores were affected only by the interaction between Phase and Day ($X^2_3 = 46.000$, $p < 0.0001$) but not by Phase alone ($X^2_2 = 3.742$, $p = 0.154$). All hand pain scores were lower during CBD gel application (Treatment phase) than Baseline (Table 2). All hand pain scores were also lower during Washout phases compared to Baseline (Table 2, $p < 0.0001$), and there was no difference between Treatment and Washout phases (Current pain $p = 0.963$, average pain $p = 0.997$ and maximum pain $p = 0.998$).

Current and average daily hand pain scores decreased over time within the Treatment phase (Current pain slope = − 0.098 ± 0.013 and average pain slope = − 0.094 ± 0.013) (mean ± SEM) compared to Baseline (Current pain slope = 0.938 ± 0.396, $p = 0.027$; and average pain slope = 0.873 ± 0.381, $p = 0.034$) (Fig. 4). In contrast, the change over time during the Washout phase (Current pain slope = 0.015 ± 0.105 and average pain slope = 0.014 ± 0.226) was not different from the Baseline phase ($p = 0.071$ and $p = 0.087$, respectively) or Treatment phase ($p = 0.633$ and $p = 0.672$, respectively) (Fig. 4). Maximum daily pain scores demonstrated a decreasing trend over time during the Treatment phase (slope = − 0.080 ± 0.012) and an increasing trend during Baseline (slope = 0.260 ± 0.380) and Washout (slope = 0.143 ± 0.101) (Fig. 4). However, these slopes were not significantly different ($p > 0.05$ for all comparisons).

Grip strength

Grip strength in the treated hand was affected by Phase (Baseline, Treatment and Washout) ($X^2_2 = 17.336$, $p < 0.0001$), Day ($X^2_1 = 20.021$, $p < 0.0001$) and the interaction between Phase and Day ($X^2_2 = 39.969$, $p < 0.0001$).

	Baseline	Treatment	Washout
Current pain mean	5.15 ± 0.23	4.10 ± 0.07	4.20 ± 0.16
Average pain mean	5.45 ± 0.18	4.47 ± 0.07	4.48 ± 0.15
Maximum pain mean	5.57 ± 0.28	4.36 ± 0.10	4.30 ± 0.17

Table 2. Mean (± SEM) numeric pain rating scale scores for current, average and maximum pain during the baseline, treatment and washout phases of the trial.

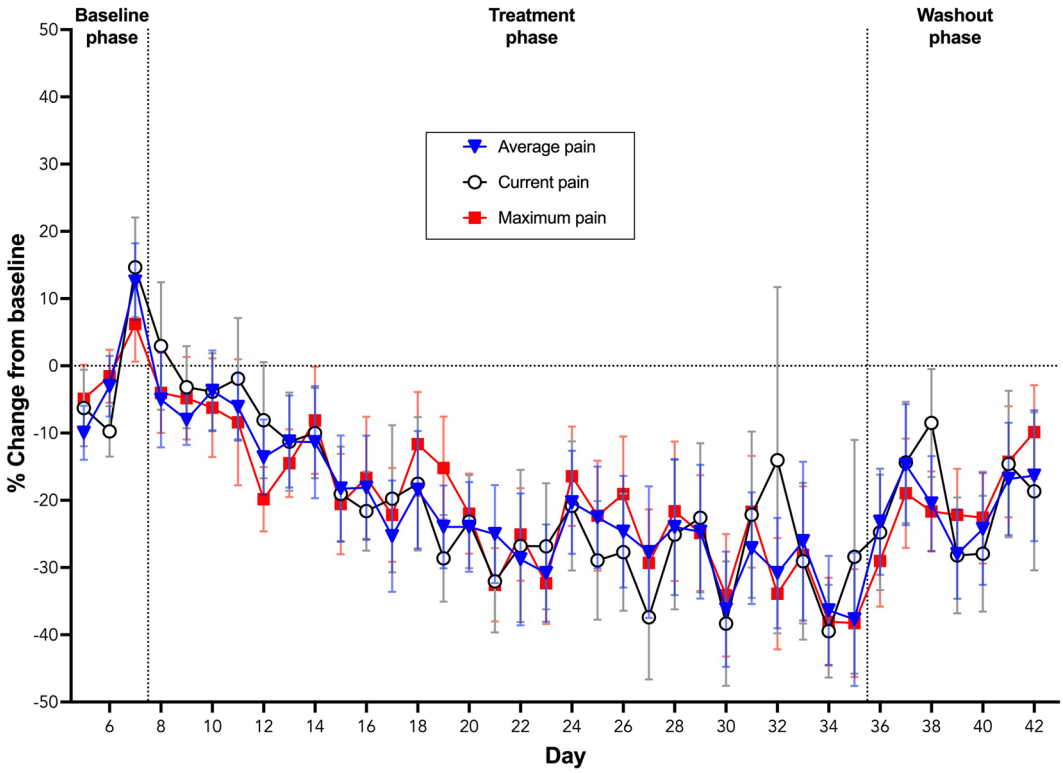

Figure 4. Percentage change from baseline (% ± SEM) for daily hand pain scores (average, current and maximum) during the baseline, treatment and washout phases of the trial.

Grip strength in the untreated hand was not affected by Phase (Baseline, Treatment and Washout) ($X^2_2 = 0.048$, $p = 0.976$), Day ($X^2_1 = 0.047$, $p = 0.828$) or by the interaction between Phase and Day ($X^2_2 = 0.021$, $p = 0.989$).

Pairwise comparisons showed no differences in Grip strength in the treated hand during the Treatment or Washout phases relative to Baseline. However, Grip strength in the treated hand increased over time during the Treatment phase (slope = 0.013 ± 0.004) (mean ± SEM) compared to the Baseline phase (slope = − 0.041 ± 0.009, $p < 0.0001$) (Fig. 5). In contrast, the change over time during the Washout (slope = − 0.022 ± 0.035) was not different from either the Baseline ($p = 0.942$) or Treatment phase ($p = 0.675$) (Fig. 5).

Functional index for hand osteoarthritis

Participant FIHOA scores were not affected by either Phase ($X^2_2 = -2.788$, $p = 1.000$) or Week ($X^2_1 = -10.098$, $p = 1.000$).

Subjective QoL NRS measures

Fatigue scores were not affected by Day ($X^2_1 = 1.522$, $p = 0.217$) or Phase ($X^2_2 = 4.869$, $p = 0.088$). Sleep scores were affected by Day ($X^2_1 = 9.985$, $p = 0.002$), but not by Phase ($X^2_2 = 3.831$, $p = 0.147$). Stiffness scores were affected by Phase ($X^2_2 = 15.565$, $p < 0.0001$) and Day ($X^2_1 = 16.919$, $p < 0.0001$). Anxiety scores were affected by Phase ($X^2_2 = 25.093$, $p < 0.0001$) and Day ($X^2_1 = 9.448$, $p = 0.002$). Regardless of Phase, sleep scores increased across days ($Z = 3.154$, $p = 0.002$), while a decrease across days was recorded for stiffness ($Z = -4.086$, $p < 0.0001$) and anxiety ($Z = -3.026$, $p = 0.002$).

Overall scores were lower during the Treatment phase for fatigue ($p = 0.014$), stiffness ($p = 0.004$) and anxiety ($p < 0.0001$) (Fig. 6) compared to the Baseline phase. During Washout, scores for fatigue ($p = 0.009$) and anxiety ($p < 0.0001$) remained lower compared to the Baseline phase, while scores for stiffness did not differ compared to either Baseline ($p = 0.054$) or the Treatment phases ($p = 0.772$) (Fig. 6).

Urinary cannabinoid concentration

Urine samples taken from participants on the last day of the Treatment phase (day 35, Week 5) with transdermal CBD showed detectable urinary cannabinoids including CBD (10.12 ± 2.89 ng/mL) (mean ± SEM); the primary metabolite 7-OH-CBD (25.79 ± 5.13 ng/mL); and the terminal metabolite 7-COOH-CBD (9.88 ± 1.03 ng/mL) (Fig. 7). There was no detection of THC or THC metabolites in any of the urine samples.

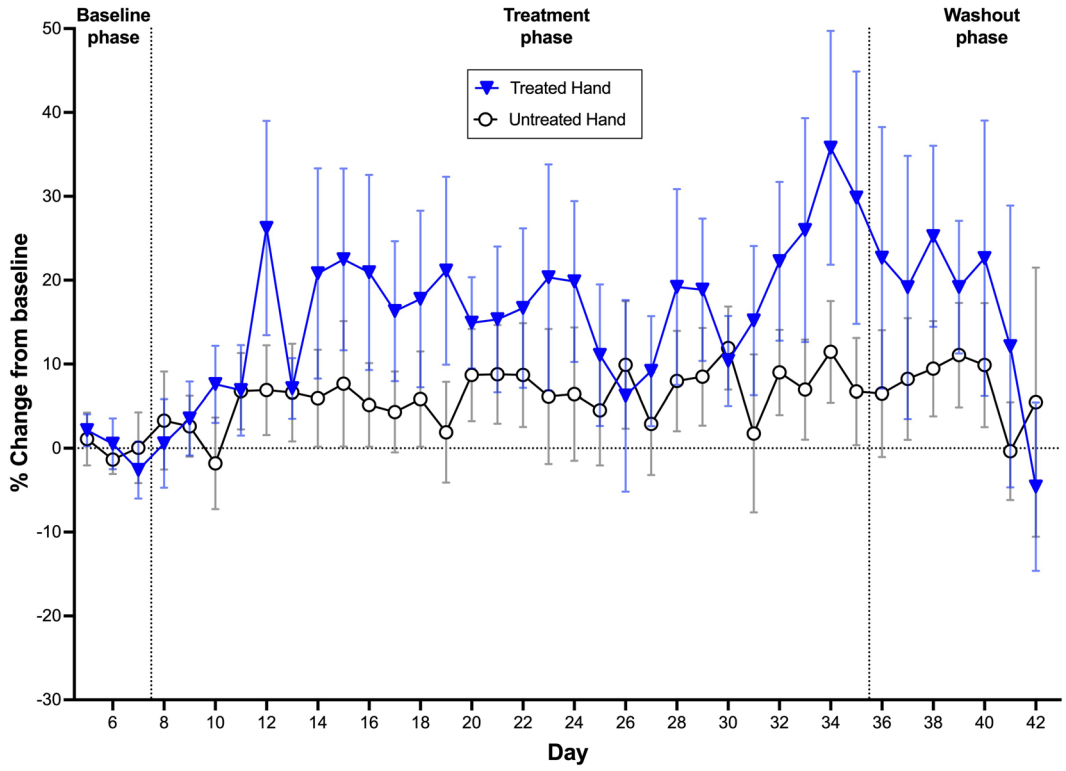

Figure 5. Percentage change from baseline (% ± SEM) for daily grip strength scores of the treated and untreated hands during the baseline, treatment and washout phases of the trial. *Note* the grip strength of the untreated hands is not used as a control and acts only as a reference point.

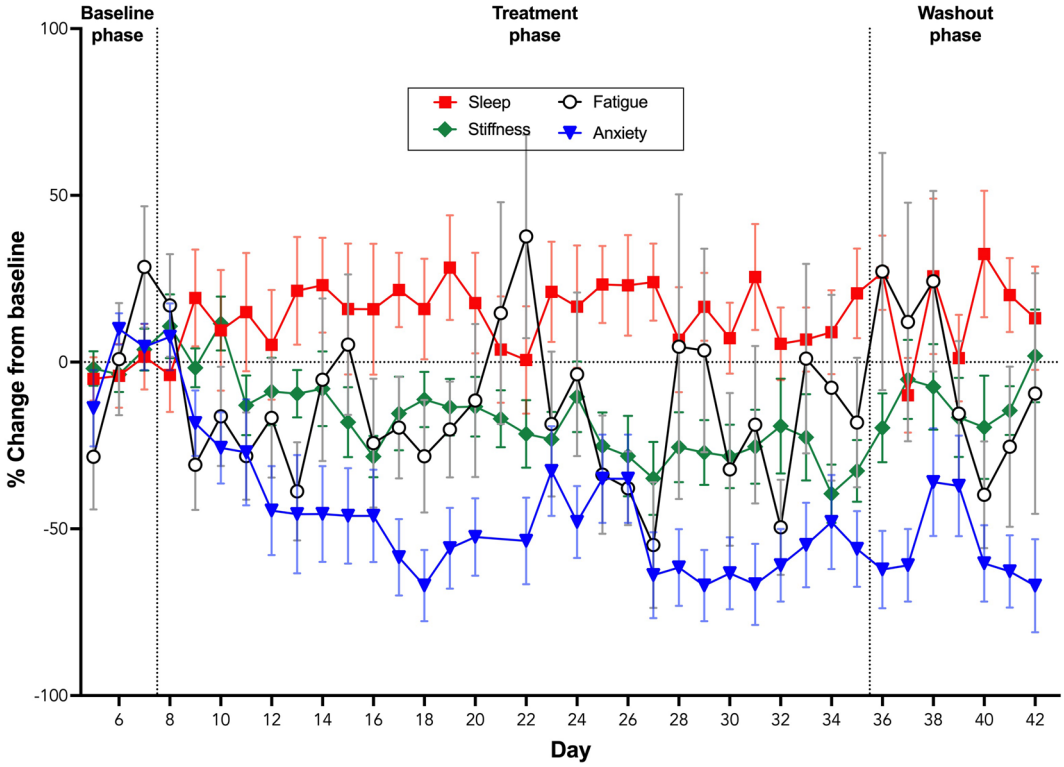

Figure 6. Percentage change from baseline (% ± SEM) for daily self-report of anxiety, fatigue, sleep and stiffness scores during the baseline, treatment and washout phases of the trial.

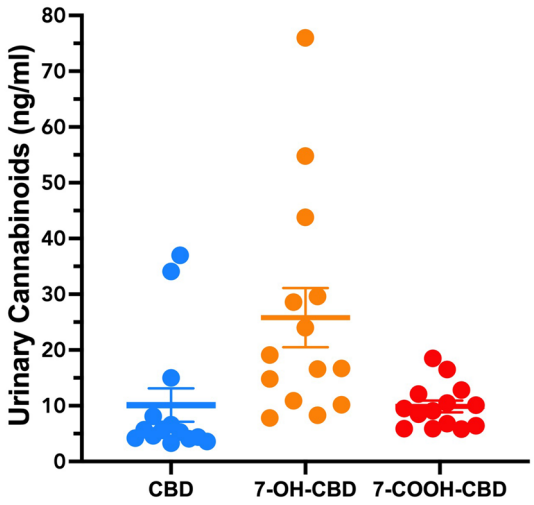

Figure 7. Urinary cannabinoid concentrations of participants (n = 15) at the end of the treatment phase (day 35).

Adverse effects

During weekly follow-up phone calls with the trial coordinator, a total of 31 mild adverse events (AE) reports were received ('headache'(n = 6), 'back pain'(n = 4), 'neck pain' (n = 3), 'shoulder pain' (n = 3), 'reflux' (n = 3), 'allergy' (n = 3), 'pain' (n = 2), 'could not sleep' (n = 2), 'gastritis' (n = 1), 'cramps' (n = 1), 'pain in body' (n = 1), 'full body pain' (n = 1) and 'inflammation' (n = 1)). One 'moderate' AE report was received ('tooth extraction pain after surgery'). Most of these adverse effects resolved within the day.

Discussion

The current study explored the effects of a novel, transdermal 4% w/w CBD gel applied three times a day over a four-week treatment phase in patients with symptomatically active hand OA. Innovative features of the trial include the use of a novel smartphone application and Bluetooth squeeze ball dynamometer technology. The primary outcome, namely a significant reduction in hand pain relative to baseline, was met. There was also a significant improvement in hand functionality, measured by grip strength of the treated hand during the Treatment phase compared to the Baseline. However, self-reported hand functionality, measured by the FIHOA questionnaire, was not significantly improved by treatment. Participants in this study also experienced significant improvement in QoL measures relating to anxiety, stiffness and fatigue, but not sleep quality. Systemic absorption of the study drug was confirmed by the presence of CBD and its metabolites in urine samples. Participants demonstrated a high level of proficiency with the technological aspects of the trial.

Self-reported current, average and maximum hand pain were significantly reduced during treatment with transdermal CBD gel. Summary data (Table 2) suggests a somewhat variable reduction in pain across participants. Differences in the structure and integrity of participants skin can affect transdermal absorption[71,72] and this may partly explain variations in responses to treatment between participants. When normalised by baseline values, however, a ~ 30% reduction in pain scores become evident (Fig. 4). A reduction of approximately 2-points, or 30% in an 11-point NPRS is considered a clinically significant difference[73]. Despite these findings, it is well known that placebo responses contribute significantly to pain reductions seen in many randomised clinical trials of medicinal cannabis and other interventions. Caution is therefore necessary in interpreting these results and placebo-controlled randomised clinical trials will be necessary to give definitive evidence of efficacy[74].

Urinalysis conducted at the end of the Treatment phase confirmed that CBD achieved some systemic absorption after topical application of the gel. Reductions in anxiety and fatigue measures in participants could conceivably involve central effects of topically applied CBD. Urinary concentrations of CBD and its metabolites were modest however relative to those reported following orally administered CBD (120–480 mg)[75]. The long latency in the return of pain during washout might indicate possible development of a depot of CBD in the stratum corneum of the skin[35].

The effect of CBD on pain and inflammation is not entirely understood due to the highly complex signalling mechanisms that are engaged by the drug[76]. As well has having indirect modulatory effects on CB1 and CB2 cannabinoid receptors, CBD also affects the serotonin 1A receptor (5-HT1A), G protein-coupled receptors 55 (GPR55) and 18 (GPR18) and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) and TRP ankyrin 1 (TRPA1), amongst others[12,21,23]. Preclinical evidence suggests that modulation of TRPV1, TRPA1, CB1 and CB2 receptors provides analgesic and anti-inflammatory effects relevant to the development of OA[25,26,29,30,77], and that CBD reduces inflammation[78]. It is plausible that CBD provides indirect analgesic effects by moderating synovitis, synovial thickening and effusion in hand OA[79]. Future studies of transdermal CBD would therefore benefit from the additional use of objective measures of hand OA such as X-ray imaging and biomarkers of hand OA to determine possible mechanisms of action or disease modifying effects[80,81].

Pain is the cardinal driver for treatment-seeking in hand OA and is often used to gauge disease progression and the effectiveness of treatment[82–84]. Damage to an osteoarthritic joint can cause a combination of inflammatory, nociceptive, and neuropathic pain that is generally chronic and difficult to treat[85]. These differing pain phenotypes are suggested in the wide variability of treatment response between patients and may also signal the subjective perception of pain itself[86]. The complication of inadequate pain relief in hand OA is compounded by the limited range of treatment options currently available[36]. Consequently, transdermal CBD may present a novel and safe treatment option for hand OA.

Hand OA leads to a deterioration in grip strength[55]; in one study, women with hand OA had average grip strength measures 60% less than controls[87]. Grip strength is considered a simple, reliable and inexpensive measure of hand function[5,42]. In the current study, there were encouraging improvements in grip strength during the treatment phase. It could be speculated that this improvement related to the daily use of the squeeze ball dynamometer. However, there is only low-quality evidence indicating small beneficial effects of exercise on grip strength in hand OA[87,88]. Furthermore, the grip strength of the untreated hand was not improved during the Treatment phase, despite daily use of the squeeze ball dynamometer.

Despite improved grip strength, there were no improvements in participants' FIHOA scores. FIHOA requires participants to answer 10 questions around their hand functionality considering a range of activities in the previous week. Notably, some of these queries may not be relevant to all participants. For example, "*For women*—are you able to sew? *For men*—are you able to use a screwdriver?" This may distort results and this would be compounded further if the non-dominant hand of participants was used as the treated hand in this study. Notably, most of the participants in this study were over the age of 60 years and female, in line with general population estimates for hand OA[1,36]. The sensitivity of FIHOA in detecting functional improvement in this cohort remains somewhat unclear.

Participants in this study reported significant improvements in subjective measures of anxiety, stiffness and fatigue, but not sleep quality, during the Treatment phase of the study. CBD has demonstrated anxiolytic effects in previous studies; however, these effects are generally seen at oral CBD doses ≥ 300 mg[89–93]. Consequently, it is likely that the reductions in subjective anxiety, and fatigue, are an indirect effect resulting from improved pain outcomes in the current study rather than a direct pharmacological effect of CBD. Similarly, the significant improvements in subjective stiffness may be an indirect effect of the anti-inflammatory properties of CBD[21,23–26,28–30,94] which in turn could be responsible for the objective increase in grip strength. The improvements in pain outcomes in the current study did not appear to improve sleep.

Significant limitations in the current study should be acknowledged: this was a non-randomised, interventional, feasibility trial involving a small number of participants. A significant placebo effect is seen

in many randomised controlled trials of interventions for chronic pain and the lack of placebo is therefore a significant limitation. No blood samples were taken during the study limiting our understanding of the pharmacokinetics of the study drug. Positive aspects of the current study include use of novel smartphone technology that was secure and instantaneous, and led to excellent rates of compliance and retention in study participants. This internet-based study provided a cost-effective and convenient methodology for participants with varying levels of functional impairment due to their hand OA, benefits that have been demonstrated in other internet and/or smartphone application-based studies of hand OA[84,95].

Conclusion

The current study suggests that transdermal CBD gel may have a beneficial effect on pain and grip strength in participants with symptomatic hand OA but requires further exploration in a randomised controlled trial. There has been an urgent call for proof-of-concept trials, including those with negative results, to help illuminate the pathogenic mechanisms of hand OA[5]. This pilot study contributes towards closing this evidence gap and demonstrates that transdermal CBD may provide some promise for a safe treatment option for symptomatically active hand OA. Further research should incorporate a double blind, randomised study design with greater participant numbers and more comprehensive pharmacokinetic and biomarker analysis.

Data availability

The trial data are available from the corresponding author on reasonable request.

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Author contributions

I.S.M., D.L., P.G., M.E.T., R.L. and Z.B. were involved in the conception and design of the research project and/or output. D.L., P.G., R.L., L.J., M.E.T., G.T., R.M. were involved in data acquisition. Z.B., D.L., P.G., R.L., M.B.P.,

G.T., R.M., R.K. and I.S.M. contributed to the analysis and interpretation of the research data; and all authors were involved in drafting and critically revising the manuscript and approved the final submitted version.

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Competing interests
Author I.S.M. acts as a consultant to Kinoxis Therapeutics and has received honoraria from Janssen. He has also served as an expert witness in various medicolegal cases involving cannabis and cannabinoids. I.S.M. hold patents on cannabinoid therapies (PCT/AU2018/05089 and PCT/AU2019/050554) and has received consulting fees from the Medicinal Cannabis Industry Australia (MCIA). Avecho Biotechnology Ltd donated the investigational product for this trial and did not receive payment for their contributions. P.G, R.L, L.J and M.E.T are employees of Avecho Biotechnology Ltd. The NTF Group did not receive payment for their contribution to this study and provided free access to the squeeze ball dynamometers and the 10tiv smartphone application. G.T is the owner and director of The NTF Group. R.M was an employed consultant of The NTF Group and has no other competing interests to declare. Z.B, D.L, M.B.P and R.C.K have no disclosures to report.

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CHAPTER 6. EFFECTS OF CANNABIDIOL ON PSYCHOSOCIAL STRESS, SITUATIONAL ANXIETY, AND NAUSEA IN A VIRTUAL REALITY ENVIRONMENT: A PROTOCOL FOR A SINGLE-CENTRE RANDOMISED CLINICAL TRIAL

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- Developed the study design
- Prepared the clinical trial protocol
- Completed the human research ethics application
- Conducting participant recruitment and data acquisition
- Prepared the protocol manuscript for submission to a peer-reviewed journal

BMJ Open

Effects of cannabidiol on psychosocial stress, situational anxiety and nausea in a virtual reality environment: a protocol for a single-centre randomised clinical trial

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ABSTRACT

Introduction The non-intoxicating plant-derived cannabinoid, cannabidiol (CBD), has demonstrated therapeutic potential in a number of clinical conditions. Most successful clinical trials have used relatively high (≥300 mg) oral doses of CBD. Relatively few studies have investigated the efficacy of lower (<300 mg) oral doses, typical of those available in over-the-counter CBD products.

Methods We present a protocol for a randomised, double-blind, placebo-controlled, parallel-group clinical trial investigating the effects of a low oral dose (150 mg) of CBD on acute psychosocial stress, situational anxiety, motion sickness and cybersickness in healthy individuals. Participants (n=74) will receive 150 mg of CBD or a matched placebo 90 min before completing three virtual reality (VR) challenges (tasks) designed to induce transient stress and motion sickness: (a) a 15 min 'Public Speaking' task; (b) a 5 min 'Walk the Plank' task (above a sheer drop); and (c) a 5 min 'Rollercoaster Ride' task. The primary outcomes will be self-reported stress and nausea measured on 100 mm Visual Analogue Scales. Secondary outcomes will include salivary cortisol concentrations, skin conductance, heart rate and vomiting episodes (if any). Statistical analyses will test the hypothesis that CBD reduces nausea and attenuates subjective, endocrine and physiological responses to stress compared with placebo. This study will indicate whether low-dose oral CBD has positive effects in reducing acute psychosocial stress, situational anxiety, motion sickness and cybersickness.

Ethics and dissemination The University of Sydney Human Research Ethics Committee has granted approval (2023/307, version 1.6, 16 February 2024). Study findings will be disseminated in a peer-reviewed journal and at academic conferences.

Trial registration number Australian New Zealand Clinical Trials Registry (ACTRN12623000872639).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will use a rigorous randomised, double-blind, placebo-controlled design to investigate the effects of a low oral dose (150 mg) of cannabidiol (CBD).
⇒ The dose of CBD provided (ie, 150 mg) will be comparable to those available over-the-counter in many countries.
⇒ Virtual reality will be used to administer safe, realistic and precisely reproducible test paradigms that induce transient stress and nausea in volunteers.
⇒ Blood samples will not be obtained to verify plasma CBD concentrations as venepuncture has the potential to induce extraneous stress.

INTRODUCTION

Cannabidiol (CBD) is a non-intoxicating constituent of the *Cannabis sativa* plant.[1 2] It has a good safety and tolerability profile[3–7] and a diverse range of pharmacological targets, including the serotonin receptors (eg, 5-HT1A), G protein-coupled receptors (eg, GPR55 and GPR18) and transient receptor potential ion channels (eg, TRPA1).[8–10] CBD has demonstrated therapeutic potential in several clinical conditions,[4 5] including anticonvulsant effects in paediatric epilepsy,[11–13] anxiolytic effects in anxiety disorders,[14 15] antipsychotic effects in schizophrenia[16 17] and 'anti-addiction' effects in substance use disorders.[18 19] These clinical benefits are typically observed at relatively high oral doses of CBD (eg, ~300–1500 mg).[4 5]

In regions such as North America and Europe, CBD is available as both a prescription drug and a 'nutraceutical product'.[20] These nutraceutical or 'wellness' products are typically oral formulations (eg, oils, capsules, gummies) that contain low doses of CBD (ie, ≤150 mg/day) and are widely available in health food stores and pharmacies.[20 21] In Australia, regulation of 'low-dose CBD products' (containing ≤150 mg/day) was recently eased to allow patients without a prescription

access to registered products in pharmacies. However, registration of such products requires approval by Australia's medicines regulator based on demonstrated efficacy and safety.[22] With no products having been registered in the ~3 years since these regulatory changes were enacted (December 2020),[22] questions about whether CBD can demonstrate efficacy at these lower doses have been raised.

Indeed, a recent review found little high-quality evidence to support the efficacy of CBD (in any conditions) at doses ≤200 mg. This review acknowledged, however, that such doses were under-studied.[21] Some promising results have been obtained with public speaking tasks designed to induce 'psychosocial stress' in healthy volunteers when 300 mg CBD was administered.[23 24] Therefore, further research investigating the anxiolytic effects of low to moderate oral doses of CBD is warranted. It should be noted that the oral bioavailability of CBD is limited (~13%–19%) but may be enhanced by certain lipid-rich formulations or by administration with fatty foods.[6 25] The current study will use a proprietary blend of tocopherol phosphates (so called 'Tocopheryl Phosphate Mixture' (TPM)), which has been shown to increase the bioavailability of lipid-soluble substances.[26 27]

Virtual reality (VR) technologies are increasingly being used to investigate psychosocial stress and anxiety in laboratory studies.[28 29] This approach allows for minimal resourcing relative to 'real-world' studies, customisable and reproducible test paradigms and the accurate monitoring and recording of key outcomes.[29 30] Furthermore, VR provides the advantage of simulating physiologically provoking activities without real danger, for example, walking a plank over a sheer drop. However, the use of VR is often accompanied by motion sickness (a pattern of symptoms that arise from exposure to stimuli involving significant visual or physical motion) and cybersickness (a subtype of motion sickness that arises specifically due to exposure to VR).[31–34] CBD has shown antinausea and antiemetic effects in preclinical studies involving laboratory animals.[35–37] Interestingly, two of these studies demonstrated that CBD administered intraperitoneally at low doses (2.5–10 mg/kg) but not higher doses (25 and 40 mg/kg) reduced toxin-induced vomiting in house musk shrews.[35 36] CBD also reduced vomiting in human studies when used in combination with Δ^9-tetrahydrocannabinol to treat chemotherapy-induced nausea and vomiting.[38] Accordingly, the current study will investigate CBD's possible antinausea effects in participants by exposure to VR scenarios.[29]

We have developed a series of three unique VR challenges for the current trial. The 'Public Speaking' task was adapted from studies that explored the anxiolytic effects of CBD during public speaking challenges[23 24 39] and will allow us to determine the effects of CBD during social threat (ie, psychosocial stress). The 5 min 'Walk the Plank' task has been modified from previous VR studies requiring participants to walk along a narrow virtual plank above a precipitous drop, inducing physiological markers of acute anxiety[40–42] (ie, 'situational anxiety'). Finally, the 'Rollercoaster Ride' task challenges participants to complete a virtual rollercoaster ride and has been modelled from VR rollercoaster ride paradigms that have been reliably used to induce motion sickness and cybersickness in participants.[32 43 44]

In summary, the current protocol describes a study that aims to investigate the effects of low-dose (150 mg) CBD versus placebo on VR-induced acute psychosocial stress, situational anxiety, acute motion sickness and cybersickness in healthy individuals.

METHODS

Study design

This study is a randomised, double-blind, placebo-controlled, parallel-group, clinical trial comparing the efficacy of low-dose CBD (150 mg) versus placebo. The study is known as the CAPSTAN (Cannabidiol for Acute Psychosocial Stress and Nausea) clinical trial. A crossover design was deemed unsuitable due to the high likelihood of trial-order effects (eg, habituation to the VR scenarios).[32]

The trial sponsor is the University of Sydney, and the trial site is the Brain and Mind Centre in Sydney, Australia. The study has been approved by the University of Sydney Human Research Ethics Committee (HREC; 2023/307, version 1.6, 16 February 2024) and registered on the Australian New Zealand Clinical Trials Registry (15 August 2023). The study is financially supported by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for cannabinoid research at the University of Sydney. Recruitment commenced on 9 October 2023 and is anticipated to conclude in mid-2024.

Participant population

Inclusion criteria

We aim to recruit 74 participants who will be: (a) healthy adults aged between 18 and 50 years; (b) proficient in English and able to provide informed consent; (c) residing in the Greater Sydney region of New South Wales, Australia and (d) willing to follow the protocol requirements.

Exclusion criteria

The following exclusion criteria will apply:

- Self-reported regular use (ie, more than two times a week) in the past 2 weeks of:
  - Cannabinoid-containing products (eg, cannabis or CBD).
  - Psychotropic drugs (prescriptive or illicit) (eg, cannabis, amphetamines, cocaine, ecstasy (MDMA), LSD (acid), antidepressants, antiepileptics, opioids, benzodiazepines).
  - Medication that may affect the stress response (eg, corticosteroids, beta-blockers).
- Self-reported history of allergic reaction (eg, urticaria or anaphylaxis) to cannabis or cannabinoid-containing products.

- Self-reported history of liver disease, renal disease, epilepsy or heart disease (medically controlled high blood pressure <140/90 mm Hg is acceptable).
- Current (ie, within the past 2 weeks) otological (vestibular) disease.
- A history of repeated episodes of syncope.
- Pregnant, lactating, or trying to conceive.
- Self-reported history of drug and/or alcohol dependence (or suspected drug and/or alcohol dependence as determined by the trial physician).
- A medically diagnosed anxiety disorder (eg, social anxiety disorder) within the past 12 months.
- Current suicidal ideation (ie, a score >0 on question 9 of the Patient Health Questionnaire) or suspected suicidal ideation as determined by the trial physician.
- Current depression, anxiety and stress scores outside the 'healthy range' on the Depression Anxiety Stress Scale-21[45] (ie, >moderate scores for depression (>20), anxiety (>14) and stress (>25)).
- A chronic medical condition (mental or physical) that is uncontrolled, that is, has been either newly diagnosed, or previously diagnosed and remains symptomatic.
- Self-reported high vulnerability to cybersickness or motion sickness.
- Frequent (ie, more than weekly) use of VR technologies, which tends to produce desensitisation towards cybersickness.[32]
- Self-reported intense fear of heights.

Recruitment and retention

Participants will be recruited via social media, word of mouth, printed or online study advertisements and direct emails to individuals who have previously registered their interest in participating in clinical trials with the Lambert Initiative for Cannabinoid Therapeutics. Participation is voluntary, and participants can withdraw at any time. Participants will be reimbursed with a $200 gift voucher as compensation for time and expenses incurred as a result of study participation.

Treatments

The treatments will be purchased from Avecho Biotechnology Limited (Clayton, Victoria), manufactured (Catalent Pharma Solutions, St. Petersburg, FL), as well as packaged and labelled (Central Pharmacy Logistics, Coburg North, VIC) at GMP-licenced facilities, stored at the Brain and Mind Centre (in a secure, temperature-controlled room), and dispensed by the trial coordinator (who is also a registered pharmacist) and another blinded investigator.

As this trial uses a non-clinical (healthy) population, a placebo comparator is the most suitable and ethical choice. Accordingly, an acute dose of CBD (as opposed to chronic administration) will be used. Indeed, the treatment of many ailments uses an ad hoc treatment regime.

Intervention

The investigational product (Avecho Biotechnology Limited, Victoria, Australia) is an oil-based, soft-gel capsule. Each gel capsule contains 75 mg of pure, synthetic (-)-CBD enantiomer and 75 mg of TPM in medium chain triglyceride oil. The capsules do not contain any other cannabinoids or cannabis constituents.

Safety

CBD is generally considered to have a good safety profile.[3 4 21 46 47] In previous studies, 150 mg CBD caused a very low frequency of mild adverse events (AEs) that did not differ from placebo.[21] The current study's comprehensive screening and exclusion criteria aims to reduce the likelihood of AEs.

Dose

A dose of 150 mg of CBD (ie, two soft-gel capsules) will be administered orally.

Control

The control is a matched placebo. The placebo is identical to the intervention but contains no CBD and will also be administered via oral ingestion.

Randomisation, allocation concealment and blinding

Participants will be randomised to one of two possible treatments in a 1:1 ratio at the beginning of their Test Day. Specifically, they will be assigned a unique randomisation number that is linked to a treatment via a prepopulated randomisation schedule. The schedule will be generated in seven balanced blocks of 10 and one balanced block of four by an independent statistician using an online random number generator and stored in a password-protected system inaccessible to blinded study personnel (centralised computerised randomisation). The schedule will only be available to the statistician, an independent researcher and the company that will package and label the treatments (Central Pharmacy Logistics).

Treatment allocation will be concealed using numbered containers (or 'sachets'). Each 'dose' will be packaged in a separate, opaque, aluminium sachet labelled with a unique randomisation number.

As this is a double-blind study, participants and the remainder of the research team will not be aware of the assigned treatment. In the event of an emergency, the principal investigator (PI) or trial physician may request the unblinding of a participant for medical care.

Eligibility screening

A study flowchart is presented in figure 1. Willing volunteers will complete a comprehensive online Screening Questionnaire using the 'Research Electronic Data Capture' (REDCap) web-based system (~20 min). Volunteers are required to complete a compulsory online declaration tick-box at the start of the questionnaire consenting to the use of the information they provide to evaluate their eligibility. The questionnaire will assess their eligibility to participate. Each volunteer who

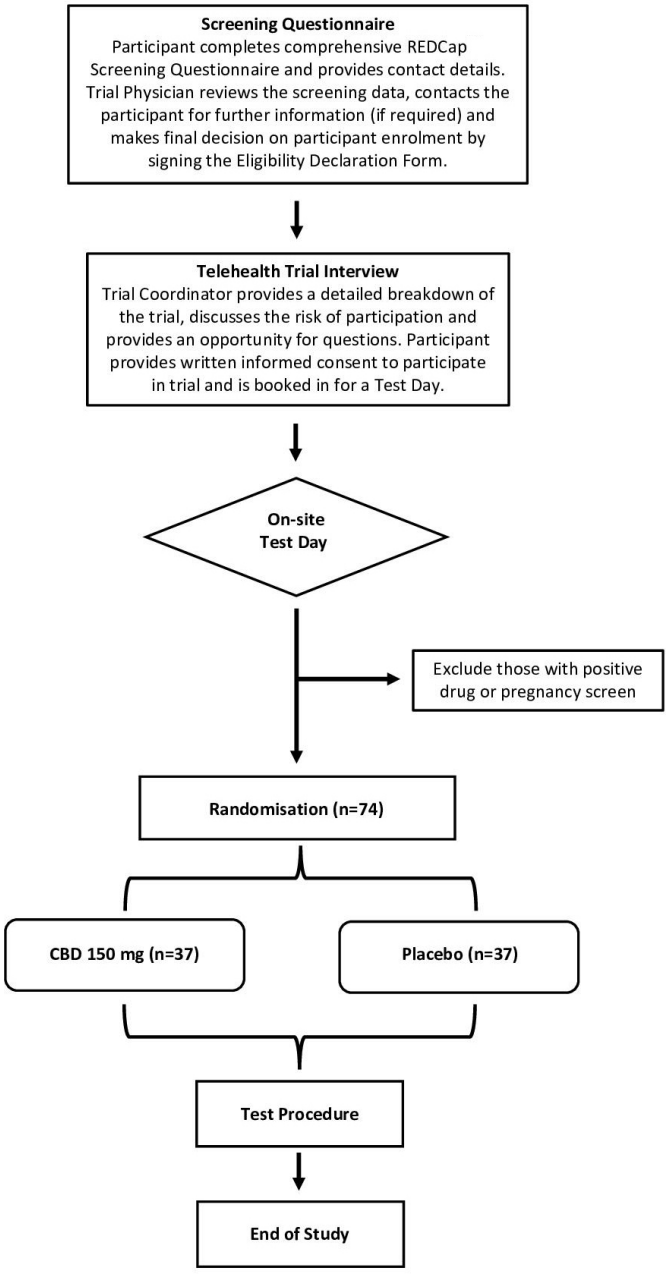

Figure 1 Study flowchart summarising the screening, enrolment and randomisation of participants in the Cannabidiol for Acute Psychosocial Stress and Nausea trial. CBD, cannabidiol; REDCap, Research Electronic Data Capture.

attempts the Screening Questionnaire will be assigned a unique screening number to anonymise their identifying information. The trial physician will review volunteers' responses and decide on their eligibility for the trial. They will document their decision by completing an eligibility declaration form and a prescription for the trial drug (valid only when the volunteer has been randomised).

Enrolment

Eligible participants will be invited to complete a telehealth interview with the trial coordinator. Here, they will receive detailed information about the trial procedures and risks and be informed that their enrolment requires a negative urine drug and pregnancy screen at the start of the experimental procedures (ie, the 'Test Day'). The trial coordinator will invite the volunteer to ask questions and to discuss participation in the trial with the trial doctor, or to take additional time to consider their decision to participate. Once the trial coordinator is confident that the volunteer understands the requirements of the trial, they will request that the participant sign the informed consent form (see online supplemental file 1). The trial coordinator will then counter-sign the consent form, collect basic demographic information and book the participant for a Test Day.

Table 1 The CAPSTAN trial experimental procedure

Time (minutes) from start	Approximate duration	Activity
0	10 min	Introduction and pretrial compliance checks
10	5 min	Randomisation
15	15 min	Pretreatment measures
30	10 min	CBD or placebo administration and caloric beverage
40	50 min	Rest period 1
90	15 min	Virtual reality orientation
105	15 min	Baseline measures
120	15 min total (2 min) (3 min) (5 min) (5 min)	Public Speaking task: Instructions Speech preparation Speech delivery Arithmetic challenge
135	10 min	Rest period 2
145	5 min total (2 min) (3 min)	Walk the Plank task: Instructions Walk the Plank task
150	10 min	Rest period 3
160	5 min total (2 min) (3 min)	Rollercoaster Ride task: Instructions Rollercoaster ride task
165	10 min	Rest period 4
175	15 min	Study close
190	–	End of Test Day

CAPSTAN, Cannabidiol for Acute Psychosocial Stress and Nausea.

Experimental procedure

Each participant will complete one Test Day (~3 hours) at the Brain and Mind Centre at the University of Sydney (table 1).

Standardisation procedures

Prior to each onsite Test Day, participants will be instructed to: (a) abstain from alcohol (≥24 hours); (b) avoid greater than one standard serving of caffeine at least 2 hours before the Test Day; (c) ensure they are

well hydrated; and (d) ensure that they are adequately fed by consuming a meal at least 2 hours before arrival to the Test Day. These factors aim to reduce the likelihood of malaise, gastrointestinal disturbances or heightened anxiety on the Test Day.

Compliance checks

Participants will complete a urinary drug screen (Drug-Check NxStep Onsite Urine Test Cup, to identify any recent use of cannabis and other psychoactive substances such as cocaine, ecstasy (MDMA), amphetamines, benzodiazepines and opioids) and, if they are female, a urine pregnancy screen, on arrival at the study site. The trial coordinator will also confirm compliance with the standardisation procedures and if there have been any changes to the participant's health status or medication use since the last contact. Participants who meet these requirements will be randomised; those who do not may be invited to return at another time if suitable.

Experimental procedures

Following randomisation, participants will be fitted with the Equivital EQ02+ LifeMonitor belt and the VR headset. There will then be a 10 min collection of pretreatment measures (see the Study outcomes section). After this, the VR headset and Equivital EQ02+ LifeMonitor belt will be temporarily removed, the treatment administered and the participant given a compulsory standardised caloric beverage to consume; specifically, 500 mL of 'Up & Go Liquid Breakfast' (Sanitarium, Berkeley Vale, NSW, Australia) containing approximately 1640 kJ, 16.8 g of protein, 8.6 g of fat and 57 g of carbohydrates. For consistency, all participants are required to consume this beverage in its entirety, which aims to potentiate the absorption of CBD in the gastrointestinal tract[6 48–50] and provide participants with sustenance during the test session. Participants will be provided with a rest period of approximately 50 min, during which they will be left alone in a quiet reception area and encouraged to undertake some low-stress reading; this delay is aimed at allowing CBD plasma concentrations to approach a near-maximal level.[48] Following this, participants will be provided with instructions on the three VR tasks and the functionality of the VR hardware during a 15 min 'VR Orientation' session. The VR headset and Equivital EQ02+ LifeMonitor belt will then be re-fitted for a 10 min collection of the pretask measures. The devices will remain fitted to participants until the end of the experimental procedure.

VR tasks

The three tasks developed for this clinical trial are the 'Public Speaking' task (for psychosocial stress), the 'Walk the Plank' task (for situational anxiety) and the 'Rollercoaster Ride' task (for motion sickness). Although these exact VR tasks have not been previously used in clinical trials or laboratory studies, similar tasks have been reported in the broader scientific literature.[29 32 40–42 51]

The 15 min 'Public Speaking' task was modelled on previous studies that found CBD to have anxiolytic effects during public speaking challenges[23 24 39] and the Trier Social Stress Test (TSST).[52] The above-mentioned public speaking tasks varied in their methodology and involved either 'simulated' public speaking tasks whereby participants delivered a speech in front of a video camera or real-life tasks where participants delivered speeches to a live audience.[23 24 39] Conversely, the TSST is a structured stress paradigm involving a 10 min speech preparation period followed by a 10 min test period during which participants complete a 5 min job application speech followed by 5 min of mental arithmetic.[53] The TSST reliably induces psychosocial stress (ie, stress involving the perception of one's worth, competence or status by others) and results in an acute and reliable cortisol response in most participants.[53–55] In one study, a VR adaption of the TSST elicited similar salivary cortisol and subjective stress responses to a real-life TSST, demonstrating that the two were equivalent.[29] The current study uses a modified VR version of the TSST involving a panel of virtual judges who withhold all feedback or affirmation (figure 2A).

The task involves a 3 min 'speech preparation period' (ie, 'please mentally prepare a speech on what attributes and experience you have that makes you the ideal candidate for your dream role') and a 10 min 'test period' consisting of (a) 5 min speech delivery period (ie, 'please deliver your speech and aim to speak for the full 5 min') and (b) a 5 min mental arithmetic challenge (ie, 'please calculate 2703–13. From the result, please subtract 13

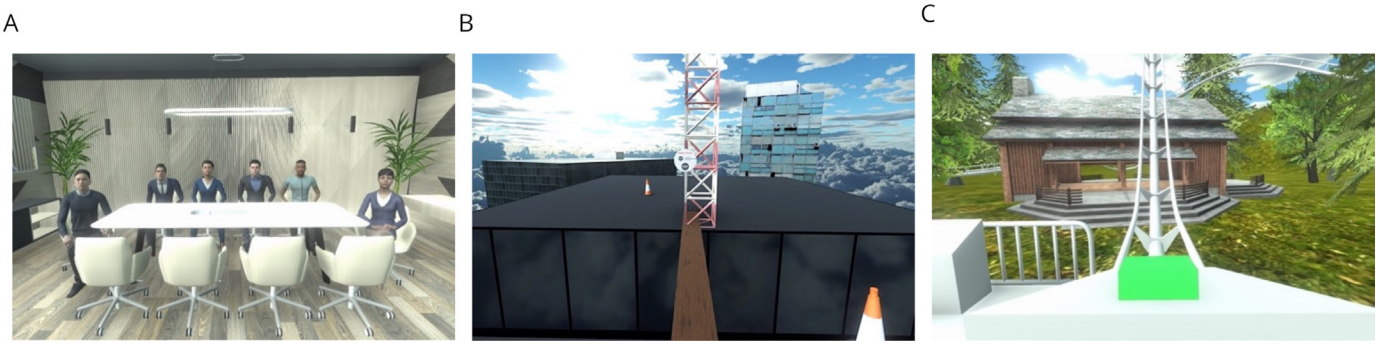

Figure 2 (A) The panel of virtual judges from the 'Public Speaking' task; (B) the roof of the building and plank from the 'Walk the Plank' task; and (C) the view from the seat of the 'Rollercoaster Ride' task.

again and state your answer out loud. Repeat this process a total of five times. At the end of this process, please recall all five of your answers aloud').

The 5 min 'Walk the Plank' task requires participants to virtually walk across a narrow virtual plank between two skyscrapers. Participants will be advised that they have become stranded on the top of the building and are required to signal for help using the safety beacon placed at the opposite end of the plank. For this task, participants will walk up and down the length of the clinic room with their movement mapped to the virtual plank and guided by virtual boundaries, signifying a safe space (figure 2B). VR studies using a similar challenge provided realistic experiences that induce physiological markers of stress that are consistent with acute anxiety (ie, 'situational anxiety').[40–42]

The 5 min 'Rollercoaster Ride' task challenges participants to complete a virtual rollercoaster ride (figure 2C). Participants will remain seated throughout this task and can indicate if they would like to stop the task early. Similar VR tasks have been shown to induce motion sickness in participants.[32 43 44] Motion sickness will be explored explicitly during the 'Rollercoaster Ride' task, while cybersickness will be explored during all three VR scenarios.

Post-trial procedures

After completing the final VR task, participants have a 10 min recovery period. After this, they will be queried on any AEs experienced (ie, 'Have you experienced any unfavourable symptoms?'), what treatment do they think they received (ie, CBD or placebo), and what are their confidence estimates (ie, 'How sure are you of your guess on which treatment you received?'). All participants will be provided with the contact details of the research team to self-report any AEs over the next 24 hours. The trial coordinator or research assistant will record all AE reports using a REDCap AE report form and communicate to the trial physician if required.

The occurrence of AEs will be discussed weekly with the trial physician. Furthermore, a blinded summary of AE reports will be emailed to the trial physician monthly, and the trial physician will indicate if the rate of AEs is unacceptably high. In the unlikely event of a severe adverse event (SAE), the trial physician and the PI will be immediately notified, and all SAEs will be reported to the trial sponsor and the HREC within 72 hours.

Data collection

A summary of the data collected during the CAPSTAN trial and time of collection is provided in figure 3.

Study outcomes

The primary outcome measures include:

- Self-reported stress ratings on a Visual Analogue Scale (VAS) (*nervous 0–100*).
- Self-reported nausea ratings on a VAS (*nauseous 0–100*).

The secondary outcome measures include:

- Salivary cortisol.
- Heart rate.
- Skin conductance.
- Vomiting or near-vomiting episodes.
- Self-reported anxiety ratings on VASs including:
  - (*tense 0–100*).
  - (*calm 0–100*).

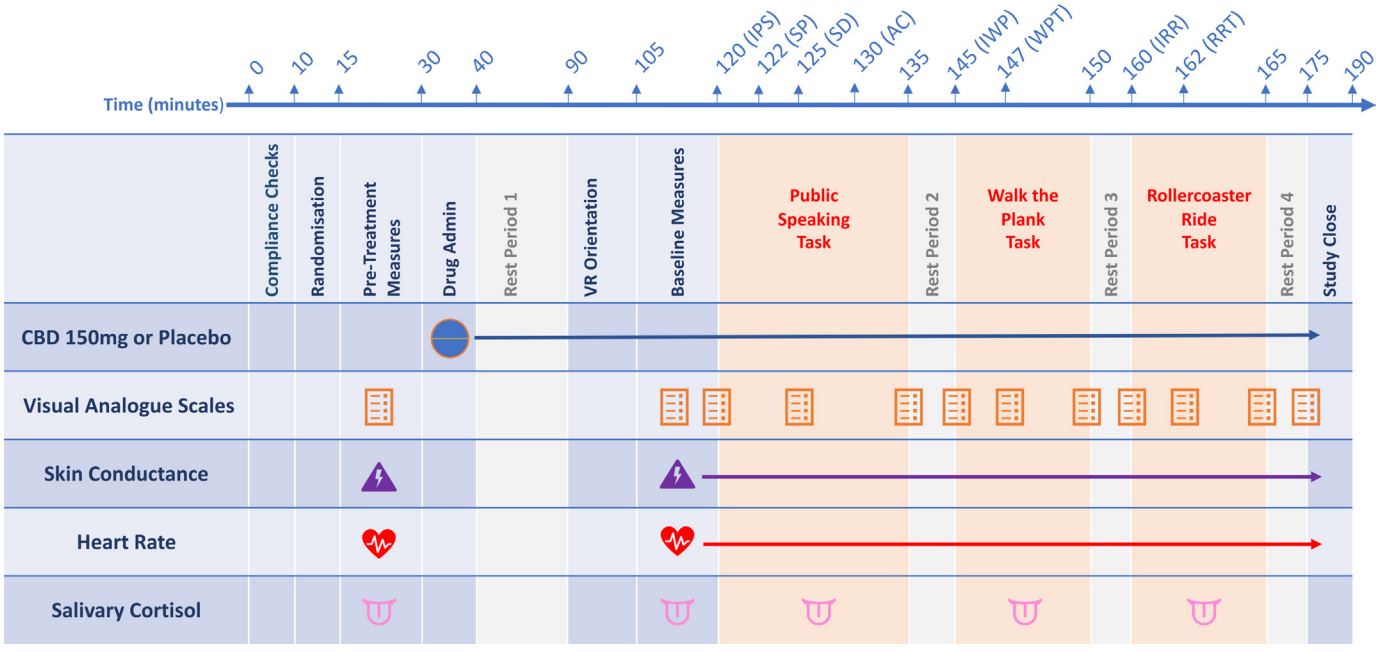

Figure 3 Data collected during the Cannabidiol for Acute Psychosocial Stress and Nausea trial 'Test Day'. AC, arithmetic challenge; IPS, instructions for the 'Public Speaking' task; IRR, instructions for the 'Rollercoaster Ride' task; IWP, instructions for the 'Walk the Plank' task; RRT, 'Rollercoaster Ride' task; SD, speech delivery; SP, speech preparation; WPT, 'Walk the Plank' task.

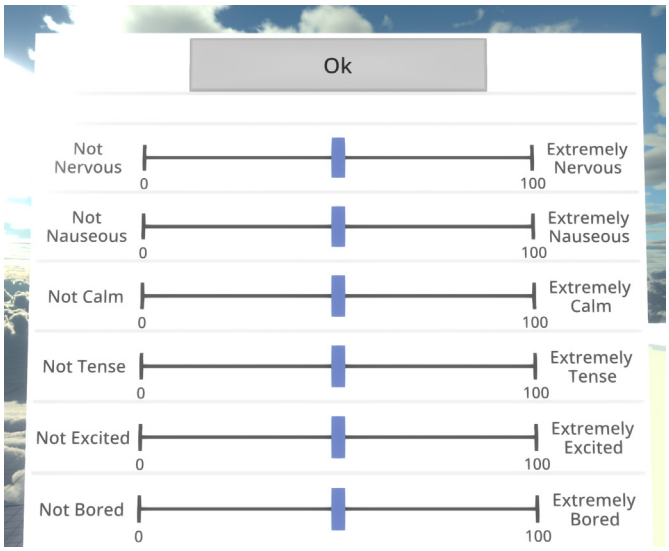

Figure 4 Self-reported Visual Analogue Scales as they appear on the virtual reality headset. Values are provided by the participants by clicking on the scales using the hand controllers.

  - (*excited 0–100*).
  - (*bored 0–100*).

The exploratory (tertiary) outcome measures are:

- Salivary testosterone and progesterone.
- Eye-tracking data including:
  - The frequency and duration of eye-closing.
  - The frequency and duration of gaze at areas of interest.

Visual Analogue Scales

VASs will be used to measure the two primary outcomes: self-reported stress (nervousness) and nausea. They will also be used to measure the secondary outcome of self-reported anxiety (figure 4). These measures will be recorded before drug administration (pretreatment measurement), at baseline, prior to the commencement of each VR task, at the completion of each VR task and at the study close. VAS measures will also be recorded prior to the performance of the speech *during* the 'Public Speaking' task (timepoint 'SD' figure 3) and prior to the performance of the walk *during* the 'Walk the Plank' (timepoint 'WPT' figure 3) task. These measures aim to capture 'anticipatory anxiety' reported prior to anxiety-inducing tasks in previous studies.[23 24] As nausea is the main interest during the 'Rollercoaster Ride' task, no VAS measures for anticipatory anxiety will be taken for this task. All VASs will appear on the screen of the VR headset, and participants will use the VR hand controllers to click on the numerical value (0–100) that best describes their current state (figure 4). Using such virtual scales allows seamless execution of self-report without disturbing the participant's sense of immersion within the virtual environment.

For a well-rounded exploration of CBD effects on anxiety, we have used VASs that query participant's affect (ie, the outward expression of an emotion).[56] Here, we consider (a) the 'valence' of an emotion (ie, its positivity or negativity) and (b) the intensity of the emotion (ie, whether it is arousing or deactivating). This provides four self-reported anxiety rating VASs, including:

- Positively arousing (*excited 0–100*).
- Positively deactivating (*calm 0–100*).
- Negatively arousing (*tense 0–100*).
- Negatively deactivating (*bored 0–100*).

Salivary cortisol, testosterone and progesterone

During the experimental procedure, oral fluid samples will be collected from participants five times using Salivette collection tubes (Sarstedt AG and Co, Nümbrecht, Germany). These samples will be collected immediately before drug administration, before the first VR task, and after each VR task. Participants will be advised to open the Salivette tube, place the pad in their mouth for 2 min or until soaked with saliva, then return the pad to the tube and firmly seal it. The samples will be centrifuged for 2 min at 1000× *g* and analysed simultaneously for cortisol (a secondary outcome) and testosterone and progesterone (exploratory outcomes) using an in-house developed mass spectrometry method.[57 58]

Heart rate

Heart rate will be measured for 10 min immediately before drug administration (baseline measurement), for 10 min at baseline and continuously throughout all three VR tasks using the EQ02+ LifeMonitor and belt, as described in previous studies[59 60] (Equivital Ltd, Cambridge, UK; https://www.adinstruments.com/partners/equivital). This is a wireless, medical-grade monitoring system that records a range of physiological measures (such as ECG, breathing rate, tri-axial acceleration, galvanic skin response, skin temperature) using a wearable vest and permits live data streaming and download using the LabChart software.

Skin conductance

Skin conductance will be measured for 10 min immediately before drug administration (baseline measurement), for 10 min at baseline and continuously throughout all three VR tasks.

Skin conductance of the forehead will be measured using the Equivital GSR Sensor connected to the EQ02+ LifeMonitor and belt. Skin conductance of the fingers will be measured using MLT117F/10 GSR finger electrodes connected to a FE116 GSR Amp with a PLCF1 front-end interface used with PowerLab C software (ADInstruments, Oxford, UK), a system used in previous studies.[61 62] Research suggests that forehead skin conductance may correlate with motion sickness, while finger skin conductance correlates with acute stress.[32 63] Therefore, both will be measured in the current study.

Vomiting episodes

The Test Day source document will record vomiting episodes (if any) throughout the experimental procedure.

Eye-tracking

Eye-tracking data will be collected continuously throughout the VR tasks using the VR headset. These measures will provide highly precise, objective data by which to examine participant's compliance (frequency and duration of eye closing) and engagement and response (frequency and duration of gaze at areas of interest, that is, the panel of judges in the 'Public Speaking' task or the plank in the 'Walk the Plank' task) during the VR challenges.[64] Gazing at predefined points of interest (eg, the judges in the 'Public Speaking' task or the plank in the 'Walk the Plank' task) is based on the 'Eye-Mind Hypothesis' that describes the tendency for people to direct their gaze towards what they are thinking about.[64–66] Both eye closing and gaze away from points of interest may correlate to fear or avoidance behaviours.[67]

Data management

Participant information collected for this trial will be securely stored and treated as confidential. Participants' identifying information will be anonymised using unique codes: initially, a screening number and, later, a randomisation number. The key to these codes will be securely stored in password-protected files inaccessible from the internet. Clinical trial data will be collected and managed using REDCap, a secure, online programme supported by the University of Sydney; access is password-protected and will only be available to approved research staff. Hard copies of patient data will be securely stored in locked filing cabinets at the study site. Only the study investigators have access to the participant data. All trial data will be stored securely for at least 15 years. The findings of this clinical trial will be disseminated via conferences, publications and media, as applicable. Participants will be informed of the results of the study at the conclusion of the trial. No participants will be identified in any report or publication of this study or its results.

Data and safety monitoring

Data monitoring will occur monthly for all new participant entries logged into the REDCap system; a designated team member will adhere to a standardised process of data review, raising queries and locking forms once the review has been completed. Safety monitoring of AEs will be managed according to sponsor and HREC requirements. As this is a small, single-centre, low risk, clinical trial using an acute, low-dose CBD, an independent data safety monitoring committee will not be formed. However, an independent 'Expert Group' has been formed and will be consulted by the research team and HREC in the unlikely instance of a SAE. The Expert Group comprises three research physicians with extensive experience with CBD clinical trials. The decision to terminate the trial lies with the PI based on safety data and recruitment targets.

Roles and responsibilities

The study investigators have led the design of this study and are responsible for the management and conduct of this clinical trial. The study investigators will conduct the analysis and will make all publication-related decisions.

Statistical methods

Sample size estimation

The target sample size was determined a priori using power calculation software (G*Power V.3.1.9.6, University of Kiel, Germany). In an earlier investigation, Linares *et al*[23] found that 150 mg CBD decreased subjective ratings of anxiety on the Visual Analogue Mood Scale during a simulated public speaking test, although non-significantly (placebo: 18.6±15.9 mm, n=15; CBD: 7.6±15.5 mm; n=15; Cohen's d=0.70).[23]

Using an equivalent effect size (Cohen's d=0.70), a power (1–ß) of 0.8 and a two-sided α=0.05, we estimate that n=68 participants will be required to detect a significant effect of CBD on anxiety. Clinical trials conducted by the Lambert Initiative for Cannabinoid Therapeutics have indicated participant retention of ≥90%.[48 68] Therefore, the n=74 will be recruited to account for attrition.

Statistical analysis plan

The primary and secondary outcomes and eye-openness will be analysed using generalised linear mixed models (GLMM), while eye gaze will be analysed using a mixed-effects multinomial logistic regression. Treatment, time and the treatment×time interaction will be included as fixed effects, and the participant will be included as a random effect, with other covariates included as appropriate to improve goodness of fit (eg, sex, age, time of day). To refine the models, we will use corrected Akaike Information Criterion.[69] We will calculate Δm between models and exclude models with Δm>2 as having substantially less support.[70] No covariance structure will be specified (unstructured). To identify the best distribution and link for the GLMM, the data type, residual plots, Shapiro-Wilk normality test, Levene's test for homogeneity of variance and Pearson's dispersion test will be used. Type III Wald χ^2 tests will be used to generate main effects p values. A priori planned uncorrected pairwise comparisons will be performed to compare:

- Subjective ratings of stress on a stress VAS (*nervous 0–100*) across treatments at (timepoint t=125 (SD), figure 3).
- Subjective ratings of stress on a stress VAS (*nervous 0–100*) across treatments at (timepoint t=147 (WPT), figure 3).
- Subjective ratings of nausea on a nausea VAS (*nauseous 0–100*) across treatments at (timepoint t=165, figure 3).
- Subjective ratings of nausea on a nausea VAS (*nauseous 0–100*) across treatments at (timepoint t=175, figure 3) as these are the primary outcome measures.

Dunn-Šidák corrected pairwise comparisons will be performed where additional significant main and interaction effects are present. Statistical significance will be accepted as p<0.05. The statistical analysis plan will be

finalised before the last participant Test Day and will be available on request.

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Contributors ISM, DM, HM, MB-P, NSL, RF and ZB were involved in the conception and design of the research project. ZB drafted the manuscript and all authors were involved in critically revising it. ISM is the principal investigator who has overall responsibility for the design, conduct and decision to submit for publication. MB-P is the study statistician, NSL will provide medical oversight, HM and RF created the virtual reality challenges in collaboration with ISM and ZB. ZB is the trial coordinator responsible for collecting trial data. All authors have read and approved the final manuscript.

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Competing interests ISM acts as a consultant to Kinoxis Therapeutics and has received honoraria from Janssen. He has also served as an expert witness in various medicolegal cases involving cannabis and cannabinoids. ISM holds patents on cannabinoid therapies (PCT/AU2018/05089 and PCT/AU2019/050554) and has received consulting fees from the Medicinal Cannabis Industry Australia (MCIA). DM has also received consulting fees from MCIA. ZB, HM, NSL, RF and MB-P have no disclosures to report.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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CHAPTER 7. THE CANNABIDIOL FOR ACUTE PSYCHOSOCIAL STRESS AND NAUSEA (CAPSTAN) CLINICAL TRIAL: PRELIMINARY RESULTS

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MANUSCRIPT IN PREPARATION FOR JOURNAL SUBMISSION

7.1 Abstract

Introduction: The non-intoxicating, plant-derived cannabinoid CBD has therapeutic potential in a number of health conditions. Clinical trials that demonstrate efficacy typically utilise higher (≥ 300 mg) oral doses of CBD. Relatively few studies have investigated the efficacy of lower (≤ 150 mg) oral doses of CBD, typically seen in over-the-counter products. Previous studies have suggested anxiolytic effects of CBD at ≥ 300 mg while preclinical research has described anti-nausea effects of CBD in animal models. Here, we investigated the acute effects of 150 mg CBD on anxiety and nausea in healthy participants.

Methods: A randomised, double-blind, placebo-controlled, parallel-group clinical trial was conducted at the University of Sydney between October 26, 2023, and June 20, 2024. Healthy volunteers ≥ 18 years of age were recruited. Participants were administered 150 mg CBD or placebo in two soft-gel capsules 90 minutes before completing three virtual reality (VR) challenges designed to induce transient anxiety and nausea: (1) a 15-minute 'Public Speaking' task, (2) a five-minute 'Walk the Plank' task, and (3) a five-minute 'Rollercoaster Ride' task. The primary outcomes were subjective anxiety (i.e., 'Nervous') and nausea (i.e., 'Nauseous') measured on 100 mm visual analogue scales (VASs) throughout the test session. Secondary outcomes included salivary cortisol, heart rate, skin conductance and other subjective feelings (i.e., calm, bored, tense and excited).

Results: Sixty-nine participants were randomised and all were included in the final sample. The VR Public Speaking and Rollercoaster Ride tasks effectively increased subjective ratings of anxiety and nausea, respectively. CBD significantly reduced self-reported anxiety immediately after the Public Speaking task although there was no significant effect of CBD at speech-delivery. CBD had no significant effects on nausea or secondary outcomes.

Conclusions: An acute dose of 150 mg CBD reduced subjective ratings of anxiety in healthy participants following a virtual public speaking task. The effect was not accompanied by autonomic (heart rate, skin conductance) or endocrine (salivary cortisol) reductions in anxiety. CBD did not influence nausea in participants completing a virtual rollercoaster task.

This study further confirms the feasibility and effectiveness of VR approaches in pharmacological studies of anxiety and nausea in healthy participants.

Ethics: The University of Sydney Human Research Ethics Committee granted approval (2023/307, Version 1.5, 28th September 2023).

Trial Registration Number: ACTRN12623000872639 (ANZCTR public trials registry, registered 15th August 2023).

Keywords: cannabidiol (CBD), cannabis, cannabinoid, stress, psychosocial, cortisol, virtual reality.

7.2 Introduction

Cannabidiol (CBD) is one of the best studied phytocannabinoids found within the *Cannabis sativa* plant [1, 2]. The pharmacological activity of CBD is complex with interactions across multiple targets such as serotonin receptors (e.g., 5-HT_{1A}), gamma-amino butyric acid receptor type A ($GABA_A$) receptors, peroxisome proliferator-activated receptor gamma (PPARγ) receptors, and transient receptor potential ion channels (e.g., TRPA1) [3-6]. A large body of clinical trial evidence indicates that CBD is non-intoxicating, has a good safety profile, and is well-tolerated even with chronic high doses [7]. In fact, individuals cannot readily differentiate between CBD and placebo in clinical trials [8, 9]. The clinical efficacy of CBD is evident in conditions such childhood epilepsies [10-12], anxiety [13-15], and psychosis [16], and is typically observed at an oral dose range of 300 - 1500 mg per day [17, 18]. Many jurisdictions such as North America, Canada, and Europe, permit access to CBD products without a prescription, in the form of over-the-counter (OTC) or 'nutraceutical' products, but these typically involve lower CBD doses [19].

A recent narrative review by Arnold *et al.,* (2022) summarised clinical trials investigating the efficacy of oral doses of CBD ≤ 400 mg per day. Overall, it reported limited evidence of efficacy below 300 mg CBD for any health condition [20]. With respect to anxiety, the review found that CBD demonstrated evidence of efficacy at doses between 300 - 400 mg, particularly in healthy volunteers engaged in public speaking tasks designed to induce 'psychosocial stress' [13-15]. Notably, one study showed a clear trend towards anxiolytic effects when 150 mg CBD was administered prior to a public speaking task [13]. Hence, further investigation of the effects of oral, 'low-dose' (i.e., 150 mg) CBD in anxiety may be warranted.

Virtual reality (VR) has been successfully used to create anxiety-inducing, public speaking tasks that are comparable to 'real-life' tasks [21, 22]. This technology offers considerable benefits for pharmacological studies in human participants, including a safe and reproducible test environment [22, 23]. However, the use of VR is often accompanied with nausea associated with motion sickness (due to exposure to significant visual or physical motion) or cybersickness (due to the specific exposure to VR technology) [24-26]. Interestingly, CBD has demonstrated anti-emetic and anti-nausea effects in preclinical animal models [27-29], while clinical studies found that CBD combined with Δ^9-tetrahydrocannabinol (THC) can be an effective anti-nausea agent in cancer patients with chemotherapy-induced

nausea and vomiting (CINV) [30]. The possible anti-nausea effects of CBD administered alone have yet to be examined in clinical studies.

In the current study, a customised VR paradigm was developed to simultaneously investigate the efficacy of 150 mg CBD in anxiety and nausea in healthy individuals, and the feasibility of using VR technology in a clinical trial . Three VR challenges were designed for the current trial. The 'Public Speaking' task was based on previous clinical trials that investigated 'psychosocial stress' during a public speaking challenge [13-15] and the Trier Social Stress Test (TSST) - considered the 'gold-standard' test paradigm to induce psychosocial stress [31]. Briefly, participants were given three-minutes to mentally prepare a speech and five-minutes to deliver the speech; this was followed by a 'surprise' five-minute mental arithmetic challenge. These challenges were conducted in front of virtual panel of judges who provided no reassuring feedback. The 'Walk the Plank' task was based on previous VR paradigms that induced 'situational anxiety' [32-34]. This type of anxiety is considered distinct from psychosocial stress as it does not utilise a social stressor, but rather simulates an immediate threat (i.e., a precipitous height). Participants were required to walk across a virtual plank placed between two high-rise building. Finally, the 'Rollercoaster Ride' task required participants to complete five rounds of a virtual rollercoaster, as used in previous studies of motion sickness and cybersickness [25, 35, 36]. For the purposes of this study, motion sickness was measured only during the Rollercoaster Ride task (i.e., exposure to significant visual motion), whereas cybersickness was measured during all three VR tasks (i.e., exposure to VR technology).

The CAPSTAN trial was completed in late June 2024 and given the deadline for the current thesis, only a partial analysis and preliminary write-up of the trial is presented here.

7.3 Methods

Detailed methods can be found in the published protocol paper (Chapter 6, [37]). The study was a randomised, double-blind, placebo-controlled, parallel-group, clinical trial investigating the efficacy of a low, oral dose of CBD (150 mg) on anxiety and nausea. The study was known as the CAPSTAN (Cannabidiol for Acute Psychosocial Stress and Nausea) clinical trial. It should be noted that a crossover design was considered unsuitable for the current study due to a high likelihood of trial-order effects (e.g., habituation to the VR scenarios) [25].

The trial sponsor was the University of Sydney, and the trial site was the Brain and Mind Centre in Sydney, Australia. The study was approved by the University of Sydney Human Research Ethics Committee (HREC; 2023/307, Version 1.5, 28th September 2023) and registered on the Australian New Zealand Clinical Trials Registry (ACTRN12623000872639, 15th August 2023). The study was financially supported by the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically funded centre for cannabinoid research at the University of Sydney. Recruitment commenced on 26th October 2023 and concluded on 20th June 2024.

Data Analysis

Briefly, the primary and secondary outcomes were analysed using generalised linear mixed models (GLMM). Treatment, time, and the treatment × time interaction were included as fixed effects, and the Participant as a random effect; covariates were included sequentially, and the Corrected Akaike Information Criterion was determined if the inclusion of any covariate improved the goodness of fit [38]. The Δm was calculated between models and those with Δm>2 were excluded as they had considerably less support [39]. The data type, residual plots, Shapiro-Wilk normality test, Levene's test for homogeneity of variance and Pearson's dispersion test were used to identify the best distribution for the GLMM. In order to calculate the main effect p values, the Type III Wald $\chi 2$ tests were used. *A priori* planned uncorrected pairwise comparisons were conducted across treatments:

(1) subjective anxiety on the 'Nervous' visual analogue scale (VAS) at timepoint 'VR1 perform' (i.e., at speech delivery of the Public Speaking task)
(2) subjective anxiety on the Nervous VAS at timepoint 'VR2 perform' (i.e., performance of the Walk the Plank task)
(3) subjective nausea on the 'Nauseous' VAS at timepoint 'R3' (i.e., immediately following the Rollercoaster Ride task)
(4) subjective nausea on the Nauseous VAS at timepoint 'Study close' (i.e., 10-minutes after the Rollercoaster Ride task)

For detailed results of all outcome measures, please refer to Appendix 4. Dunn-Šidák corrected pairwise comparisons were only performed where additional significant main or interaction effects were detected and statistical significance was defined with alpha = 0.05.

Post-hoc analyses were not performed if there was a main effect of time. In these instances, outcome measures were reported descriptively in the results section.

Following completion of the planned analyses, visual inspection of primary outcome measure for anxiety (self-reported VAS ratings of Nervous) identified a separation of data between treatments immediately following the Public Speaking task at timepoint 'R1' (i.e., immediately post-task). Therefore, a pairwise comparison (corrected Dunn-Šidák) of CBD versus placebo at this timepoint was conducted (see Results section for further details). This timepoint was of particular interest given that CBD demonstrated a post-task anxiolytic effects in previous studies using public speaking tasks [14, 15].

7.4 Results

Participant Recruitment and Retention.

The flow of participant recruitment and retention is illustrated in the CONSORT diagram below (Figure 1). A total of 442 volunteers completed the online screening questionnaire. Of these, 90 were deemed potentially eligible and were invited to complete a telephone interview. Of these, 89 provided written informed consent and 69 were randomised. Of those randomised, 34 were assigned to the CBD treatment condition and 35 to the placebo condition. All 69 randomised participants completed the test session and were included in the final analysis.

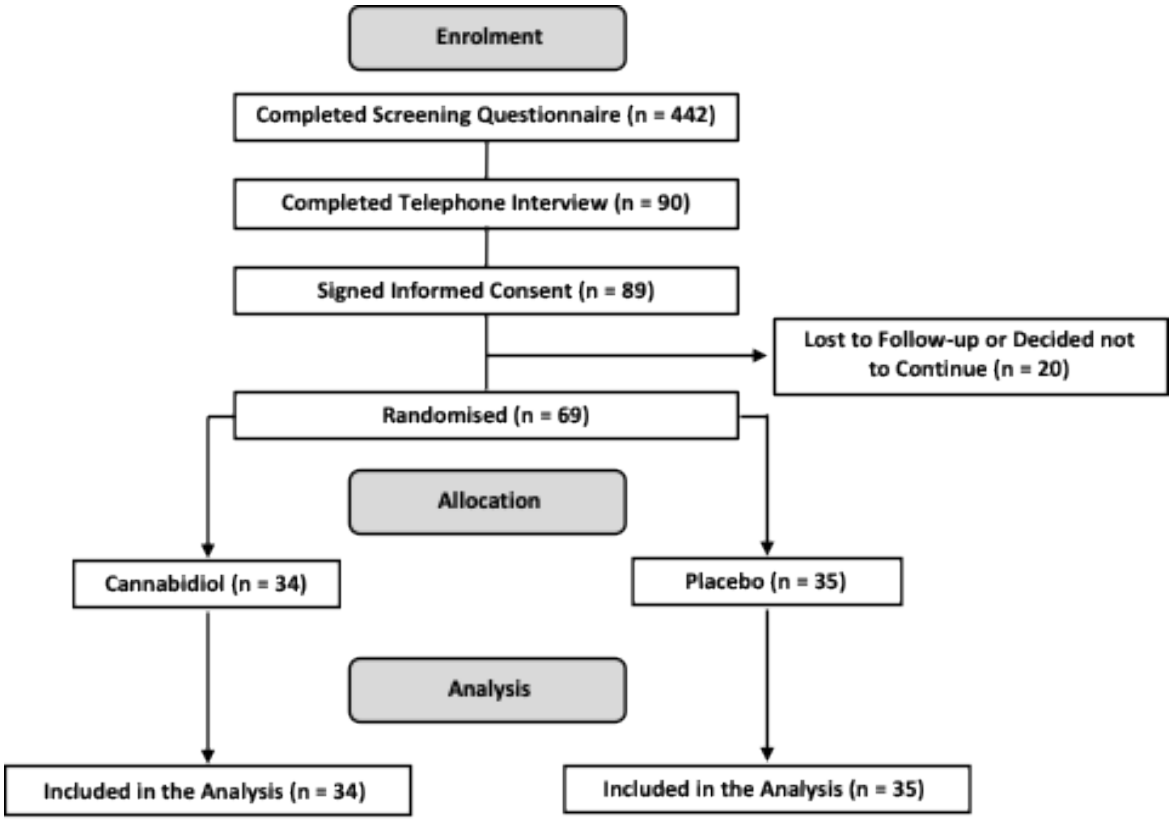


Figure 1. *CONSORT diagram of participant recruitment and retention.*

Participant Characteristics

The baseline characteristics of the participant population are summarised in Table 1. Overall, the sample was young, had a body mass index in the healthy range, and included more males (53%) than females (46%). Participants were well-educated with many having completed undergraduate (62%) and postgraduate (26%) degrees. Around 42% were currently engaged in full-time work. Ratings on the Depression Anxiety Stress Scale (DASS-21) indicated stress, anxiety, and depression levels in the normal range, consistent with the exclusion criteria for the trial (Chapter 6 [37]). The CBD and placebo groups were well-matched with no significant differences between groups in any of the demographic measures (Table 1).

Table 1. *Participant baseline characteristics (n=69).*

	Frequency (n), Mean±SD or Median [IQR]			
Characteristic	**CBD**	**Placebo**	**Total**	**p-value**
Gender (n)	34	35	69	p = 0.489
Man	18 (52.9%)	19 (54.3%)	37 (53.6%)	
Woman	16 (47.1%)	15 (42.9%)	31 (44.9%)	
Non-Binary	1 (2.9%)	0 (0%)	1 (1.4%)	
Age (years)	25.5 [20.8-34.9]	23.6 [20.5-31.8]	24.9 [20.8-33.7]	p = 0.606
Height (m)	1.7 [1.6-1.8]	1.7 [1.6-1.8]	1.7 [1.6-1.8]	p = 0.576
Weight (kg)	67.5 [55.0-80.3]	70.5 [80.0-55.0]	70.0 [55.0-80.0]	p = 0.995
BMI (kg/m^2)	21.6 [20.7-25.7]	22.9 [26.2-20.4]	22.2 [20.7-26.1]	p = 0.568
Stress score [a]	6.0 [0-10.0]	6.0 [2.0-10.0]	6.0 [2.0-10.0]	p = 0.427
Depression score [a]	2.0 [1.5-8.5]	4.0 [0-10.0]	4.0 [0-9.0]	p = 0.927
Anxiety score [a]	2.0 [0-4.5]	2.0 [0-6.0]	2.0 [0-6.0]	p = 0.630
Education:				p = 0.652
High school	2 (5.9%)	3 (8.6%)	5 (7.2%)	
TAFE	1 (2.9%)	2 (5.7%)	3 (4.3%)	
Undergraduate	20 (58.8%)	23 (65.7%)	43 (62.3%)	
Postgraduate	11 (32.4%)	7 (20.0%)	18 (26.1%)	
Employment:				p = 0.652
Full-time	15 (44.1%)	14 (40.0%)	29 (42.0%)	
Part-time	10 (29.4%)	14 (40.0%)	24 (34.8%)	
Unemployed	9 (26.5%)	7 (20.0%)	16 (23.2%)	

Values are frequency (n), Mean±SD or Median [IQR], as appropriate (i.e., where data are normal and non-normal, respectively). **Abbreviations** - BMI: Body Mass Index; IQR: Interquartile Range; SD: Standard Deviation.
[a] Based on the Depression Anxiety Stress Scale (DASS-21)

Primary Outcomes

Self-reported 'Nervous'

The primary outcome of self-reported anxiety, measured as 'Nervous' on a VAS, did not demonstrate a main effect of Treatment ($X^2_1 = 1.360$, p = 0.244) or a Treatment x Time interaction ($X^2_{10} = 10.090$, p = 0.433) (i.e., 'pretreatment', 'baseline', all three VR tasks and their associated rests intervals 'R1', 'R2' and 'R3', Figure 2).

A priori planned comparisons of VAS ratings between placebo and CBD at speech-delivery during the Public Speaking task (timepoint 'VR1 perform', Figure 2, p = 0.415) and

during the Walk the Plank (timepoint 'VR2 perform', Figure 2, p = 0.504) tasks, found no significant difference between the treatments. There was a main effect of time (X^2_{10} = 124.472, p < 0.001) and it was evident that both the Public Speaking task and the Walk the Plank task increased self-reported 'Nervous'. Indeed, ratings were lower at 'VR1 start' (mean ± standard error (SE); 32 ± 3) and 'VR2 start' (20 ± 3) than at 'VR1 perform' (58 ± 3) and 'VR2 perform' (33 ± 3), respectively (Figure 2). The Rollercoaster Ride task did not appear to affect self-reported 'Nervous' (i.e., 'VR3 start' (21 ± 3) vs. 'R3' (24 ± 3), Figure 2). The final fitted model included Gender; however, it did not have a significant effect (X^2_2 = 4.915, p = 0.086).

Despite the lack of significant group differences on planned comparisons, visual inspection of the data suggested separation of CBD and Placebo groups immediately following completion of the Public Speaking task (i.e., timepoint 'R1', Figure 2). An unplanned, exploratory comparisons of placebo and CBD groups was conducted and a significant difference between treatments uncovered at 'R1' (p=0.049, Dunn-Šidák corrected).

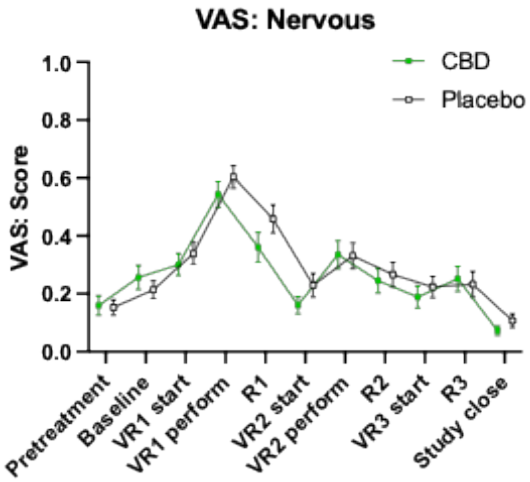


Figure 2. *Visual analogue scale (VAS) ratings of 'Nervous' in the CBD and Placebo groups. The Public Speaking task (timepoints 'VR1 start' to 'R1') reliably increased self-reported ratings of anxiety on a Nervous VAS in both groups but to a lesser extent in the CBD group than Placebo group. A significant difference between groups was evident immediately following the Public Speaking task (timepoint 'R1'). The Walk the Plank task (timepoints 'VR2 stat' to 'R2') also modestly increased self-reported ratings of anxiety in both groups but there was no difference between the CBD and Placebo groups.* ***Abbreviations:*** *VR1 start: start of the Public Speaking task (including instructions), VR1 perform: delivery of the speech, R1: Rest period 1, VR2 start: start of the Walk the Plank task (including instructions), VR2 perform: performance of the Walk the Plank task, R2: Rest period 2, VR3 start: start of the Rollercoaster Ride task, R3: Rest period 3, Study close: end of the test session.*

Self-reported 'Nauseous'

The primary outcome of self-reported nausea, measured as 'Nauseous' on a VAS, did not demonstrate a main effect of Treatment ($X^2_1 = 0.549$, $p = 0.459$) or a Treatment x Time interaction ($X^2_{10} = 9.823$, $p = 0.456$) (i.e., 'pretreatment', 'baseline', all three VR tasks and their associated rest intervals 'R1', 'R2' and 'R3', Figure 3).

A priori planned comparisons of VAS ratings between placebo and CBD following the Rollercoaster Ride task (timepoint 'R3' and 'Study Close', Figure 3, $p = 0.793$ and $p = 0.200$, respectively) found no significant difference between the treatments. There was a main effect of time ($X^2_{10} = 396.959$, $p < 0.001$) and it was evident that the Rollercoaster Ride task increased self-reported 'Nausea'. Indeed, ratings were lower at 'VR3 start' (mean $\pm$ standard error (SE); 7 ± 2) than at 'R3' (47 ± 4), Figure 3). The final fitted model included Age; however, it did not have a significant effect ($X^2_1 = 0.667$, $p = 0.414$).

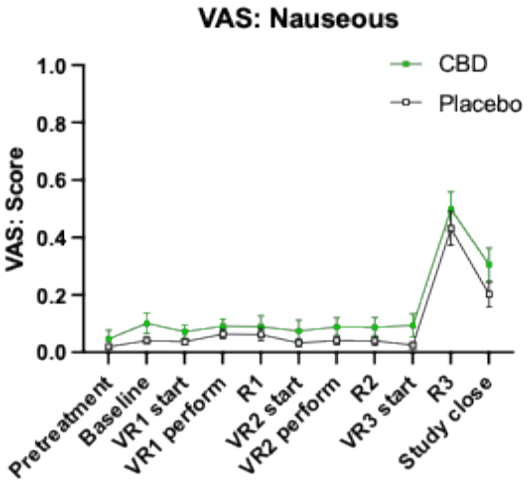


Figure 3. *Visual analogue scale (VAS) ratings of 'Nausea' in the CBD and Placebo groups. The Rollercoaster Ride task (timepoints 'VR3 start' to 'R3') reliably increased self-reported ratings of nausea on a Nauseous VAS in both groups and remained elevated at the end of the study (timepoint 'Study close'). There were no significant group differences.* ***Abbreviations:*** *VR1 start: start of the Public Speaking task (including instructions), VR1 perform: delivery of the speech, R1: Rest period 1, VR2 start: start of the Walk the Plank task (including instructions), VR2 perform: performance of the Walk the Plank task, R2: Rest period 2, VR3 start: start of the Rollercoaster Ride task, R3: Rest period 3, Study close: end of the test session.*

Secondary Outcomes

None of the secondary outcomes under consideration demonstrated significant main effects of Treatment or Treatment x Time interactions (see Appendix 4) and there were no significant differences between groups. A select number of secondary outcomes are discussed below; all found a main effect of time ($p < 0.001$, Appendix 4) and these are therefore reported descriptively below (mean $\pm$ standard error).

Self-Reported 'Tense'

Self-reported VAS ratings of 'Tense' were effectively increased during all three VR tasks; ratings were lower at 'VR1 start' (mean ± standard error (SE); 27 ± 3), 'VR2 start' (19 ± 3) and 'VR3 start' (17 ± 2), than at 'VR1 perform' (46 ± 3), 'VR2 perform' (30 ± 3), and 'R3' (35 ± 4), respectively (Figure 4a).

Self-Reported 'Calm'

Self-reported VAS ratings of 'Calm' were effectively decreased during all three VR tasks; ratings were higher at 'VR1 start' (mean ± standard error (SE); 68 ± 3), VR2 start' (76 ± 2) and 'VR3 start' (78 ± 2) than at 'VR1 perform' (47 ± 3), 'VR2 perform' (61 ± 3) and 'R3' (58 ± 3); respectively (Figure 4b).

4a **4b**

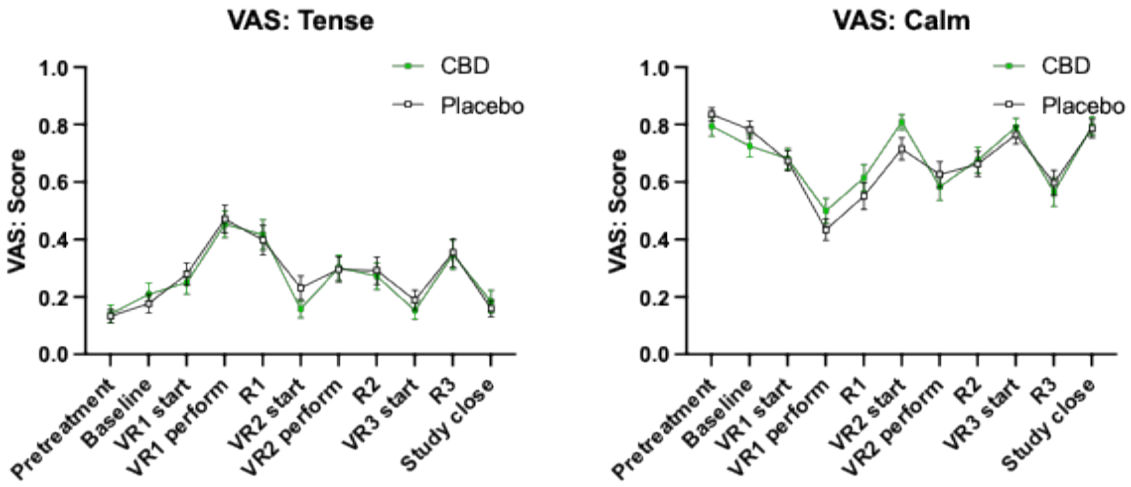


Figure 4. Panel (4a) *Visual analogue scale (VAS) ratings of 'Tense' did not differ significantly overall across the three virtual reality (VR) sessions between the CBD and placebo groups. The Public Speaking task (timepoints 'VR1 start' to 'R1') reliably increased self-reported VAS ratings of 'Tense' in both groups as did the Rollercoaster task (timepoints 'VR3 start' to 'R3').* **Panel (4b)** *VAS ratings of 'Calm' did not differ significantly overall across the three VR sessions between the CBD and placebo groups. The Public Speaking task reliably decreased self-reported ratings of 'Calm' in both groups as did the Rollercoaster task.* ***Abbreviations:*** *VR1 start: start of the Public Speaking task (including instructions), VR1 perform: delivery of the speech, R1: Rest period 1, VR2 start: start of the Walk the Plank task (including instructions), VR2 perform: performance of the Walk the Plank task, R2: Rest period 2, VR3 start: start of the Rollercoaster Ride task, R3: Rest period 3, Study close: end of the test session.*

Salivary Cortisol

Saliva was collected at the 'Pretreatment' and 'Baseline' timepoints, and during the three rest periods ('R1', 'R2', and 'R3'). Salivary cortisol concentrations for both groups are presented in Figure 5. Concentrations increased across the test session relative to Baseline.

Figure 5. *Salivary cortisol concentrations (ng/ml) did not significantly differ between CBD and Placebo groups across the five collection timepoints. A notable increase in cortisol concentrations was found over time commencing from baseline (timepoint 'Baseline' compared to 'R1','R2', and 'R3'). This was consistent with the stressful nature of the virtual reality tasks undertaken.*

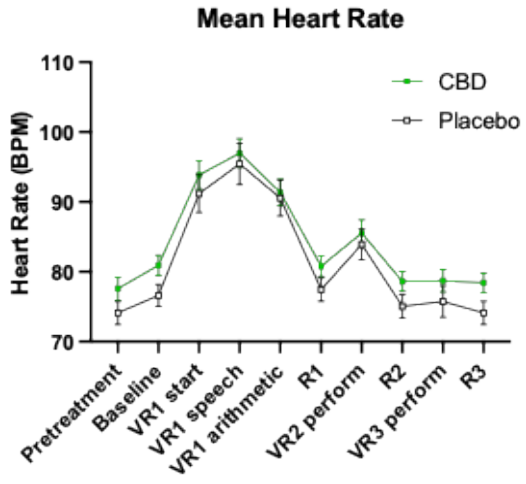
Mean Heart Rate

Regardless of treatment group, mean heart rate was effectively increased, relative to baseline, during the Public Speaking (timepoint 'VR1 speech') and Walk the Plank (timepoint 'VR2 perform') tasks, but not during the Rollercoaster Ride (timepoint 'VR3 perform') task (Figure 6a). There was an absolute difference in the mean heart rate between the CBD and Placebo groups, with the CBD group showing a higher mean heart rate. However, this difference was present during pretreatment (timepoint 'Pretreatment', Figure 6a) and it was concluded that the effect was not drug-related and simply an unexpected artefact of randomisation.

Maximum Forehead Skin Conductance.

The maximum forehead skin conductance (µs) was effectively increased across the test session (Figure 6b) relative to baseline, however, the magnitude of this increase did not differ between the CBD and Placebo groups.

6a



6b

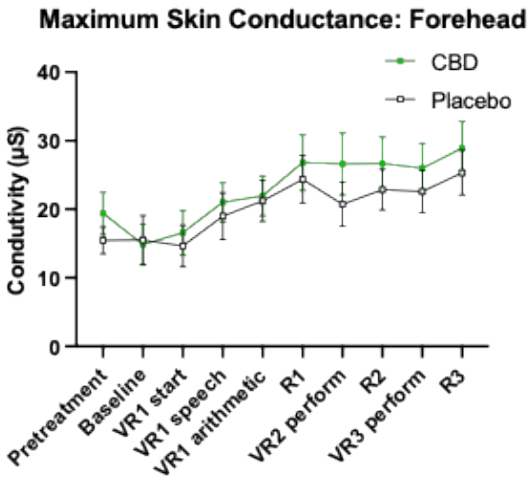


Figure 6. Panel (6a) *Mean heart rate did not show differential change across the test session between the CBD and Placebo groups although an absolute difference was evident that was independent of treatment. The Public Speaking task (timepoints 'VR1 start' to 'R1') reliably increased heart rate in both groups. The Walk the Plank task (time points 'VR2 perform' to 'R2') also tended to increase heart rate.* **Panel (6b)** *Maximum forehead skin conductance did not significantly differ across the test session between the CBD and Placebo groups. There was a reliable increase in skin conductance over time, consistent with the stressful nature of the virtual reality tasks.* ***Abbreviations:*** *VR1 start: start of the Public Speaking task (including instructions), VR1 perform: delivery of the speech, R1: Rest period 1, VR2 start: start of the Walk the Plank task (including instructions), VR2 perform: performance of the Walk the Plank task, R2: Rest period 2, VR3 start: start of the Rollercoaster Ride task, R3: Rest period 3, Study close: end of the test session.*

7.5 Discussion

This clinical trial investigated the effects of an acute 150 mg dose of CBD on psychosocial stress, situational anxiety, motion sickness, and cybersickness in healthy individuals exposed to three VR challenges. The main finding of this study was a significant decrease in self-reported anxiety at the immediate post-task timepoint (but not at the speech-delivery timepoint) of the Public Speaking task in participants treated with CBD relative to those treated with Placebo.

Three previous studies have investigated the effects of CBD on subjective anxiety during a public speaking task [13-15]. All three found that an acute dose of 300 mg significantly reduced subjective measures of anxiety. These effects were observed at specific timepoints, that is, at the speech-delivery [13] or post-task [14] timepoints only, or at both of these timepoints [15]. Two of these studies also investigated low doses of CBD, that is 150 mg CBD [13] and 100 mg CBD [15]; neither found significant effects of CBD on anxiety [13, 15].

However, the 150 mg CBD dose trended towards an anxiolytic effect on the Visual Analogue Mood Scale compared to placebo, and the lack of significance could reflect the study being underpowered [13].

With regard to the Public Speaking task in the current study, the *a priori* planned comparison of self-reported ratings of anxiety between the CBD and Placebo groups was selected at the speech-delivery timepoint ('VR1 perform', Figure 2), based on the above-mentioned trials [13, 15]. However, while the CBD group tended to have lower self-reported ratings of anxiety at the speech-delivery timepoint, this was not significant relative to the Placebo group. It was only at the post-task timepoint ('R1', Figure 2) immediately after the public speaking task that a significant difference between the two groups was evident (corrected Dunn-Šidák).

In retrospect, an *a priori* planned comparison should have been included at this post-task timepoint in the current study given that the abovementioned prior research occasionally found significant anxiolytic effects here [14, 15]. It is notable that this effect did not extend to objective autonomic or endocrine measures of anxiety and appeared modest in magnitude. The earlier study of Linares *et al* [13] also found that 150 mg CBD did not significantly alter autonomic measures of anxiety. In the current study, the presence of effect at the post-task timepoint and absence of effect at the speech-delivery timepoint are difficult to interpret. They could indicate that CBD helped participants recover faster in subjective anxiety following a public speaking task, or perhaps that its effects are more pronounced at lower levels of anxiety. Overall, these results provide further insights into the key timepoints during the public speaking task when low-dose CBD may exert anxiolytic effects.

The lack of effect of 150 mg CBD on self-reported nausea during the Rollercoaster Ride task designed to induce motion sickness is a key finding of the current trial. If anything, participants tended to report higher subjective nausea with CBD (Figure 3). The evidence base around the anti-nausea and anti-emetic effects of CBD is very limited and is largely based on animal models involving house musk shrews [27, 28]. It is important to note that these studies generally administered agents such as lithium chloride or cisplatin to induce nausea and vomiting in animals. Nausea induced by poisons and toxins is distinct from that induced from motion sickness or cybersickness and these may not be directly comparable. Indeed, there is little overlap in the pharmacological treatments that are routinely used for motion sickness (e.g., scopolamine and anti-histamines) and nausea associated with CINV (e.g., selective

serotonin (5-HT3) receptor antagonists and dopamine (D2) receptor antagonists) [40]. Nonetheless, it is possible that a 150 mg CBD dose was insufficient to provide an anti-nausea effect, given that anti-emetic effects of CBD observed in preclinical studies were demonstrated at doses of approximately 5 – 10 mg/kg CBD intraperitoneally in the *Suncus murinus* (house musk shrew) [27, 28]. It should be noted that a precise interspecies dose conversion is difficult to conduct due to the unusual animal species studied.

An important practical aim of the CAPSTAN study was to examine the feasibility and practicality of using a VR test paradigm to induce anxiety and nausea in healthy volunteers. The VR Public Speaking task was effective at inducing anxiety in participants. In contrast, the Walk the Plank task resulted in marginal changes to subjective and objective measures of anxiety suggesting that this task has limited utility. It is possible that this task was not realistic enough to induce an immediate response to danger, or that many participants in this study were unafraid heights. The Rollercoaster Ride task was effective at inducing nausea in participants. These results are consistent with previous studies that also used VR test paradigms to induce motion sickness [25, 35, 36] and suggest that the Rollercoaster Ride task is an effective method to investigate motion sickness. Regarding cybersickness, participants in the current study had negligible ratings of nausea until the final Rollercoaster Ride task, indicating that the current VR test paradigm did not reliably induce cybersickness.

Notably, a high-resolution, high-end VR device (i.e., the Varjo Aero headset) was utilised for this study, and the image quality of this device may have minimised the likelihood of cybersickness typical of VR use with older headsets [25, 35, 36]. Cybersickness was not induced across the test session, thereby disallowing the opportunity to examine the capacity of CBD to reduce this type of nausea. Taken together, the current results indicate the feasibility of using the CAPSTAN VR test paradigm to investigate psychosocial stress and motion sickness (but not situational anxiety and cybersickness) in healthy volunteers and this paradigm may prove useful in future pharmacological studies.

The current study involved a novel formulation of CBD containing TPM permeation enhancer. However, no pharmacokinetic testing was conducted in the current trial and so it is unclear whether the TPM was advantageous in increasing plasma concentrations of CBD relative to more conventional excipients. Venepuncture procedures can cause additional anxiety in public speaking tasks [31], which would be difficult to distinguish from psychosocial stress and situational anxiety and was therefore excluded from the current study. The lack of

pharmacokinetic information is a limitation of the current study. Future studies will help to clarify whether the particular study drug confers a pharmacokinetic advantage.

Future research could also involve the use of the CAPSTAN study Public Speaking and Rollercoaster Ride tasks to investigate the effects of other cannabinoids that have potential anxiolytic an anti-nausea effects. Examples include cannabigerol (CBG), which has recently demonstrated anxiolytic effects in a double-blind, placebo-controlled study of healthy adults [41] and cannabidiolic acid (CBDA), the acidic precursor of CBD, which has demonstrated notable anti-emetic properties in animal studies [42, 43].

Low-dose CBD products were approved for *Pharmacist Only* supply in Australia in 2020 [44, 45]. Legislation governing low-dose CBD supply requires that such products are registered on the Australian Register of Therapeutic Goods [44]. However, the registration process requires robust evidence of efficacy from high-quality clinical trials and several registration trials of 150 mg CBD, primarily examining effects on sleep disturbance, are yet to demonstrate clinical efficacy [46-53]. Therefore, further consideration is required around whether the anxiolytic effect obtained in the current trial during public speaking could assist in the path towards product registration. Considering that the current trial utilised a healthy population, opposed to individuals with glossophobia (i.e., the fear of public speaking), there may be some promise in this endeavour given that *Pharmacist Only* supply is best suited for relatively uncomplicated health conditions [54].

7.6 Conclusion

A low oral dose of 150 mg CBD reduced subjective anxiety following a stressful public speaking task in healthy individuals. There was no evidence of efficacy, however, in relation to motion sickness. The customised VR Public Speaking and Rollercoaster Ride tasks developed for this trial are a safe and effective method to investigate anxiety and nausea and may be useful in future pharmacological studies.

7.7 References

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CHAPTER 8. GENERAL DISCUSSION

This thesis is comprised of a series of original investigations designed to address two primary aims. Aim 1 was to investigate the knowledge, experiences, and attitudes of general practitioners and pharmacists towards medicinal cannabis products, with an emphasis on low-dose CBD. This involved two surveys that were presented in Chapters 2 and 4 and published as Bawa et al., 2023 [1] and Bawa et al., 2022 [2]. Aim 2 was to expand the current evidence base around the efficacy of low-dose CBD products by undertaking two clinical trials utilising these products: an open label trial of transdermal CBD in hand osteoarthritis (the CATCH-OP trial, published as Bawa et al., 2024 [3]) and a placebo-controlled trial of 150 mg oral CBD in anxiety and nausea in the health volunteers (the CAPSTAN trial, protocol published as Bawa et al., 2024 [4]). Both trials were successfully concluded and are described in Chapters 5, 6 and 7.

The current and final chapter of this thesis comprises two parts. The first presents a general discussion of the main findings and some limitations and caveats of the research conducted, while the second considers the wider implications of the research and the future directions for follow-on research.

8.1 Summary of Findings

The outcomes of the four major studies conducted in the thesis (Chapters 2 and 4 - 7) are summarised in Table 1 below.

Table 1. *Summary of the aims and main findings of studies conducted in this thesis*

Research Conducted	Research Aim	Main Findings
Study 1 (Chapter 2): A cross-sectional survey exploring the knowledge, experiences, and attitudes of Australian pharmacists toward medicinal cannabis	To examine Australian pharmacists' experience, knowledge, and attitudes towards medicinal cannabis and low-dose CBD products	1. Many respondents received enquiries about medicinal cannabis 2. Respondents were generally supportive of medicinal cannabis and *Pharmacist Only* low-dose CBD 3. Respondents had low levels of objective knowledge around medicinal cannabis and low-dose CBD products and only half felt comfortable supplying these products 4. Respondents required and welcomed further training and education around medicinal cannabis and low-dose CBD products
Study 2 (Chapter 4): Knowledge, experiences, and attitudes of Australian GPs towards medicinal cannabis: A 2021-2022 survey	To examine the current knowledge, experiences, and attitudes of Australian GPs around medicinal cannabis and low-dose CBD	1. Most respondents received regular enquiries about medicinal cannabis 2. Respondents had low levels of self-rated knowledge around medicinal cannabis 3. Only half of the respondents felt comfortable discussing medicinal cannabis with patients and only a fifth were prescribers 4. Only a fifth of respondents were supportive of *Pharmacist Only* low-dose CBD 5. Respondents required and welcomed further training and education around medicinal cannabis
Study 3 (Chapter 5): An open-label feasibility trial of transdermal CBD for hand osteoarthritis	To investigate the effects of a transdermal CBD gel on hand pain and functionality in patients with symptomatically active hand osteoarthritis	1. CBD decreased pain, anxiety, stiffness and fatigue ratings relative to baseline 2. CBD increased grip strength relative to baseline 3. CBD did not affect subjective ratings of hand functionality or sleep 4. A study design that incorporated novel smartphone technology was successfully used with a high level of compliance
Study 4 (Chapter 6): A randomised, double-blind placebo-controlled trial investigating the efficacy of low-dose CBD in healthy participants	To develop a research protocol to investigate the effects of a low-dose (150 mg) of CBD on anxiety and nausea in healthy individuals	1. A protocol for a novel clinical trial investigating the effects of CBD on anxiety and nausea was developed 2. Three customised virtual reality scenarios were designed to test acute psychosocial stress and situational anxiety (i.e., anxiety) and motion sickness and cybersickness (i.e., nausea) 3. A virtual reality paradigm provides a reliable and reproducible test methodology
Study 4 (Chapter 7): A randomised, double-blind placebo-controlled trial investigating the efficacy of low-dose CBD in healthy participants	To investigate the effects of an acute, low-dose (150 mg) of CBD versus placebo in virtual reality-induced anxiety and nausea in healthy individuals	1. CBD significantly reduced self-reported anxiety immediately after the Public Speaking task but not at speech-delivery 2. CBD had no significant effects on nausea or secondary outcomes 3. The Public Speaking and Rollercoaster Ride tasks effectively increased subjective ratings of anxiety and nausea, respectively 4. VR technologies can be successfully used in pharmacological studies of anxiety and nausea in healthy volunteers

Studies 1 and 2 found that Australian GP and pharmacist respondents generally supported patients having legal access to medicinal cannabis products. However, both groups of health professionals had limited overall knowledge of about these products. In Study 1, approximately two-thirds of pharmacists (67.8%) had 'low' knowledge scores (i.e., total scores < 60.0%) based on an objective knowledge quiz. Similarly, in Study 2, approximately two-thirds of GPs (66.9%) had low self-assessed knowledge. Medicinal cannabis is unlike any other mainstream therapeutic; it is not a single molecule that is used to treat a distinct health condition [5]. Rather, medicinal cannabis is a complex class of medicine, comprising numerous constituents that can be used alone or in varying ratios, with a wide range of formulations and routes of administration. An analysis of prescribing patterns in Australia revealed that medicinal cannabis was prescribed to treat up to 120 distinct medical conditions [6]. TGA data on medicinal cannabis usage indicates that over 400 products are available for prescription [7]. Furthermore, medicinal cannabis may be prescribed as a drug of last resort, or as a 'plant-based' alternative to the usual standard of care, despite limited evidence of efficacy [6, 8]. For these reasons, a considerable amount of time and experience is necessary to develop an expert-level knowledge in medicinal cannabis therapy.

Studies 1 and 2 also found that GP and pharmacist respondents were not entirely comfortable with prescribing and dispensing medicinal cannabis products. Only one-fifth (21.8%) of GPs had ever prescribed medicinal cannabis products, while just over half (53.9%) of pharmacists felt comfortable supplying medicinal cannabis products. In Australia, the process of supplying medicinal cannabis products can be complex, costly, and time-consuming [8]. Prescribers must determine the suitability of treatment, provide clinical justifications for therapy and select from an extensive range of medicinal cannabis products [9, 10]. Meanwhile, pharmacists must source individual products directly from suppliers, navigate complicated supply and security issues, and conduct health and medication checks prior to dispensing [8]. Discomfort was also expressed around managing customer enquiries: only 39.3% of pharmacist and 52.3% of GP respondents felt comfortable and confident discussing medicinal cannabis with patients. Notably, Study 2 was completed in early 2022 and was adapted from an earlier 2018 survey of GPs and medicinal cannabis [11]. During the four-year period between these two studies, the number of medicinal cannabis enquires received by GPs increased considerably (85.3% vs. 61.5% of GPs had received at least one enquiry). However, comfort with managing these enquiries remained unchanged.

Study 2 found that GP respondents were most supportive of the use of medicinal cannabis for 'serious' health conditions such as palliative care, chronic cancer pain, and chemotherapy-induced nausea and vomiting. These findings were consistent with other studies of physicians (Chapter 1.9.2). There was far less support for conditions such as depression, insomnia, and anxiety. It is important to note that the indications for which medicinal cannabis was most often prescribed (i.e., chronic non-cancer pain, anxiety, and neuropathic pain) did not necessarily correlate with those most supported by GP respondents. This suggests that prescribing patterns may be influenced by patient-driven requests. GPs have certainly indicated significant pressure from the public to prescribe medicinal cannabis products [5].

With respect to *Pharmacist Only* low-dose CBD products, more than half (58.7%) of pharmacist respondents were supportive of the provision of these products, despite few (28.4%) being familiar with the specific regulatory requirements of such products. Pharmacists are highly flexible and versatile health professionals. They have a critical role in dispensing medications and are accustomed to the regulatory context of *Pharmacist Only Medicines*. Pharmacists are also heavily involved in providing primary care to the public [12] by means of novel and specialised health initiatives such as COVID-19 vaccination clinics, the supply of emergency contraception, and more recently, the provision of antibiotics for uncomplicated urinary tract infections in women [13-15]. These measures provide convenience to consumers, promote timely access to treatment, encourage efficient use of the health care system, and reduce the burden placed on physicians [16, 17]. As such, it is likely that pharmacist respondents viewed low-dose CBD products as in-line with these other health measures.

Studies 1 and 2 found that both pharmacist and GP respondents required and welcomed further training and education around medicinal cannabis. These findings are consistent with prior research (Chapter 1.9.1 and 1.9.2). Pharmacist respondents in Study 1 noted that the most significant pharmacy-specific barrier to the provision of low-dose CBD was the lack of training around these products. Meanwhile, 79% of GP respondents in Study 2 believed that specialised training should be mandatory for medicinal cannabis prescribing. The leading method by which health professionals maintain ongoing competence in clinical practice is through CPD activities. Health professionals must meet a mandatory requirement of training hours each year by undertaking self-directed learning activities [18]. Professional

organisations may offer accredited learning activities, however, there is no 'gold-standard' or centralised training program around medicinal cannabis. Thus, health professionals must seek this knowledge out for themselves.

Given the considerable need for education around medicinal cannabis highlighted by pharmacist respondents in Study 1, a one-day medicinal cannabis pharmacist training program was developed and implemented in collaboration with Australia's peak medicinal cannabis advocacy body. Importantly, the findings of Study 1 were used to directly address the knowledge gaps highlighted by pharmacist respondents. This national, CPD-accredited training program is an example of knowledge translation in research. Such educational activities aim to maximise the benefits of research and are an important first-step to improve clinical practice [19]. A systematic review of knowledge translation initiatives in allied health disciplines, including pharmacy, found that education alone was insufficient to improve clinical practice [19]. As such, education should be combined with other knowledge translation initiatives. For pharmacists, this could include the development and use of medicinal cannabis dispensing protocols and best practice guidelines.

Pharmacists and GPs are guided by a duty of care to practice within an evidence-based framework [20, 21]. Research clarifying the efficacy of medicinal cannabis is therefore of critical importance to clinical practice. This is especially important for low-dose CBD products which are legislatively considered in a class of their own and likely to be in great demand when available in Australia. This thesis reviewed trials investigating the efficacy of oral lower doses of CBD (≤ 400 mg per day) and topical CBD preparations (Chapter 1.8). It identified a large number of clinical trials encompassing a wide range of indications. Overall, the evidence of efficacy for any particular indication was relatively weak. The most promising studies involved acute oral doses of 300 - 400 mg CBD. At these doses, CBD demonstrated some efficacy in reducing anxiety in healthy volunteers undergoing an anxiety-inducing task, as well as in patients with social anxiety disorder or Parkinson's disease. Only a few clinical trials involving topical CBD preparations were identified and most investigated 'acute' and 'chronic' pain conditions. It was found that the 'chronic' pain conditions were generally responsive to topical CBD, findings that contrasted those involving low doses of oral CBD, where little evidence of efficacy in pain conditions was apparent. One factor that may explain this discrepancy are the clear pharmacokinetic differences between topical and oral preparations of CBD, particularly in the speed and amount of drug exposure at the affected site.

Study 3 was an open-label pilot trial (CATCH-OP) investigating the effects of a transdermal CBD gel on symptomatic hand osteoarthritis. An important additional objective of this study was to determine the feasibility of using novel smartphone technology to manage an array of self-reported outcome data on a daily basis. This included a self-managed squeeze ball dynamometer that connected wirelessly via Bluetooth to a smartphone application. This technology was used with a high level of compliance and provided participants with a user-friendly experience.

Results from this study demonstrated a significant reduction in hand pain ratings on a 0-10 NPRS scale from baseline. It is worth noting that a clinically significant reduction in pain ratings is considered a reduction of approximately two-points or 30% on an 11-point NPRS [22]; a criterion that was met in this study. The objective measure of grip strength was significantly improved over time. Subjective measures of fatigue, stiffness, and anxiety were also significantly improved relative to baseline, but not subjective sleep. The review in Chapter 1.8 identified only one other previous study that investigated the effects of a transdermal CBD preparation on thumb basal joint arthritis [23]. This double-blind, placebo-controlled crossover trial involved 18 participants who administered a transdermal CBD in shea butter preparation daily, delivering a dose of 12.4 mg CBD per day for two weeks. This trial measured subjective rating of pain on a VAS and found clinically significant reductions in pain, similar to Study 3. It should be noted, however, that unlike Study 3, no differences were found in grip strength, although it is unclear how this parameter was measured [23]. Taken together, the results of these studies provide preliminary evidence of the efficacy of transdermal CBD in hand osteoarthritis that is worthy of further investigation.

Study 4 was a randomised, double-blind, placebo-controlled clinical trial (CAPSTAN) investigating the acute effects of a low, oral dose of CBD (150 mg) on anxiety and nausea in healthy participants. Importantly, the clinical trial protocol developed for this study involved a virtual reality test paradigm, allowing a precisely controlled and reproducible study environment (Chapter 6). Preliminary results from this study found that CBD significantly reduced self-reported anxiety immediately after the virtual 'Public Speaking' task but not at speech delivery. The other primary outcome relating to self-reported nausea following a 'Rollercoaster Ride' task was not affected by CBD. Similarly, various secondary outcome measures (i.e., salivary cortisol, heart rate, skin conductance, and other subjective feelings) were not affected by CBD (Chapter 7).

This thesis identified three double-blind, placebo-controlled trials (Chapter 1.8) investigating the acute effects of CBD on anxiety using a public speaking task [24-26]. All three found significant reductions in subjective ratings of anxiety with 300 mg CBD. Two of these studies also investigated lower doses of CBD, that is 100 mg [26] and 150 mg [24]. Neither found a significant effect, although 150 mg CBD showed a considerable trend towards an anxiolytic effect. Indeed, on visual inspection of the self-reported anxiety (Appendix 5) from Linares *et al* [24], 150 mg CBD was associated with the lowest anxiety ratings post-task, although the overall effect was somewhat variable [24]. These results are consistent with those presented in Study 4. The effect of 150 mg CBD at the post-task, but not speech-delivery timepoint may imply that CBD helped participants recover faster in subjective anxiety following a psychosocial stressor, or perhaps that its effects are more pronounced at lower levels of anxiety. Further studies will be required to clarify this finding. Importantly, a key outcome of Study 4 was that the VR test paradigm was effective at inducing anxiety and nausea in participants; this will be useful in future experiments and is considered a strength of Study 4 [27, 28].

There are a number of limitations associated with the research presented in this thesis. First, Study 1 involved a relatively small sample of pharmacists as recruiting from this busy cohort of health professionals proved to be challenging. Second, the proportion of medicinal cannabis prescribers amongst GP respondents in Study 2 was higher than in the general population of GPs, indicating that medicinal cannabis prescribers may have been overrepresented. As such, the findings from both studies 1 and 2 may not be representative of the wider population of pharmacist and GP professionals. Third, Study 3, despite yielding promising results, is unable to provide robust evidence of efficacy as it is an open-label trial (i.e., without a placebo control). Importantly, clinical trials investigating cannabinoids for pain may be particularly susceptible to placebo effects [29]. Indeed, a meta-analysis of 20 randomised, double-blind, placebo-controlled trials of (mostly psychotropic) cannabinoids for pain reported significant placebo responses in these trials. The media coverage around these trials was notably high and positive in tone and may have contributed to the placebo effects, even though the publicity did not necessarily align with the clinical outcomes [29]. Fourth, both Study 3 and 4 utilised novel investigational products (transdermal and oral, respectively) that contained a Vitamin-E-based permeation enhancer (i.e., 'Tocopheryl Phosphate Mixture (TPM)'). Therefore, the results of both studies may not be generalisable to the same dose of

other CBD products lacking this excipient. Finally, for Study 4, no venous blood samples were taken to determine plasma CBD concentrations, meaning that the apparent pharmacokinetic advantage of TPM remains hypothetical [30].

8.2 Future Direction

As consumer demand for medicinal cannabis products continues to rise, the issues of insufficient training and discomfort around prescribing and dispensing these products are likely to become more important to address. The development of a 'gold-standard' medicinal cannabis training program tailored to the individual roles and needs of pharmacists and GPs could greatly assist in resolving these issues. Chapter 3 of this thesis describes a rudimentary road map for developing such a program in a one-day workshop format. Importantly, these training programs must accommodate for the rapidly changing landscape of medicinal cannabis. This will be particularly important for pharmacists if and when *Pharmacist Only* low-dose CBD products become available for supply, as such products are likely to be in great demand.

Study 3 found promising but preliminary evidence of efficacy of transdermal CBD as an intervention for hand osteoarthritis. Therefore, a randomised, double-blind, placebo-controlled trial is warranted to confirm these initial findings. Such a trial should be thoroughly blinded to minimise the influence of placebo effects [29]. Study 3 required that participants treat only their most painful hand with the transdermal CBD gel given that hand osteoarthritis does not always present bilaterally. However, in a real-world situation, it is likely that participants would find the application of treatment to both hands more convenient and this might be incorporated into future trials to improve ecological validity. The FIOHA hand functionality questionnaire was found to be somewhat outdated (e.g., "For women—are you able to sew? For men—are you able to use a screwdriver?") and the use of an alternative questionnaire may be more suitable. One example is the Michigan Hand Outcomes Questionnaire, that enquires about individual hands or hand dominance [31], and could be useful in if both hands are to be treated. The use of pre-post hand X-rays would be useful as an objective measure of structural changes to the hand during treatment, that could indicate a therapeutic benefit. Finally, a future trial could also include the collection of blood samples at the start and end of the trial to determine changes in relevant biomarkers of osteoarthritis

over time. While these are not routinely used for diagnostic purposes or to determine disease severity, they are being increasingly investigated for these purposes. Examples include inflammatory biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP), or cartilage breakdown biomarkers such as collagen type II C-telopeptide (CTX-II) and cartilage oligomeric matrix protein (COMP) [32].

Study 4 provides further evidence of the efficacy of low-dose CBD in treating anxiety but not nausea. The anxiolytic effect was not accompanied by significant autonomic effects and is therefore considered modest but is consistent with a similar prior trial of 150 mg CBD [24]. Further investigation of this low-dose CBD effect is worthwhile. Such future research might involve improving the sensitivity of the 'Public Speaking' task by focusing *a priori* statistical analysis at the post-task time-point. The study design could also be focused, for an example, by removing the 'Walk the Plank' task which was not as effective at inducing the required effect as the other VR scenarios. Furthermore, the trial procedures could be simplified by removing the measurement of skin conductance of the finger and forehead; these did not produce compelling results and added to the complexity of the trial protocol. A longer post-drug administration rest period might result in improved CBD plasma concentrations [33, 34]. While no anti-nausea effects were identified in this study, this outcome was highly exploratory and it is possible that an acute 150 mg CBD dose was insufficient to produce such an effect. Indeed, anti-emetic effects in animal studies involving house musk shrews were demonstrated at doses of approximately 5 – 10 mg/kg CBD intraperitoneally, considerably higher than that used in Study 4, even when approximate interspecies scaling is taken into account [35, 36]. Nonetheless, the 'Rollercoaster Ride' was effective at inducing nausea in participants. Future studies could examine higher doses of CBD or alternative cannabinoids that have similarly demonstrated anti-emetic effects in preclinical studies. For an example, cannabidiolic acid (CBDA), the acidic precursor of CBD, has demonstrated notable anti-emetic properties in animal studies even at very low doses [37, 38].

8.3 Conclusion

Low-dose CBD is a unique class of medicinal cannabis product that has attracted considerable consumer and regulatory attention. In Australia, legislative changes have helped

to distinguish low-dose CBD from other medicinal cannabis products with an aim of permitting over-the-counter access in pharmacies. However, there have been significant delays to this access, which first requires product registration on the ARTG and therefore definitive evidence of efficacy from robust clinical trials. Nonetheless, there are a number of ongoing trials for this purpose. This thesis identified a large number of clinical trials investigating the efficacy of CBD at lower doses (i.e., ≤ 400 mg per day) and found that very little evidence of efficacy exists at ≤ 150 mg CBD. To expand this limited pool of evidence, two clinical trials were conducted. One open-label trial found preliminary evidence of efficacy in participants with hand osteoarthritis who used a transdermal CBD product (~ 30 mg per day) over four weeks. A double-blind, placebo-controlled study investigating the efficacy of an acute low-dose of CBD (i.e., 150 mg) on anxiety and nausea found evidence of a modest anxiolytic effect in a psychosocial stress paradigm. These clinical trials cannot single-handedly satisfy the need for efficacy data highlighted by health professionals. However, they will contribute to a growing body of evidence around the efficacy of low-dose CBD products that will ultimately assist health professionals to perform their duties, a current priority given the advent of Schedule 3 low-dose CBD in Australia. For health professionals who are responsible for the safe and judicious supply of these products to consumers, the delicate balance between evidence-based medicine and patient-centred care is clearly being tested. This thesis broadly characterised the impact that medicinal cannabis, including low-dose CBD, is having on such health professionals. It found that the availability of low-dose CBD products is driving an emerging area of clinical practice that is not currently well-understood. Surveys conducted on Australian pharmacists and GPs identified a considerable knowledge gap around medicinal cannabis, including low-dose CBD. As such, the findings from the pharmacist survey were used to develop and implement a specialised pharmacist training program around medicinal cannabis, including low-dose CBD. This approach showcases a strategic method of translating evidence generated in research for clinical practice improvement and serves as a guide for future educational initiatives in this area. Overall, this thesis identified two pillars of support that can aid pharmacists and GPs in this emerging area of clinical practice; the first is ongoing efforts to provide high-quality educational initiatives and the second is to expand the evidence base around the efficacy of low-dose CBD products for specific indications.

8.4 References

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CHAPTER 9. APPENDICES

Appendix 1

The Australian medicines schedules. Adapted from the Australian Poisons Standard (June 2024).

Schedule	Title	Description
Schedule 1	Blank	This Schedule is intentionally blank.
Schedule 2	Pharmacy Medicine	Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person.
Schedule 3	Pharmacist Only Medicine	Substances, the safe use of which requires professional advice but which should be available to the public from a pharmacist without a prescription.
Schedule 4	Prescription Only Medicine Or Prescription Animal Remedy	Substances, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.
Schedule 5	Caution	Substances with a low potential for causing harm, the extent of which can be reduced through the use of appropriate packaging with simple warnings and safety directions on the label.
Schedule 6	Poison	Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.
Schedule 7	Dangerous Poison	Substances with a high potential for causing harm at low exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.
Schedule 8	Controlled Drug	Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.
Schedule 9	Prohibited Substance	Substances which may be abused or misused, the manufacture, possession, supply or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory Health Authorities.
Schedule 10	Substances of such danger to health as to warrant prohibition of supply and use	Substances which are prohibited for the purpose or purposes listed for each poison.

Appendix 2

Pharmacists and Medicinal Cannabis Literature Review

This appendix presents a literature review conducted around the knowledge, attitudes and experiences of pharmacists in relation to medicinal cannabis and summarises the methods used and results. Chapter 1.9.1 of this thesis discusses the major findings of this literature review.

Method

A review of the scientific literature 10-years preceding May 2023 was conducted and identified 13 studies [1-13]; these investigated the knowledge, attitudes and experiences of approximately 4,000 pharmacists in relation to medicinal cannabis. The characteristics of these studies are summarised in Table 1. Eight studies were conducted in the United States of America, two in Canada and one each in Australia, Jordan and Bulgaria. All studies utilised a cross-sectional design including 12 survey questionnaires and one semi-structured interview.

Data Analysis

The results of these studies were synthesised as follows. First, all of the original questions and their response scales were extracted. Then, the questions were grouped by common 'theme'. A total of five 'broad themes' (i.e., *Subjective Knowledge*, *Objective Knowledge*, *Perceptions*, *Experience* and *Training*) and a numerous 'sub-themes' were identified. Next, the response scales were 'standardised'; that is, converted to a common (and, therefore, comparable) three-point metric of agreement - in this case, 'agree', 'disagree' and 'neither agree nor disagree' - using a systematic process detailed in Table 2. Finally, the most 'popular response' (i.e., one selected by the 'most participants' in the study) was identified and these results summarised by theme (Table 3).

Table 1. *Characteristics of cross-sectional studies reviewing pharmacists around medicinal cannabis.*

Study	Region	Sample	Method	CBD Focus
Bazzari and Bazzari (2023)	Amman, Jordan	60 community pharmacists	**Design:** anonymous cross-sectional study utilising a survey **Distribution:** hard-copy survey distributed to community pharmacists (timeframe not specified)	No
Emmerling et al., (2021)	Wisconsin, USA	93 pharmacists practising in community (38.4%) inpatient (26.3%) and ambulatory care (17.2%)	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** online survey using the Qualtrics platform to a practice-based network of pharmacists (Pharmacy Practice Enhancement and Action Research Link (PearlRx)) from August - October 2020	No
Hwang and Arneson., (2016)	Minnesota, USA	587 pharmacists	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** online survey using the Qualtrics platform to all pharmacists whose email addresses were registered with the Minnesota Board of Pharmacy from March - May 2015	No
Isaac et al., (2016)	Australia	34 registered pharmacists including practising (73.0%), academia (9.0%) and leading representatives of professional organisations (18.0%)	**Design:** anonymous cross-sectional study design utilising a semi-structured interview **Distribution:** convenience sampling of registered Australian pharmacists using email, phone and face-to-face invitations and advertisements in newsletters and social media sites of professional organisations from July - November 2015	No
Kirilov et al., (2020)	Bulgaria	101 community pharmacy managers	**Design:** cross-sectional study design utilising a survey **Distribution:** on a random principle to pharmacies from August - September 2019	Yes
Mitchell et al., (2016)	Canada	769 hospital pharmacists	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** online survey using the FluidSurveys platform to hospital pharmacists in Canada through various pharmacy organisations from January - February 2015	No

Study	Region	Sample	Method	CBD Focus
Nichols et al., (2021)	USA	272 community pharmacy preceptors	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** online survey using the Qualtrics platform to pharmacists registered with education offices at participating schools from January - April 2020.	Yes
Patel et al., (2021)	California Bay Area, USA	103 community pharmacy preceptors	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** hard-copy surveys distributed in-person to community pharmacists between January - March 2020.	Yes
Reece et al., (2021)	Connecticut, USA	355 pharmacists including community pharmacists (47.2%) and hospital pharmacists (21.5%) *others not defined	**Design:** cross-sectional study design utilising a survey **Distribution:** online survey using Google forms to pharmacists whose email addresses were available from the State of Connecticut's Commission of Pharmacy database from October - December 2017	No
Shea et al., (2020)	Colorado, USA	51 Community pharmacists	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** hard-copy surveys distributed to a convenience sample of community pharmacies during the summer of 2018	No
Szaflarski et al., (2020)	USA	451 respondents including neurologists (n=151), nurses and nurse practitioners (n=150) and pharmacists (n=150 of which 24.0% 'community hospital', 14.7% 'academic hospital', 18.7% 'private practice', 46.7% 'other'	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** online survey using the Qualtrics platform to the emails addresses of health professional panels developed by Qualtrics form August - September of 2018	Yes
Szyliowicz and Hilsenrath (2019)	California Bay Area, USA	474 responders, 84% of which were pharmacists and 16% 'other' (i.e., technicians and pharmacy students)	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** online survey using the SurveyMonkey platform emailed to members of the California Pharmacists Association in October 2017	No

Study	Region	Sample	Method	CBD Focus
Vaillancourt et al., (2022)	Canada	1,148 pharmacists and pharmacy students i.e., 1,030 pharmacists from community (56.4%), hospital (29.4%), 'other' (5.1%), consultant or primary care (3.5%), government (1.6%), industry (1.0%), academia (0.9%), or military (0.4%)	**Design:** anonymous cross-sectional study design utilising a survey **Distribution:** online REDCap (Research Electronic Data Capture) platform survey link shared on social media and with pharmacist associations and colleges across Canada from July 2020 - October 2021	No

Table 2. *The standardisation and conversion of scales used in cross-sectional studies of pharmacists around medicinal cannabis.*

Reference	Scale utilised	Conversion metric		
		Disagree	Neither agree nor disagree	Agree
Bazzari and Bazzari (2023)	Level of agreement on a 5-point scale (very low, low, moderate, high, very high)	• very low agreement • low agreement	• moderate agreement	• high agreement • very high agreement
Emmerling et al., (2021)	Level of familiarity on a 5-point scale (not familiar at all, slightly familiar, moderately familiar, very familiar, extremely familiar)	• not familiar at all • slightly familiar	• moderately familiar	• very familiar • extremely familiar
Emmerling et al., (2021)	Level of knowledge on a 5-point scale (not knowledgeable at all, slightly knowledgeable, moderately knowledgeable, very knowledgeable, extremely knowledgeable)	• not knowledgeable at all • slightly knowledgeable	• moderately knowledgeable	• very knowledgeable • extremely knowledgeable
Hwang and Arneson., (2016)	Level of competency on a scale of 1-7 (1 = poor; 7 = excellent).	1-3	4	5-7
Hwang and Arneson., (2016)	Level of concern on a scale of 1-7 (where 1 = no concern; 7 = most concern).	1-3	4	5-7

Reference	Scale utilised	Conversion metric		
		Disagree	Neither agree nor disagree	Agree
Patel et al., (2021)	Level of confidence on a 4-point scale (not confident, somewhat confident, moderately confident and very confident).	• not confident	• somewhat confident	• moderately confident • very confident
Szaflarski et al., (2020)	Level of knowledge on a 5-point Likert scale (not knowledgeable at all, somewhat, moderately, very or extremely knowledgeable)	• not knowledgeable at all • somewhat knowledgeable	• moderately knowledgeable	• very knowledgeable • extremely knowledgeable
Szyliowicz and Hilsenrath (2019)	Level of knowledge on a 7-point scale (no knowledge, very little knowledge, some knowledge, moderate knowledge, substantial knowledge, high level of knowledge and professional level of knowledge).	• no knowledge • very little knowledge • some knowledge	• moderate knowledge	• substantial knowledge • high level of knowledge • professional level of knowledge

Table 3. *Summary of the most 'popular response' (i.e., one selected by the 'most participants' in the study) of cross-sectional studies reviewing pharmacists around medicinal cannabis.*

Theme	Result	Notes	Reference
Subjective knowledge			
I have sufficient knowledge about medicinal cannabis	Most participants (66.7%) disagreed		Mitchell et al., (2016)
	Most participants (63.3%) disagreed		Szyliowicz and Hilsenrath (2019)
	Most participants (47.5%) disagreed	Regarding efficacy	Reece et al., (2021)
	Most participants (46.7%) disagreed	Regarding adverse effects, interactions and contraindications	Bazzari and Bazzari (2023)
	Most participants disagreed*		Isaac et al., (2016)
I have sufficient knowledge of CBD	Most participants (72.8%) disagreed		Patel et al., (2021)
	Most participants (63.5%) disagreed		Emmerling et al., (2021)
	Most participants (61.5%) disagreed	Regarding recommending a specific CBD product	Nichols et al., (2021)
	Most participants (58.9%) disagreed		Nichols et al., (2021)
	Some participants (20.8%) disagreed (most participants (63.2%) agreed)**	Regarding epilepsy	Szaflarski et al., (2020)
I am knowledgeable on medicinal cannabis drug interactions	Most participants (84.0%) disagreed	Regarding CBD	Kirilov et al., (2020)
	Most participants (71.6%) disagreed**	Regarding the effects of phytocannabinoids on hepatic enzymes	Szaflarski et al., (2020)
	Most participants (69.0%) disagreed	Regarding non-prescription CBD	Patel et al., (2021)
	Most participants (56.1%) disagreed		Reece et al., (2021)
	Most participants (60.2%) disagreed	Regarding non-prescription CBD products	Patel et al., (2021)

Theme	Result	Notes	Reference
I am knowledgeable on medicinal cannabis contraindications	Most participants (68.5%) disagreed**	Regarding the effects on the foetus during pregnancy	Szaflarski et al., (2020)
	Most participants (66.5%) disagreed**	Regarding transmission through breast milk	Szaflarski et al., (2020)
I am knowledgeable on the mechanism of action of medicinal cannabis	Most participants (88.6%) disagreed**	Regarding phytocannabinoids other than CBD and THC	Szaflarski et al., (2020)
	Most participants (59.4%) disagreed**	Regarding the effect on neuronal function	Szaflarski et al., (2020)
	Most participants (43.4%) disagreed**	Regarding the central nervous system	Szaflarski et al., (2020)
	Most participants (43.0%) disagreed**	Regarding CBD	Szaflarski et al., (2020)
	Most participants (40.0%) disagreed**	Regarding THC	Szaflarski et al., (2020)
I am knowledgeable on the pharmacology of medicinal cannabis	Most participants (85.7%) disagreed	Regarding pharmacokinetics	Hwang and Arneson., (2016)
	Most participants (84.3%) disagreed	Regarding pharmacodynamics	Hwang and Arneson., (2016)
	Most participants (83.4%) disagreed	Regarding pharmacology	Patel et al., (2021)
	Most participants (82.5%) disagreed	Regarding the endocannabinoid system	Patel et al., (2021)
	Most participants (75.7%) disagreed	Regarding pharmacology	Hwang and Arneson., (2016)
	Most participants (70.5%) disagreed**	Regarding the half-life of medicinal cannabis products	Szaflarski et al., (2020)
	Most participants (69.6%) disagreed**	Regarding the protein-binding capacity of medicinal cannabis products	Szaflarski et al., (2020)
	Most participants (67.0%) disagreed**	Regarding endocannabinoids, synthetic cannabinoids, and phytocannabinoids	Szaflarski et al., (2020)
	Most participants (66.1%) disagreed**	Regarding how medicinal cannabis products are metabolised	Szaflarski et al., (2020)
	Most participants (58.3%) disagreed	Regarding safety of CBD products	Patel et al., (2021)

Theme	Result	Notes	Reference
	Over half disagreed [exact results not provided]	Regarding protein-binding capacity, bioavailability and half-life	Emmerling et al., (2021)
I am knowledgeable on the adverse effects of medicinal cannabis	Most participants (92.2%) disagreed		Szyliowicz and Hilsenrath (2019)
	Most participants (67.4%) disagreed**	Regarding recreational use in the short term	Szaflarski et al., (2020)
	Most participants (46.3%) disagreed		Reece et al., (2021)
	Some participants (31.3%) disagreed (most participants (38.8%) neither agreed nor disagreed) **	Regarding recreational use in the long term	Szaflarski et al., (2020)
I am knowledgeable on the types and formulations of medicinal cannabis	Most participants (93.5%) disagreed	The stability of active ingredients in cannabis-based products	Emmerling et al., (2021)
	Most participants (87.3%) disagreed	Regarding the role of terpenes	Emmerling et al., (2021)
	Most participants (87.0%) disagreed	Regarding the production of medicinal cannabis products	Emmerling et al., (2021)
	Most participants (84.4%) disagreed	Regarding CBD	Patel et al., (2021)
	Most participants (78.2%) disagreed**	Regarding the role of terpenes	Szaflarski et al., (2020)
	Most participants (73.2%) disagreed**	Regarding stability of products	Szaflarski et al., (2020)
	Most participants (73.2%) disagreed		Szyliowicz and Hilsenrath (2019)
	Most participants (72.5%) disagreed**	Regarding manufacturing	Szaflarski et al., (2020)
	Most participants (70.7%) disagreed**	Regarding hemp, CBD and cannabis oils	Szaflarski et al., (2020)
	Most participants (69.6%) disagreed	Regarding issues with labelling accuracy of active ingredients	Emmerling et al., (2021)
	Most participants (69.1%) disagreed	Regarding the differences between hemp, CBD and cannabis oils	Emmerling et al., (2021)
	Most participants (67.8%) disagreed**	Regarding labelling accuracy	Szaflarski et al., (2020)

Theme	Result	Notes	Reference
	Most participants (65.8%) disagreed**	Regarding the differences in bioavailability of various product types	Szaflarski et al., (2020)
I am familiar with the dosing of medicinal cannabis products	Most participants (93.6%) disagreed	Regarding cannabinoid content testing for products sold on pharmacies	Emmerling et al., (2021)
	Most participants (91.8%) disagreed	Regarding the maximum doses of medicinal cannabis products that can be purchase online	Emmerling et al., (2021)
	Most participants (90.7%) disagreed	Regarding the maximum doses that can be purchased from pharmacies	Emmerling et al., (2021)
	Most participants (89.7%) disagreed	Regarding cannabinoid content testing for products sold online	Emmerling et al., (2021)
	Most participants (85.4%) disagreed		Emmerling et al., (2021)
	Most participants (84.4%) disagreed	Regarding the dose of active ingredient in medicinal cannabis products available in pharmacies	Emmerling et al., (2021)
	Most participants (82.3%) disagreed		Szyliowicz and Hilsenrath (2019)
	Most participants (81.5%) disagreed	Regarding the doses of medicinal cannabis products available for purchase online	Emmerling et al., (2021)
	Most participants (71.6%) disagreed**	Regarding clinical trials versus those used in non-approved CBD products	Szaflarski et al., (2020)
	Some participants (29.1%) disagreed (most participants (39.0%) neither agreed or disagreed)**		Szaflarski et al., (2020)
I am knowledgeable on the CBD content of products	Most participants (86.2%) disagreed	Regarding CBD products	Emmerling et al., (2021)
	Most participants (70.5%) disagreed**	Regarding approved and unapproved CBD products	Szaflarski et al., (2020)
	Most participants (67.4%) disagreed**	Regarding approved CBD products	Szaflarski et al., (2020)
	Some participants (44.0%) disagreed (most participants (56%) agreed)	Regarding CBD products	Kirilov et al., (2020)
	Most participants (91.5%) disagreed	Regarding doses used in clinical trials and non-approved products	Emmerling et al., (2021)

Theme	Result	Notes	Reference
I am knowledgeable on the regional and regulatory laws around CBD products	Most participants (86.2%) disagreed	Regarding CBD concentration in approved and non-approved products	Emmerling et al., (2021)
	Most participants (76.6%) disagreed	Regarding CBD concentration in approved products	Emmerling et al., (2021)
	Most participants (72.8%) disagreed		Patel et al., (2021)
	Most participants (70.5%) disagreed**	Regarding approved and unapproved CBD products	Szaflarski et al., (2020)
	Most participants (63.2%) disagreed**	Regarding the uses of approved purified CBD products	Szaflarski et al., (2020)
I have sufficient knowledge of medicinal cannabis to counsel patients	Most participants (56.1%) disagreed	Regarding drug-drug interactions	Reece et al., (2021)
	Most participants (47.5%) disagreed	Regarding efficacy	Reece et al., (2021)
	Most participants (46.7%) disagreed	Regarding adverse effects, interactions, and contraindications of cannabinoids	Bazzari and Bazzari (2023)
	Most participants (46.3%) disagreed	Regarding side effects	Reece et al., (2021)
Objective Knowledge			
Objective knowledge of medicinal cannabis adverse effects	Most participants (86.1%) answered correctly	Regarding possible euphoric effects of CBD Participants provided with a statement and asked to select true/false/I don't know	Nichols et al., (2021)
	Most participants (84%) answered correctly	Regarding the possible side effects of CBD Question format not provided	Kirilov et al., (2020)

Theme	Result	Notes	Reference
	Participants correctly identified anxiety (71.7%), memory/cognitive impairment (70.0%), insomnia (50.0%), Tachycardia (51.7%) and orthostatic hypotension (21.7%) but incorrectly identified loss of appetite (46.7%), constipation (28.3%), glaucoma (21.7%), anaemia (15.0%) and hyperglycaemia (8.3%).	Regarding common adverse effects Participants provided with a list and asked to select correct and incorrect options	Bazzari and Bazzari (2023)
	Most participant (72.7%) answered incorrectly	Regarding the possible side effects of CBD Participants provided with a list and asked to select all of the correct options	Nichols et al., (2021)
Objective knowledge of medicinal cannabis safety	Participants correctly identified warfarin (71.7%), phenytoin (55.0%), alprazolam (51.7%), pregabalin (45.0%), fluoxetine (41.7%) and diphenhydramine (31.7%) but incorrectly identified omeprazole (33.3%), acetaminophen (23.3%), ibuprofen (15.0%) and amoxicillin (10.0%).	Regarding drugs that have moderate or major interactions medicinal cannabis Participants provided with a list and asked to select correct and incorrect options	Bazzari and Bazzari (2023)
	4.6% answered correctly	Regarding the most prominent CYP-mediated drug interactions with CBD Participants provided with a statement and asked to select true/false/I don't know	Nichols et al., (2021)
	Participants correctly identified pregnancy (80.0%), cardiac arrhythmia (60.0%), cardiovascular disorders (60.0%), schizophrenia (45.0%) and major depressive disorder (41.7%) but incorrectly identified glaucoma (25.0%), cancer (21.7%) and hypothyroidism (20.0%).	Regarding contraindications Participants provided with a list and asked to select correct and incorrect options	Bazzari and Bazzari (2023)

Theme	Result	Notes	Reference
Objective knowledge of the cannabinoid content in plant and products	Most participants (84.0%) answered correctly**	Regarding the difference in effects of cannabis-based products based on the cannabinoid content Participants provided with a statement and asked to select yes/no/I don't know	Szaflarski et al., (2020)
	Most participants (78%) answered correctly	Regarding the difference between marijuana and industrial hemp Question format not provided	Kirilov et al., (2020)
	Most participants (38.8%) did not know the answer (31.5% answered correctly)**	Regarding the number of phytocannabinoids present in the cannabis plant Participants asked to select one option from a list of 6 options	Szaflarski et al., (2020)
Objective knowledge regarding regional and regulatory laws of medicinal cannabis products: cannabis-based products	Most participants (83.7%) answered correctly	Regarding whether CBD products containing THC are controlled substance Participants provided with a statement and asked to select true/false/I don't know	Nichols et al., (2021)
	Most participants (74.1%) answered correctly**	Regarding the legality of cannabis for medical purposes Participants provided with a statement and asked to select true/false/I don't know	Szaflarski et al., (2020)
	Most participants (72.8%) answered correctly	Regarding federal laws around CBD products Participants provided with a statement and asked to select true/false/I don't know	Nichols et al., (2021)
	Most participants (54.4%) answered correctly	Regarding whether food products and dietary supplements are legally allowed to contain CBD Participants provided with a statement and asked to select true/false/I don't know	Nichols et al., (2021)
	Most participants (47.7%) answered correctly**	Regarding the legality of hemp for medical purposes Participants provided with a statement and asked to select true/false/I don't know	Szaflarski et al., (2020)

Theme	Result	Notes	Reference
	Most participants (37.7%) answered correctly**	Regarding the legality of isolated plant-derived cannabinoids for medical purposes Participants provided with a statement and asked to select true/false/I don't know	Szaflarski et al., (2020)
	87.0%, 46.0%, 25.0% and 17.0% correctly identified 'Cannabis extracts in oral pill form', 'Inhaled marijuana from cannabis extract', 'Topical cannabis lotion or ointment' and 'Smoked marijuana leaves' respectively.	Regarding permitted dosage forms Participants provided with a list and asked to select correct options	Hwang and Arneson., (2016)
	95.2% had partial knowledge, 3.8% had no knowledge and only 0.9% had full knowledge.	Regarding approved dosage forms of medicinal cannabis Participants provided with a set of 5 items and asked to respond with Yes/No	Reece et al., (2021)
Objective knowledge regarding regional and regulatory laws of medicinal cannabis products: access requirements	Most participants (88%) answered correctly	Regarding whether patients needed to enrol in the state's patient registry in order to obtain medical cannabis Participants provided with a list and asked to select correct options	Hwang and Arneson., (2016)
	Most participants (77%) answered incorrectly	Regarding the need for a prescription to obtain medical cannabis Participants provided with a list and asked to select correct options	Hwang and Arneson., (2016)
	86.0% had partial knowledge and only 11.6% had full knowledge.	Regarding patient registration for a medical cannabis program Participants provided with a set of 5 items and asked to respond with Yes/No	Reece et al., (2021)
	79.1% had partial knowledge, 19.4% had full knowledge and 1.5% had no knowledge	Regarding the role(s) of the dispensary pharmacists Participants provided with a set of 5 items and asked to respond with Yes/No	Reece et al., (2021)

Theme	Result	Notes	Reference
Objective knowledge regarding regional and regulatory laws of medicinal cannabis products: approved indications	Most participants correctly identified cancer-related pain (90%), seizures or epilepsy (73%), and terminal illness with less than one year of life expectancy (69%) but less than half correctly identified glaucoma (46%), amyotrophic lateral sclerosis (43%), acquired immune deficiency syndrome (40%), [14-17]'s syndrome (24%), and Crohn's disease (24%).	Regarding approved medical conditions for the use of medical cannabis Participants provided with a list and asked to select correct options	Hwang and Arneson., (2016)
	Participants correctly identified nausea associated with cancer chemotherapy (58.3%), seizures in Lennox-Gastaut syndrome (35.0%) and anorexia in AIDS patients (28.3%) but incorrectly identified pain associated with cancer (66.7%), chronic neuropathic pain (51.7%), resistant major depressive disorder (41.7%) and weight loss in obese patients (18.3%).	Regarding approved indications Participants provided with a list and asked to select correct and incorrect options	Bazzari and Bazzari (2023)
	79.7% had partial knowledge, 20.3% had full knowledge and no participants had no knowledge	Regarding approved indications Participants provided with a set of 6 items and asked to respond with Yes/No	Reece et al., (2021)
Beliefs, attitudes and perceptions			
I am confident in my knowledge of medicinal cannabis	Most participants (75.7%) disagreed	Regarding the quality of non-prescription CBD products	Patel et al., (2021)
	Most participants (60.2%) disagreed	Regarding the warnings and contraindications of non-prescription CBD products	Patel et al., (2021)
	Most participants (58.3%) disagreed	Regarding the safety of non-prescription CBD products	Patel et al., (2021)

Theme	Result	Notes	Reference
	Most participants (58.2%) disagreed	Regarding the endocannabinoid system	Patel et al., (2021)
	Most participants (52.4%) disagreed	Regarding the various formulations of non-prescription CBD	Patel et al., (2021)
	Most participants (49.5%) disagreed	Regarding the pharmacology of MC	Patel et al., (2021)
	Most participants (41.7%) disagreed	Regarding the legality of non-prescription CBD products	Patel et al., (2021)
I am comfortable counselling on medicinal cannabis	Most participants (88.0%) disagreed		Hwang and Arneson., (2016)
	Most participants (77.6%) disagreed	Regarding patients	Mitchell et al., (2016)
	Most participants (74.9%) disagreed	Regarding other health professionals	Mitchell et al., (2016)
	Most participants (59.0%) disagreed	Regarding recreational marijuana	Shea et al. (2020)
	Some participants (22.9%) disagreed (most participants (57.6%) agreed)		Vaillancourt et al., (2022)
	Some participants (47.0%) disagreed (most participants (53.0%) agreed)		Shea, L. A., et al. (2020)
I am comfortable counselling patients about CBD	Most participants (69.0%) disagreed	Regarding drug interactions	Patel et al., (2021)
	Most participants (63.1%) disagreed	Regarding safety	Patel et al., (2021)
	Most participants (57.6%) disagreed	Regarding efficacy	Patel et al., (2021)
	Most participants (52.4%) disagreed	Regarding the legal status of CBD	Patel et al., (2021)
	Most participants (48.7%) disagreed		Nichols et al., (2021)
I am confident with recommending CBD products	Most participants (70.9%) disagreed	Regarding non-prescription CBD use for various health conditions	Patel et al., (2021)
	Most participants (69.%) disagreed	Regarding providing evidence-based recommendations on non-prescription CBD	Patel et al., (2021)
	Most participants (55.9%) disagreed	Regarding recommending a specific CBD product for patient use	Nichols et al., (2021)

Theme	Result	Notes	Reference
I support the legalisation of medicinal cannabis	Most participants (90.6%) agreed **	Regarding approved CBD products for epilepsy	Szaflarski et al., (2020)
	Most participants (80.5%) agreed**	Regarding when prescribed by a medical provider	Szaflarski et al., (2020)
	Most participants (71.5%) agreed		Emmerling et al., (2021)
	Most participants (68.0%) agreed	Regarding recommending approved CBD products	Emmerling et al., (2021)
	Most participants (66.9%) agreed	Regarding medical and recreational use	Vaillancourt et al., (2022)
	Most participants (66.7%) agreed		Vaillancourt et al., (2022)
	Most participants (63.0%) agreed	Regarding when prescribed by a medical provider	Emmerling et al., (2021)
	Most participants (59.6%) agreed**	Regarding approved and unapproved CBD products through dispensaries	Szaflarski et al., (2020)
	Most participants (43.3%) agreed**	Regarding use for recreational purposes	Szaflarski et al., (2020)
	The majority of participants agreed*		Isaac et al., (2016)
	Some participants (37.1%) agreed (most participants (41.3%) disagreed)	Regarding recreational cannabis	Emmerling et al., (2021)
	Some participants (26.8%) agreed (most participants (67.0%) disagreed)	Regarding recommending unapproved medicinal cannabis products if medicinal cannabis was legalised	Emmerling et al., (2021)
I have concerns around medicinal cannabis	Most participants (74.4%) agreed	Lack of research around CBD in most disease states	Nichols et al., (2021)
	Most participants (54.8%) agreed	Regarding safety	Hwang and Arneson., (2016)
	Most participants (54.5%) agreed	Regarding the consistency of quality of medical cannabis products	Hwang and Arneson., (2016)
	Most participants (52.3%) agreed	Regarding federal regulations	Hwang and Arneson., (2016)
	Most participants (48.7%) agreed	Regarding psychoactive effects and addiction	Hwang and Arneson., (2016)
	Participants agreed*	Regarding long term effects	Isaac et al., (2016)

Theme	Result	Notes	Reference
	Participants agreed*	Regarding the need for high quality products	Isaac et al., (2016)
	Most participants (67.2%) disagreed	Regarding legal repercussions to counselling on medical cannabis	Vaillancourt et al., (2022)
	Most participants (62.3%) disagreed	Regarding legal repercussions to dispensing medical cannabis	Vaillancourt et al., (2022)
	Most participants (61.6%) disagreed	Regarding medical cannabis as a gateway drug	Vaillancourt et al., (2022)
	Most participants (47.4%) disagreed	Regarding misuse	Vaillancourt et al., (2022)
	Most participants (43.4%) disagreed	Regarding limited evidence of efficacy	Hwang and Arneson., (2016)
	Most participants (51.3%) neither disagreed or agreed	Regarding legal repercussions to providing advice on recreational cannabis	Vaillancourt et al., (2022)
Medicinal cannabis is effective	Most participants (81.6%) agreed**	Regarding CBD for epilepsy	Szaflarski et al., (2020)
	Most participants (74.5%) agreed		Szyliowicz and Hilsenrath (2019)
	Most participants (55.2%) agreed		Mitchell et al., (2016)
	Most participants (46.0%) agreed	Regarding CBD use in many disease states	Nichols et al., (2021)
There is stigma associated with medicinal cannabis	Most participants (82.3%) agreed**	Regarding recommending CBD for treating epilepsy	Szaflarski et al., (2020)
	All participants agreed*		Isaac et al., (2016)
Medicinal cannabis is safe	Most participants (54.8%) disagreed	Regarding drug interactions, contraindications, and adverse reactions	Hwang and Arneson., (2016)
	Most participants (44.6%) agreed	Cannabis for medical purposes	Mitchell et al., (2016)
Medicinal cannabis is beneficial	Most participants (50.0%) disagreed		Bazzari and Bazzari (2023)
	Most participants (47.9%) neither agreed nor disagreed		Mitchell et al., (2016)

Theme	Result	Notes	Reference
	Most participants (46.0%) agreed		Nichols et al., (2021)
Medicinal cannabis is medically useful	Most participants (77.8%) agreed**	Regarding CBD use for epilepsy	Szaflarski et al., (2020)
	Most participants (41.7%) neither agreed nor disagreed	Regarding approved drugs	Bazzari and Bazzari (2023)
	Most participants (40.0%) disagreed		Bazzari and Bazzari (2023)
Pharmacists play an important role in the use of medicinal cannabis	Most participants (91.9%) agreed	Regarding counselling	Mitchell et al., (2016)
	Most participants (69.5%) agreed	Regarding dispensing	Vaillancourt et al., (2022)
	Most participants (68.6%) agreed	Regarding intervention	Vaillancourt et al., (2022)
	46% of participants agreed (not clear whether this is 'most participants')	Regarding counselling	Hwang and Arneson., (2016)
	The majority of participants agreed*	Regarding access and safe use	Isaac et al., (2016)
There are expectations placed on pharmacists regarding medicinal cannabis	Most participants (46.2%) neither agreed nor disagreed	Regarding prescribers approving of pharmacists recommending medicinal cannabis for patient use	Nichols et al., (2021)
	Most participants (35.3%) neither agreed nor disagreed	Regarding patient disappointment if pharmacists did not recommend CBD products	Nichols et al., (2021)
I intent to have more involvement in the supply of medicinal cannabis products	Most participants (42.1%) agreed	Regarding counselling patients on CBD products	Nichols et al., (2021)
	Most participants (40.3%) neither agreed nor disagreed	Regarding the recommendation of CBD products for patient use	Nichols et al., (2021)
Experience with medicinal cannabis			
How often are you queried about medicinal cannabis?	Most participants (61.4%) were queried monthly, 18.3% weekly, 10.6% never and 9.8% daily	Regarding therapeutic uses of CBD products	Nichols et al., (2021)

Theme	Result	Notes	Reference
	Most participants (61.1%) were queried monthly, 34.8% were never queried and 2.6% were queried weekly		Vaillancourt et al., (2022)
	Most participants (57.0%) were queried monthly, 20% were queried daily or weekly and 22% were never queried		Shea, L. A., et al. (2020)
	Most participants were queried (55.0%) monthly, 23.2% never, 16.3% weekly and 5.7% daily	Regarding drug interactions with CBD products	Nichols et al., (2021)
	Most participants (54.5%) were queried monthly, 24.8% never, 15.0% weekly, 5.7% daily	Regarding the adverse effects of CBD products	Nichols et al., (2021)
	Most participants (53.8%) were queried monthly		Mitchell et al., (2016)
	Most participants were queried monthly (41%), weekly (31%), daily (16%) or never (12%).	Regarding CBD products	Kirilov et al., (2020)
	Most participants (41.0%) were queried monthly, 33.7% were never queried, 17.9% weekly, and 7.3% daily	Regarding recommending a specific CBD product	Nichols et al., (2021)
	Most participants (58.1%) were never queried, 22.0% monthly, 13.8% weekly and 6.1% daily	Regarding actually recommending a specific CBD product	Nichols et al., (2021)

Theme	Result	Notes	Reference
	Most participants (55.9%) were never queried, 27% were queried monthly, 10.8% queried weekly and 6.5% queried daily	Regarding CBD	Emmerling et al., (2021)
	Most participants (48.3%) were never queried, 39.5% queried monthly and 2.5% were queried weekly	Regarding recreational cannabis	Vaillancourt et al., (2022)
	Most participants (43.0%) were never queried, 41% were queried monthly and 16% queried weekly	Regarding recreational cannabis	Shea, L. A., et al. (2020)
What medical conditions have you observed medicinal cannabis used for?	Pharmacists noted that most patients used CBD solely for good health and well-being	Regarding CBD	Kirilov et al., (2020)
	From a set list, pharmacists noted that CBD was most commonly used for pain, cancer and anxiety	Regarding CBD	Kirilov et al., (2020)
	Most listed AIDS-associated anorexia and wasting syndrome, chronic pain, multiple sclerosis, oncology-related anorexia, and nausea or vomiting		Mitchell et al., (2016)
	The three top indications or the uses of medical cannabis were cancer associated with severe/chronic pain, nausea or vomiting, or cachexia or severe wasting and seizures including those characteristic of epilepsy		Vaillancourt et al., (2022)

Theme	Result	Notes	Reference
Experience miscellaneous: What are the most common questions received about medicinal cannabis?	Indications, uses, and efficacy (33%), followed by drug interactions (30%), where to purchase (19%), and how long marijuana is detected in the body (12%).		Shea, et al. (2020)
Experience miscellaneous: What is the demand for CBD products based on the patients' age?	Pharmacists noted that most patients were 30 - 44 years old (50%)		Kirilov et al., (2020)
Experience miscellaneous: What are the most common products sold in the pharmacy?	Topical creams and lotions (85.7%), oral oils and tinctures (67.2%), oral capsules and tablets (54.6%), and edible foods and beverages (18.5%). Prescription Epidiolex was not commonly sold (5.0%).		Nichols et al., (2021)
Training and Education			
Do you require further education around medicinal cannabis?	Most participants (93.0%) agreed	Regarding state-specific rules and regulations, pharmacotherapy and available types and forms of products on the market	Hwang and Arneson., (2016)
	Most participants (92.1%) agreed		Szyliowicz and Hilsenrath (2019)
	Most participants (91.3%) agreed		Szyliowicz and Hilsenrath (2019)
	Most participants (86.6%) agreed	Regarding CBD	Emmerling et al., (2021)
	Most participants (80.9%) agreed**	Regarding CBD for epilepsy.	Szaflarski et al., (2020)
	Most participants (75.5%) agreed	Regarding CBD products	Nichols et al., (2021)
	Most participants agreed*		Isaac et al., (2016)

Theme	Result	Notes	Reference
What previous education around medicinal cannabis have you received?	Most received no education during their pharmacy undergraduate degree (66.0%), some received no continued education or formal training (64.5%) and some obtained some self-directed education (69.4%)		Mitchell et al., (2016)
	Most participants (53.4%) disagreed that they learnt enough about medicinal cannabinoids during their undergraduate studies		Bazzari and Bazzari (2023)
	Most participants (70.7%) had a mixed education which included continuing pharmacy education, on-the-job training, webinars, conferences, accredited organization certifications, or pharmacy school classes	Regarding CBD	Nichols et al., (2021)
	Most participants (54.8%) had not read the relevant regional regulations and 12.1% were not aware that such regulations existed	Regarding regional/regulatory medicinal cannabis laws	Mitchell et al., (2016)
Training and education miscellaneous: Do you have reliable resources available in your pharmacy on CBD products?	Most participants (57.7%) disagreed		Nichols et al., (2021)
Training and education miscellaneous: Which clinical resources do you use to answer questions about medicinal cannabis?	Tertiary drug databases (e.g., Lexicomp, Micromedex, Facts and Comparisons) or primary literature (38%), the internet (30%) and personal knowledge or peers (16%). Roughly, 16% did not know where to research a question about marijuana.		Shea, L. A., et al. (2020)

Theme	Result	Notes	Reference
Training and education miscellaneous: Do you know where to find information about medicinal cannabis?	54.7% agreed		Szyliowicz and Hilsenrath (2019)

*Semi-structured interview design

**Mixed sample where 33.3% were pharmacists

Abbreviations - CBD: cannabidiol, THC: Δ^9-tetrahydrocannabinol and AIDS: Acquired immunodeficiency syndrome

Results

1.1 Subjective Knowledge

Eleven studies investigated pharmacists' 'subjective knowledge', or perceived levels of knowledge, in relation to medicinal cannabis (Table 3). Overall, participants had low self-assessed knowledge of medicinal cannabis and CBD.

Five studies asked participants whether they thought they had sufficient knowledge of medicinal cannabis 'in general'. Most of the participants in all five studies disagreed [1, 4, 6, 9, 12].

Four studies asked participants whether they had sufficient knowledge of CBD 'in general' [2, 7, 8, 11]. Here, one study found that participants had sufficient knowledge of CBD when used for epilepsy [11] but otherwise they did not, as demonstrated in the final three studies [2, 7, 8].

Seven asked participants whether they thought they had sufficient knowledge on 'specific topics.' The topics assessed included drug interactions [5, 8, 9, 11], contraindications [8, 11], mechanism of action [11], pharmacology [2, 3, 8, 11], adverse events [9, 11, 12], product types [2, 8, 11, 12], product dosing [2, 11, 12], the CBD content of products [2, 5, 11] and the regional and regulatory laws governing CBD [2, 8, 11]. Strikingly, most of the participants in these studies disagreed in 57 out of 60 questions across these topics.

Across these specific topics, knowledge was poorest around product dosing (i.e., the content of medicinal cannabis products available through pharmacies or online). Indeed, eight out of ten questions in this topic scored high disagreement levels (≥ 80%) by participants. Other topic areas that reflected poor knowledge included pharmacology (four out of 11 questions with disagreement levels ≥ 80%) and product types (four out of 13 questions with disagreement levels ≥ 80%).

Finally, two studies asked whether participants had sufficient knowledge to 'counsel patients' - and again - both found that most participants disagreed [1, 9].

1.2 Objective Knowledge

Six studies queried pharmacists' objective knowledge on 'specific topics' regarding medicinal cannabis (Table 3), these included adverse effects [1, 5, 7], safety [1, 7], cannabinoid content [5, 11] and regional and regulatory requirements [1, 3, 7, 9, 11].

Overall, results of objectively-assessed knowledge were mixed. Nonetheless, each 'specific topic' indicated a high level of objective knowledge by some participants.

1.2.1 Adverse Effects

Three studies measured pharmacists' objective knowledge regarding the adverse effects of medicinal cannabis. Overall, results were mixed.

Indeed, while two found that participants had good knowledge around the possible side effects of CBD [5, 7], one did not [7].

A fourth study [1] found that while most participants could correctly identify anxiety and cognitive impairment with good level of accuracy (i.e., ≥ 70%) from a list of adverse effects, they could not reliably identify other options (e.g., insomnia, tachycardia and orthostatic hypotension) - and sometimes incorrectly identified other adverse effects (e.g., loss of appetite, constipation and glaucoma).

1.2.2 Safety

Two studies explored pharmacists' objective knowledge around the safety of medicinal cannabis. Overall, knowledge was poor.

One study found that less than 5% of participants were able to correctly identify liver-mediated drug interactions with CBD [7].

The second study found that participants were only able to correctly identify, with good level of accuracy (i.e., ≥ 70%), 1) warfarin from a list of possible drug interactions and 2) pregnancy from a list of possible contraindication [1]. Participants identified other options less accurately (< 70%) or incorrectly.

1.2.3 Cannabinoid Content

Two studies explored pharmacists' objective knowledge around the cannabinoid content of medicinal cannabis products. Findings were mixed.

While most participants in these studies answered two out of three questions correctly regarding the difference between cannabis and industrial hemp [5] and the difference in effect based on a products' cannabinoid content [11], many participants (38.8%) did not know the answer to the final question regarding the number of phytocannabinoids in the cannabis plant [11].

1.2.4 Regional and Regulatory Laws

Five studies investigated pharmacists' objective knowledge around the regional and regulatory laws governing the supply of medicinal cannabis

Four of these did so by asking participants about the legality of various cannabis-based products [3, 7, 9, 11]. Overall, participants were knowledgeable - attributed to six out of eight questions in this topic area being answered correctly by most participants in the first two studies [7, 11]. Nonetheless, the third study noted that most participants (95.2%) had a 'partial knowledge' of this topic area [9] while the final study found that participants could only correctly identify 'cannabis extracts in oral pill form' from a list as a permitted dosage form with a high level of accuracy (i.e., ≥ 70%) [3].

Two studies queried participants' objective knowledge around regulatory access to medicinal cannabis [3, 9]. Results were mixed. In one study, most participants answered correctly (88.0%) regarding patient enrolment but answered incorrectly (77.0%) regarding the need for a prescription [3]. In the other study, most participants only had 'partial knowledge' around patient registration (86.0%) and the role of the pharmacist (79.1%)[9].

Finally, three studies asked participants about the approved indications of medicinal cannabis [1, 3, 9]. Generally, knowledge in this area was lacking. The first study found that most participants (79.7%) only had a partial knowledge in this area [9]. The second study found that while participants were able to correctly identify cancer-related pain and epilepsy from a list of options with good level of accuracy (i.e., ≥ 70%), they identified other indications less accurately (< 70%). The third study found that participants did not correctly identify any indication with good level of accuracy (i.e., ≥ 70%) and incorrectly identified other indications.

1.3 Beliefs

Eleven studies explored pharmacists' beliefs around towards medicinal cannabis (Table 3).

Overall, participants lacked confidence around medicinal cannabis therapy and were not comfortable with counselling patients on therapy. Nonetheless, they supported the legalisation of cannabis and believed their role of counselling patients on therapy was an essential one. Participants were particularly supportive around CBD for epilepsy. The biggest concern for pharmacist was the lack of research around CBD in most disease states.

1.3.1 Comfort and Confidence

Six studies investigated pharmacists' 'comfort' and 'confidence' towards medicinal cannabis [3, 6-8, 10, 13].

One explored whether pharmacists were confident in their knowledge of medicinal cannabis 'in general'. Most of the participants in this study disagreed in all seven questions exploring this topic [8].

Four asked participants whether they were comfortable counselling on medicinal cannabis 'in general' [3, 6, 10, 13]. While results were mixed, there was a greater level of disagreement (i.e., 88.0% - 59.0% across four out of six questions) [3, 6, 10] than agreement (i.e., 57.6% - 53.0% across two out of six questions) [10, 13] by most participants in these studies.

Two further studies asked participants whether they were 1) comfortable counselling on CBD products and 2) confident with CBD product recommendations [7, 8]. Most of the participants in these studies disagreed with all eight questions across these topics [8]. Indeed, unease with CBD products is clearly highlighted.

1.3.2 Legalisation

Four studies queried whether pharmacists supported the legalisation of medicinal cannabis [2, 4, 11, 13].

Results varied, however, there was far greater support by most participants in these studies in ten out of 12 questions, particularly (agreement levels ≥ 80%) for prescriber-

obtained medicinal cannabis and CBD for epilepsy [11]. Support was least favoured for recreational cannabis and unapproved medicinal cannabis products [2].

1.3.3 Concerns

Four studies explored pharmacists' concerns around medicinal cannabis. Overall, results were mixed but tended towards greater concern.

Indeed, concern was expressed by most participants in these studies (i.e., seven out of 13 questions) around the lack of research around CBD [7], the safety and long-term effects of medicinal cannabis use [3, 4], product quality [3, 4] and the federal regulations governing use [3].

Conversely, concern was not expressed by most participants in these (i.e., five out of 13 questions) around the misuse [13], lack of evidence of efficacy [3] and the potential legal repercussions to counselling on or dispensing medicinal cannabis [13].

1.3.4 Use of Medicinal Cannabis

Seven studies considered pharmacists' beliefs around 'specific topics' relating to the use medicinal cannabis. These included efficacy [6, 7, 11, 12], stigma [4, 11], usefulness [1, 11] and safety [1, 6, 7].

Four of these did so by asking participants if they thought medicinal cannabis was 'effective' and two did so by asking participants if there was a 'stigma' associated with the use of medicinal cannabis Most participants in these studies agreed in all six questions across these topics.

Two asked participants if medicinal cannabis was 'useful'. While results were mixed most participants agreed that it was useful, especially around CBD use for epilepsy [11]. Interestingly, this emphasis on CBD for use in epilepsy was also noted in two questions around efficacy and stigma (both with agreement levels ≥ 80%) [11].

Participants were also asked if medicinal cannabis was 'safe' in two studies [3, 6], 2) and 'beneficial' in three studies Overall, participants were neutral in their levels of agreement (i.e., levels of agreement and disagreement were approximately evenly distributed in these studies).

1.3.5 The Role of the Pharmacist

Five studies queried pharmacists' perspectives around their role in the use of medicinal cannabis [3, 4, 6, 7, 13].

Four of these asked participants if pharmacists played an important role in the use of medicinal cannabis [3, 4, 6, 13]. Most of the participants in these studies agreed in all questions, particularly (agreement levels ≥ 80%) around counselling others on medicinal cannabis [6].

1.4 Experiences

Six studies investigated pharmacists' experiences in the supply of medicinal cannabis products (Table 3).

Overall, participants were regularly queried on medicinal cannabis, particularly around the therapeutic uses of CBD products. Participants often received questions about indications, uses and efficacy. The most common products sold in the pharmacy were topical creams and lotions.

All six studies asked participants how often they were queried about medicinal cannabis [2, 5-7, 10, 13]. Responses were 'standardised', that is, converted to a comparable four-point metric ('monthly', 'weekly', 'daily' or 'never') detailed in Table 4 below.

Table 4. Frequency of medicinal cannabis queries received by pharmacists.

Monthly	Weekly	Daily	Never
Includes: • Monthly • Once a month • Less than twice per month • Less than once per month • Seldom	Includes: • Weekly • Once a week • Once per week or more • Often	Includes: • Daily • Once a day • Once a day or more • Regularly	Includes: • Never

Five studies found that most participants were queried monthly [5-7, 10, 13]. Regardless, participants also received daily or weekly queries but to a lesser extent. Common queries included those around indications, efficacy and drug interactions [10].

Three asked participants what medical conditions they had seen medicinal cannabis used for; all three noted serious chronic health conditions such as cancer and pain [5, 6, 13].

Finally, one asked participants about the most common CBD products sold in the pharmacy; topical creams and lotions, oral oils and tinctures and oral capsules and tablets were noted by most participants in this study [7].

1.5 Training and Education around Medicinal Cannabis

Nine studies investigated the training and education of pharmacists in relation to medicinal cannabis (Table 3).

Overall, participants noted a strong need for further education and an inconsistent history of training in medicinal cannabis.

Three of these asked participants about their previous education on medicinal cannabis [1, 6, 7]. Findings were inconsistent. Indeed, two questions noted that more than half of participants received no undergraduate training [1, 6] while another two questions found training was largely self-directed [6, 7].

This inconsistency was noted once again by two studies that found various sources of information were used to either self-direct training [7] or answer questions about medicinal cannabis [10].

Finally, six studies asked participants if they required further education around medicinal cannabis [2-4, 7, 11, 12]. Unsurprisingly, most of the participants agreed in all seven questions across this topic. Particular importance (agreement levels ≥ 80%) was placed on state-specific regulations, pharmacotherapy and the types and formulations of medicinal cannabis [3], CBD [2] and its use in epilepsy [11].

1.6 References

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Appendix 3

Physicians and Medicinal Cannabis Literature Review

This appendix presents a literature review conducted around the knowledge, attitudes and experiences of physicians in relation to medicinal cannabis and summarises the methods, used and results. Chapter 1.9.2 of this thesis discusses the major findings of this literature review.

Methods

A review of the scientific literature 10 years preceding May 2023 was conducted and identified 16 studies which investigated the knowledge, attitudes, experiences and training requirements of approximately 3,800 primary care physicians (i.e., GPs and physicians of family and internal medicine) regarding medicinal cannabis [1-16]. The characteristics of these studies are summarised in Table 1. Five of the studies were conducted in the United States of America, three in Canada, two in Ireland, two each in Europe and the Middle East and one each in Australia and New Zealand. All of the studies utilised a cross-sectional design including 14 survey questionnaires and two semi-structured interviews.

Data Analysis

The results of these studies were synthesised as follows. First, all of the original questions and their response scales were extracted. Then, the questions were grouped by common 'theme'. A total of five 'broad themes' (i.e., *Subjective Knowledge*, *Objective Knowledge*, *Perceptions*, *Experience* and *Training*) and a numerous 'sub-themes' were identified. Next, the response scales were 'standardised'; that is, converted to a common (and, therefore, comparable) four-point metric of agreement - in this case, 'agree', 'disagree', 'neither agree nor disagree' and 'I don't know/unchosen'- using a systematic process detailed in Table 2. Finally, the most 'popular response' (i.e., one selected by the 'most participants' in the study) was identified and these results summarised by theme (Table 3).

Table 1. *Characteristics of cross-sectional studies reviewing physicians around medicinal cannabis.*

Study	Region	Sample	Method
Abo Ziad et al., (2022)	Israel	152 participants: specialists in family medicine (65.5%), residents in family medicine (32.4%), general practitioners (2.0%) and missing data (2.6%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the study questionnaire was distributed among participants at staff meetings in clinics, at continuous education programs in the Department of Family Medicine and directly to physicians at their clinics (timeframe not specified)
Adler et al., (2022)	Israel	201 participants: primary care physicians (75.0%), primary care residents (20%) and 'no specialty (5%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** to primary care physicians in health maintenance organizations between November 2020 - March 2021
Crowley et al., (2017)	Ireland	565 participants: GPs (85.3%), GP specialists (77.5%) , trained GP managing opioid users (34.3%) and academic GPs (23.0%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the online study questionnaire was distributed to all GPs in the Irish College of General Practitioners (ICGP) in early 2016
Di Giovanni et al., (2022)	Canada	82 family physicians	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the online study questionnaire was distributed by REDCap using the Saskatchewan Medical Association between January to February 2020
Hachem et al., (2022)	Canada	70 participants: attending physicians or medical residents (68.6%), nurses (14.3%), pharmacists (8.6%) and 'other' 6 (8.6%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the online study questionnaire was distributed by REDCap using 24 healthcare associations and an advertisement placed in Canadian Medical Association Journal between April - December 2021

Study	Region	Sample	Method
Hordowicz et al., (2022)	Poland	173 participants: 58 physicians with internal medicine or GP specialty (i.e., 34%). The remainder were physicians with or without specialist training (some with more than one specialty) and 5 medical interns.	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the online study questionnaire was distributed by Google Forms using Medical Chambers, online courses, professional newsletters and social media between June to October 2020
Jean-Jacques et al., (2021)	Florida, America	46 participants: medicinal cannabis -qualified physicians (56.5%), 'other' physicians or physicians (30.5%), medical staff (i.e., dispensary or medical clinic) (21.8%), medicinal cannabis businessperson (17.4%), medicinal cannabis patients (21.7%) and professor (2.2%) - multiple options available	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the hard copy or online study questionnaire (using Qualtrics) was distributed at the American Medical Marijuana Physicians Association annual meeting in Orlando, Florida in October 2019
Karanges et al., (2018)	Australia	640 GPs and GP registrars: GPs 589 (92.1%) and GP registrars 51 (7.9%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the hard copy study questionnaire was distributed at GP educational seminars held in five major Australian cities between August and November 2017
Kruger et al., (2018)	Michigan ,USA	244 physicians: primary care (52%), specialty (48%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the online study questionnaire was distributed using Qualtrics to physicians in a university-affiliated health system between May - July 2020
Ng et al., (2021)	Ontario, Canada	11 family physicians	**Design:** anonymous cross-sectional study design using semi-structured interviews **Distribution:** semi-structured telephone interviews were conducted using a snowball sampling method between January and October 2019

Study	Region	Sample	Method
Oldfield et al., (2020)	New Zealand	76: GPs (88.2%), GP registrars (3.9%), trainee interns (2.6%) and 'not stated' (5.3%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the survey was conducted using a snowball sampling method of a convenience sample of GPs attending continuing medical education sessions between June and October 2018
Philpot et al., (2019)	Minnesota, USA	62 participants: primary care providers including physicians (i.e., medical doctors, doctor of osteopathy, Bachelor of Medicine Bachelor of Surgery (MBBS)) (75.6%) and nurse practitioners and physician assistants (27.4%)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** the online survey was distributed via email to a convenience sample of GPs from Mayo Clinic between January - February 2018
Rosenbaek et al., (2023)	Denmark	427 GP participants	**Design:** anonymous cross-sectional study design using a survey **Distribution:** a postal invitation to participate in a national online survey sent to Danish GPs whose details were obtained from national registries between September 2018 - July 2019.
Sajdeya et al., (2021)	Florida, USA	116 registered medicinal cannabis physicians: comprising of family practice 41(35.0%) and internal medicine 19 (16.0%); the remainder were other medical specialists (participants could select more than one specialty)	**Design:** anonymous cross-sectional study design using a survey **Distribution:** disseminated via email by a Consortium of nine universities that conduct medicinal cannabis research to a database of physicians between June and October 2020

Study	Region	Sample	Method
Schauer et al., (2022)	USA	Sub-sample of 483 family practice doctors who completed a physician's survey (from an original sample of 1506 participants: family practice doctors 483 (32.1%), 1506 physicians including: family practice doctors 483 (32.1%), internists 518 (34.4%), nurse practitioners 252 (16.7%) and oncologists 253 (16.8%))	**Design:** anonymous cross-sectional study design using a survey **Distribution:** physicians completed the online 2018 DocStyles survey which included questions around medicinal cannabis
Van Hout et al., (2017)	Ireland	565 GPs: 482 (85.3%) GPs, 435 (77.5%) GP specialists, trained GP managing opioid users 194(34.3%) and 129 (23.0%) academic GPs	**Design:** anonymous cross-sectional study design using a survey that included a section of open-ended questions **Distribution:** the online survey was administered on 'Survey Monkey' to all GPs in the Irish College of General Practitioner (ICGP) database for one month in mid-2015

Table 2. *The standardisation and conversion of scales used in cross-sectional studies of physicians around medicinal cannabis.*

Reference	Scale used	Conversion metric			
		Disagree	Neither agree nor disagree	Agree	Other
Abo Ziad et al., (2022)	Level of agreement on a 5-point scale of extent (not at all, to a small extent, to a reasonable extent, to a great extent, and to a very great extent)	• not at all • to a small extent	• to a reasonable extent	• to a great extent • to a very great extent	NA
Adler et al., (2022)	Level of agreement on a 5-point scale (agree: 4-5, somewhat agree: 3, disagree: 1-2)	• disagree: 1-2	• somewhat agree: 3	• agree: 4-5	NA
Crowley et al., (2017)	Level of agreement on a 5-point Likert scale (only agree and strongly agree levels provided)	• not provided	• not provided	• agree or strongly • agree	NA
Di Giovanni et al., (2022)	Level of agreement on a 3-point Likert scale (yes, no and sometimes)	• no	• sometimes	• yes	NA
Di Giovanni et al., (2022)	Level of agreement on a 5-point Likert scale of comfort (not at all, slightly, somewhat, moderately or very)	• not at all • slightly	• somewhat	• moderately • very	NA
Di Giovanni et al., (2022)	Level of agreement on a 3-point Likert scale of training (no, I do not have adequate training, I have some knowledge, but would benefit from more training and yes, I have adequate training)	• no, I do not have adequate training	• I have some knowledge, but would benefit from more	• I have adequate training	NA
Hordowicz et al., (2022)	Level of agreement on a 5-point Likert scale of experience (none/minimal, treated up to 10 cases	• none/minimal	• treated up to 10 cases	• treated more than 10 cases	NA
Hordowicz et al., (2022)	Level of agreement on a 5-point Likert scale (no, rather not, neither agree nor disagree, rather yes and yes)	• no • rather not	• neither agree nor disagree	• rather yes • yes	NA

Reference	Scale used	Conversion metric			
		Disagree	Neither agree nor disagree	Agree	Other
Hordowicz et al., (2022)	Level of agreement on a 5-point Likert scale of safety (much worse than, worse than, similar to, better than and much better than)	• worse than • much worse than	• similar to	• better than • much better than	NA
Hordowicz et al., (2022)	Level of agreement on a 6-point Likert scale of significance (unchosen, the least significant, rather not significant, moderately significant, rather significant, the most significant)	• the least significant • rather not significant	• moderately significant	• rather significant • the most significant	Unchosen
Karanges et al., (2018)	Level of agreement on a 5-point Likert scale (strongly disagree, slightly disagree, neutral, slightly agree and strongly agree)	• strongly disagree • slightly disagree	• neutral	• slightly agree • strongly agree	NA
Kruger et al., (2018)	Level of agreement on a 5-point Likert scale of knowledge (not knowledgeable at all, slightly knowledgeable, moderately knowledgeable, very knowledgeable and extremely knowledgeable)	• not knowledgeable at all • slightly knowledgeable	• moderately knowledgeable	• very knowledgeable • extremely knowledgeable	NA
Kruger et al., (2018)	Level of agreement on a 5-point Likert scale of competency (not competent at all, slightly competent, moderately competent, very competent and extremely competent)	• not competent at all • slightly competent	• moderately competent	• very competent • extremely competent	NA
Kruger et al., (2018)	Level of agreement on a 5-point Likert scale of comfort (very uncomfortable, somewhat uncomfortable, neither comfortable nor uncomfortable, somewhat comfortable and very comfortable)	• very uncomfortable • somewhat uncomfortable	• neither comfortable nor uncomfortable	• somewhat • comfortable very comfortable	NA

Reference	Scale used	Conversion metric			
		Disagree	Neither agree nor disagree	Agree	Other
Philpot et al., (2019)	Level of agreement on a 5-point Likert scale (strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree and strongly disagree)	• strongly agree • somewhat agree	• neither agree nor disagree	• somewhat disagree • strongly disagree	NA
Philpot et al., (2019)	Level of agreement on a 6-point Likert scale of helpfulness (1, very helpful; 2, somewhat helpful; 3, neither helpful nor not helpful; 4, somewhat not helpful; 5, not at all helpful; 6, don't know)	• 4-5	• 3	• 1-2	6 ('don't know')
Philpot et al., (2019)	Level of agreement on a 6-point Likert scale of extent (1, a great deal; 2, quite a bit; 3, somewhat; 4, very little; 5, not at all; 6, don't know)	• 4-5	• 3	• 1-2	6 ('don't know')
Rosenbaek et al., (2023)	Levels of agreement on 6-point Likert scale of knowledge (to a very high extent, to a high extent, somewhat, to a lesser extent, not at all and do not know/not relevant)	• to a lesser extent • not at all	• somewhat	• to a very high extent • to a high extent	'do not know/not relevant'
Rosenbaek et al., (2023)	Levels of agreement on 6-point Likert scale of attitude (very positive, predominantly positive, neither positive nor negative, predominantly negative, very negative, and do not know/not relevant	• predominantly • negative very negative	• neither positive nor negative	• very positive • predominantly positive	'do not know/not relevant'
Sajdeya et al., (2021)	Levels of agreement on 3-point Likert scale of usefulness (not very useful, useful, very useful)	• not very useful	• useful	• very useful	NA

Reference	Scale used	Conversion metric			
		Disagree	Neither agree nor disagree	Agree	Other
Sajdeya et al., (2021)	Levels of agreement on 4-point Likert scale of influence(no influence, somewhat influence, influence, most influence)	• no influence	• somewhat influence	• influence most influence	NA
Sajdeya et al., (2021)	Levels of agreement on 5-point Likert scale of frequency (never, rarely, sometimes, often and always)	• never • rarely	• sometimes	• often • always	NA
Sajdeya et al., (2021)	Levels of agreement on 5-point Likert scale of likelihood (very unlikely, unlikely, not sure, likely and very likely)	• very unlikely • unlikely	• not sure	• likely • very likely	NA

Table 3. *Summary of the most 'popular response' (i.e., one selected by the 'most participants' in the study) of cross-sectional studies reviewing physicians around medicinal cannabis.*

Theme	Result	Notes	Reference
Subjective Knowledge			
I have sufficient knowledge 'in general' about medicinal cannabis	Most participants (82.9%) disagreed	Regarding legally accessing medicinal cannabis products	Karanges et al., (2018)
	Most participants (80.2%) disagreed		Di Giovanni et al., (2022)
	Most participants (79.2%) disagreed	Regarding prescribing	Rosenbaek et al., (2023)
	Most participants (78.2%) disagreed	Regarding effects	Karanges et al., (2018)
	Most participants (63.0%) disagreed		Adler et al., (2022)
	Most participants (61.0%) disagreed		Kruger et al., (2018)
	Participants disagreed*	Regarding administration	Ng et al., (2021)
I am knowledgeable on the different medicinal cannabis product types and formulations	Most participants (86.1%) agreed**	Regarding Sativex	Oldfield et al., (2020)
	Most participants (61.3%) agreed	Regarding the safety of approved versus illicit cannabis	Philpot et al., (2019)
	Most participants (56.6%) agreed	Regarding pharmaceutical-grade cannabis	Oldfield et al., (2020)
	Most participants (68.1%) disagreed		Karanges et al., (2018)
	Most participants (64.4%) disagreed	Regarding 'street' versus approved cannabis	Karanges et al., (2018)
	Most participants (60.7%) neither agreed nor disagreed	Regarding the efficacy of approved versus illicit cannabis	Philpot et al., (2019)
I am knowledgeable on regional/regulatory requirements around medicinal cannabis	Most participants (97.2%) agreed	Regarding the Cannabis Act	Di Giovanni et al., (2022)
	Most participants (78.0%) agreed	Regarding the current regulatory approach to medicinal cannabis	Di Giovanni et al., (2022)
	Most participants (72.9%) agreed	Regarding driving regulation	Hachem et al., (2022)
	Most participants (78.9%) disagreed	Regarding medicinal cannabis access in Canada	Karanges et al., (2018)

Theme	Result	Notes	Reference
	Most participants (70.0%) disagreed	Regarding the position statement of a key medical organisation	Karanges et al., (2018)
Objective knowledge			
Objective knowledge of the potential risks associated with medicinal cannabis	Most participants (95.1%) answered correctly	Regarding cannabis overdose	Kruger et al., (2018)
	Most participants (89.3%) answered correctly	Post-traumatic stress disorder	Kruger et al., (2018)
	Most participants (66.4%) answered correctly	Regarding motor vehicle crashes	Kruger et al., (2018)
	Most participants (65.2%) answered incorrectly	Regarding occupational accidents or injuries	Kruger et al., (2018)
	Most participants (65.2%) answered incorrectly	Regarding the development psychoses	Kruger et al., (2018)
	Most participants (58.2%) answered incorrectly	Regarding lower birth weight during pregnancy	Kruger et al., (2018)
Objective knowledge of the efficacy of medicinal cannabis in various conditions	Most participants (98.0%) answered correctly	Regarding dementia	Kruger et al., (2018)
	Most participants (93.4%) answered correctly	Regarding Irritable Bowel Syndrome	Kruger et al., (2018)
	Most participants (84.4%) answered correctly	Regarding depression secondary to chronic pain/MS (	Kruger et al., (2018)
	Most participants (80.3%) answered correctly	Regarding cancer	Kruger et al., (2018)
	Most participants (74.6%) answered correctly	Regarding chemotherapy induced nausea and vomiting	Kruger et al., (2018)
	Most participants (72.1%) answered correctly	Regarding Generalised Anxiety Disorder	Kruger et al., (2018)
	Most participants (69.7%) answered correctly	Regarding glaucoma	Kruger et al., (2018)
	Most participants (68.0%) answered correctly	Regarding anorexia	Kruger et al., (2018)
	Most participants (64.3%) answered correctly	Regarding non-chemotherapy related nausea and vomiting	Kruger et al., (2018)

Theme	Result	Notes	Reference
	Most participants (54.1%) answered correctly	Regarding chronic pain	Kruger et al., (2018)
	Most participants (68.9%) answered incorrectly	Regarding spasticity secondary to multiple sclerosis	Kruger et al., (2018)
	Most participants (67.6%) answered incorrectly	Regarding sleep issues in individuals with chronic pain/MS	Kruger et al., (2018)
Objective knowledge of harm reduction strategies associated with medicinal cannabis	Most participants (100.0%) answered correctly	Regarding using ice in bong to reduce potency	Kruger et al., (2018)
	Most participants (100.0%) answered correctly	Regarding using a concentrate rather than raw plant	Kruger et al., (2018)
	Most participants (99.2%) answered correctly	Regarding using longer stemmed pipes	Kruger et al., (2018)
	Most participants (99.2%) answered correctly	Regarding using strains that have a high THC/CBD ratio	Kruger et al., (2018)
	Most participants (97.5%) answered correctly	Regarding using a bong/water pipe	Kruger et al., (2018)
	Most participants (93.4%) answered correctly	Regarding adding a filter	Kruger et al., (2018)
	Most participants (52.5%) answered correctly	Regarding avoiding use while pregnant	Kruger et al., (2018)
	Most participants (93.4%) answered incorrectly	Regarding vaping rather than smoking	Kruger et al., (2018)
	Most participants (65.6%) answered incorrectly	Regarding using strains that have a high CBD/THC ratio	Kruger et al., (2018)
	Most participants (64.8%) answered incorrectly	Regarding ingestion rather than inhalation	Kruger et al., (2018)
	Most participants (52.0%) answered incorrectly	Regarding avoiding driving within 6 hours of use	Kruger et al., (2018)
	Most participants (18.4%) answered incorrectly	Regarding avoiding mixing with tobacco	Kruger et al., (2018)
Objective knowledge of the effective doses of medicinal cannabis	Most participants (89.0%) were unsure	Regarding effective dose of CBD	Kruger et al., (2018)
	Most participants (88.0%) were unsure	Regarding effective dose of THC	Kruger et al., (2018)

Theme	Result	Notes	Reference
Objective knowledge of the cannabinoid content of medicinal cannabis products	Most participants (96.0%) answered incorrectly	Regarding low-dose THC products	Kruger et al., (2018)
	Most participants (93.0%) answered incorrectly	Regarding low-dose CBD products	Kruger et al., (2018)
	Most participants (84.0%) answered incorrectly	Regarding high-dose CBD products	Kruger et al., (2018)
	Most participants (74.0%) answered incorrectly	Regarding high-dose THC products	Kruger et al., (2018)
	Some participants (27.0%) answered correctly**	Regarding Sativex	Oldfield et al., (2020)
Objective knowledge - miscellaneous	Most participants (93.6%) agreed	Regarding illegal use of medicinal cannabis for medical therapy	Philpot et al., (2019)
	Most participants (73.0%) answered correctly	Regarding the endogenous cannabinoid system	Kruger et al., (2018)
	Most participants (84.0%) answered correctly	Regarding THC being responsible for the 'high' of cannabis	Kruger et al., (2018)
	Some participants (32.4%) answered correctly**	Regarding the formulation of Sativex	Oldfield et al., (2020)
Beliefs, attitudes and perceptions			
I am supportive of medicinal cannabis 'in general'	Most participants (65.2%) agreed		Schauer et al., (2022)
	Most participants (59.7%) agreed		Philpot et al., (2019)
	Most participants (58.1%) agreed	Regarding medicinal cannabis as a legitimate medical therapy	Philpot et al., (2019)
	Most participants (56.5%) agreed	Regarding the availability of medicinal cannabis on prescription	Karanges et al., (2018)
	Most participants (38.7%) agreed	Regarding the availability of medicinal cannabis from providers	Philpot et al., (2019)
	Most participants agreed [exact % not provided]	Regarding the increased availability of medicinal cannabis products	Hordowicz et al., (2022)
	Participants agreed*	Regarding availability of medicinal cannabis for therapeutic purposes	Van Hout et al., (2017)

Theme	Result	Notes	Reference
	Most participants (68.4%) disagreed	Regarding overall support for prescribing medicinal cannabis	Rosenbaek et al., (2023)
	Most participants (51.3%) neither agreed nor disagreed		Abo Ziad et al., (2022)
I support the legalisation of medicinal cannabis	Most participants (58.6%) agreed		Crowley et al., (2017)
	Most participants agreed [exact % not provided]		Hordowicz et al., (2022)
	Most participants (45.4%) neither agreed nor disagreed		Abo Ziad et al., (2022)
	Most participants (72.4%) either disagreed or neither agreed nor disagreed (only result provided was 27.6% of participants agreed)		Crowley et al., (2017)
	Participants neither agreed nor disagreed*		Van Hout et al., (2017)
	Participants neither agreed nor disagreed*		Van Hout et al., (2017)
Physicians have a role in prescribing medicinal cannabis	Most participants (78.6%) agreed	Regarding GPs with specialised medicinal cannabis training	Karanges et al., (2018)
	Most participants (63.2%) agreed	Regarding a shared arrangement with GPs and specialists	Karanges et al., (2018)
	Most participants (44.6%) agreed	Regarding specialists	Karanges et al., (2018)
Physicians have a role in recommending medicinal cannabis	Most participants (90.1%) agreed	Regarding pain specialists	Abo Ziad et al., (2022)
	Most participants (80.3%) agreed	Regarding oncologist	Abo Ziad et al., (2022)
	Some participants (36.8%) agreed	Regarding family physicians	Abo Ziad et al., (2022)
	Some participants (28.3%) agreed	Regarding 'other' physicians	Abo Ziad et al., (2022)
	Some participants (17.8%) agreed	Regarding orthopaedic surgeons	Abo Ziad et al., (2022)
	Some participants (9.2%) agreed	Regarding psychiatrists	Abo Ziad et al., (2022)
	Most participants (67.8%) disagreed		Abo Ziad et al., (2022)

Theme	Result	Notes	Reference
I am willing to prescribe medicinal cannabis	Participants disagreed*		Ng et al., (2021)
	Most participants (37.3%) neither agreed nor disagreed		Karanges et al., (2018)
I am comfortable using medicinal cannabis for treatment of my patients	Most participants (78.7%) disagreed	Regarding concerns with prescribing medicinal cannabis	Oldfield et al., (2020)
	Most participants (64.0%) disagreed	Regarding integrating medicinal cannabis into treatment regimens	Kruger et al., (2018)
	Most participants (49.0%) disagreed	Regarding identifying harmful use of medicinal cannabis	Kruger et al., (2018)
	Most participants (46.3%) agreed	Regarding identifying contraindications	Di Giovanni et al., (2022)
I am comfortable counselling on medicinal cannabis	Most participants (51.9%) disagreed		Karanges et al., (2018)
	Most participants (50.0%) agreed		Philpot et al., (2019)
	Most participants (48.4%) agreed	Regarding safe driving	Di Giovanni et al., (2022)
	Most participants (42.7%) agreed	Regarding recreational use	Di Giovanni et al., (2022)
There are factors influencing medicinal cannabis recommendations	Most participants (88.0%) agreed	Regarding safety concern	Sajdeya et al., (2021)
	Most participants (83.0%) agreed	Regarding comorbidities	Sajdeya et al., (2021)
	Most participants (82.0%) agreed	Regarding the specific condition	Sajdeya et al., (2021)
	Most participants (82.0%) agreed	Regarding patient's preference	Sajdeya et al., (2021)
	Most participants (79.0%) agreed	Regarding medication use	Sajdeya et al., (2021)
	Most participants (69.0%) agreed	Regarding patient occupation/responsibilities	Sajdeya et al., (2021)
	Most participants (68.0%) agreed	Regarding age	Sajdeya et al., (2021)
There risks associated with cannabis use	Most participants (77.3%) agreed	Regarding the risk of schizophrenia in young people	Crowley et al., (2017)
	Most participants (66.0%) agreed	Regarding increased use if decriminalised	
	Participants agreed*		Ng et al., (2021)

Theme	Result	Notes	Reference
	Participants agreed*	Regarding impact on young people and their families	Van Hout et al., (2017)
	Participants agreed*	Regarding adverse health consequences	Van Hout et al., (2017)
	Most participants (43.6%) neither agreed nor disagreed	Regarding medicinal cannabis having significant interactions with medical therapies.	Philpot et al., (2019)
Medicinal cannabis can provide health benefits	Most participants (49.7%) agreed		Hordowicz et al., (2022)
	Most participants (44.0%) agreed		Karanges et al., (2018)
Medicinal cannabis can improve patients' quality of life	Most participants (35.5%) did not know	Regarding quality of life through energy level	Philpot et al., (2019)
	Most participants (32.3%) did not know	Regarding quality of life through the ability to work	Philpot et al., (2019)
	Most participants (31.2%) did not know	Regarding quality of life through a sense of hope	Philpot et al., (2019)
	Most participants (29.0%) neither agreed nor disagreed	Regarding quality of life through physical functioning	Philpot et al., (2019)
	Most participants (27.4%) either did not know or neither agreed nor disagreed	Regarding quality of life through mood	Philpot et al., (2019)
	Most participants (29.0%) either agreed, neither agreed nor disagreed or did not know	Regarding quality of life through enjoyment of life	Philpot et al., (2019)
	Most participants (26.2%) neither agreed nor disagreed	Regarding quality of life through social engagement	Philpot et al., (2019)
There are barriers to prescribing medicinal cannabis	The top reasons were abuse and diversion to the general public	Regarding barriers to use being abuse and diversion	Abo Ziad et al., (2022)
	Top reasons were the lack of evidence to support use and the risk of drug interaction	Regarding barriers to recommending use	Hachem et al., (2022)
	Top reasons were lack of knowledge around dose and the lack of evidence to support use	Regarding barriers to prescribing	Hachem et al., (2022)

Theme	Result	Notes	Reference
	Top reasons were not knowing which dose of cannabis to prescribe and not having prescribing privileges	Regarding barriers to prescribing	Hachem et al., (2022)
	Top reasons were the need for specialist or ministry approval and prohibitive cost to patient	Regarding barriers to prescribing	Oldfield et al., (2020)
	Top reasons were insufficient evidence base and prohibitive cost to patient	Regarding barriers to prescribing	Oldfield et al., (2020)
	The top reasons were insufficient evidence base and insufficient understanding of prescribing process		Oldfield et al., (2020)
Medicinal cannabis is a research priority	The top 3 choices were chronic pain, cancer and anxiety	Regarding clinical conditions	Jean-Jacques et al., (2021)
	The top 3 choices were dosing and/or product choice, complications from smoking or vaping marijuana and drug interactions	Regarding safety issues	Jean-Jacques et al., (2021)
	The top 3 options were the different THC/CBD ratios, different modes of consumption (smoking, vaping, and concentrates) and different terpene content	Regarding types of medicinal cannabis	Jean-Jacques et al., (2021)
	The top 3 options were research in middle aged/older adults, research in adolescents/young adults and research in persons in nursing homes	Regarding populations using medicinal cannabis	Jean-Jacques et al., (2021)
	The top 3 options were the human endocannabinoid system, improving clinical training for providers and improving clinical practice		Jean-Jacques et al., (2021)
The use of medicinal cannabis is associated with significant adverse effects	Most participants (82.7%) agreed	Regarding mental health	Crowley et al., (2017)
	Most participants (64.9%) agreed	Regarding driving impairment	Karanges et al., (2018)

Theme	Result	Notes	Reference
	Most participants (60.0%) agreed	Regarding physical health	Crowley et al., (2017)
	Most participants (58.4%) agreed	Regarding impact on the developing brain	Karanges et al., (2018)
	Most participants (56.5%) agreed	Regarding cognitive impairment	Karanges et al., (2018)
	Most participants (56.3%) agreed	Regarding addiction and dependence	Karanges et al., (2018)
	Most participants (49.9%) agreed	Regarding psychosis	Karanges et al., (2018)
	Most participants (35.0%) agreed		Adler et al., (2022)
THC is associated with clinically significant adverse effects	Most participants (61.3%) agreed	Regarding psychosis and psychotic disorders	Hordowicz et al., (2022)
	Most participants (59.6%) agreed	Regarding worsening of psychiatric conditions	Hordowicz et al., (2022)
	Most participants (44.5%) agreed	Regarding interactions	Hordowicz et al., (2022)
	Most participants (41.5%) agreed	Regarding impact on brain development	Hordowicz et al., (2022)
	Most participants (41.1%) agreed	Regarding low birth weight in pregnancy	Hordowicz et al., (2022)
	Most participants (38.1%) agreed	Regarding motor impairment	Hordowicz et al., (2022)
	Most participants (30.6%) agreed	Regarding vertigo and dizziness	Hordowicz et al., (2022)
	Most participants (51.5%) disagreed	Regarding euphoria or high	Hordowicz et al., (2022)
	Most participants (34.7%) disagreed	Regarding addiction	Hordowicz et al., (2022)
	Most participants neither disagree nor agree (29.5%)	Regarding sedation	Hordowicz et al., (2022)
Psychoses is a significant adverse effect of medicinal cannabis	Most participants (92.7%) agreed	Regarding psychotic episodes	Di Giovanni et al., (2022)
	Most participants (82.9%) agreed	Regarding psychotic events at high doses	Abo Ziad et al., (2022)
	Most participants (26.5%) agreed**	Regarding psychosis/schizophrenia	Oldfield et al., (2020)
	Most participants (89.0%) agreed	Regarding anxiety	Di Giovanni et al., (2022)

Theme	Result	Notes	Reference
Anxiety and depression are significant adverse effects of medicinal cannabis	Most participants (75.6%) agreed	Regarding low mood	Di Giovanni et al., (2022)
	Most participants (62.5%) agreed	Regarding anxiety in new users	Abo Ziad et al., (2022)
Neurological effects are a significant adverse effect of medicinal cannabis	Most participants (95.1%) agreed	Regarding 'feeling high'	Di Giovanni et al., (2022)
	Most participants (90.2%) agreed	Regarding disorganised thoughts	Di Giovanni et al., (2022)
	Most participants (80.5%) agreed	Regarding memory loss	Di Giovanni et al., (2022)
	Most participants (78.3%) agreed	Regarding neurological effects	Abo Ziad et al., (2022)
	Most participants (50.0%) agreed	Regarding ataxia	Di Giovanni et al., (2022)
	Most participants (42.7%) agreed	Regarding seizures	Di Giovanni et al., (2022)
Sedation is a significant adverse effect of medicinal cannabis	Most participants (92.7%) agreed	Regarding drowsiness	Di Giovanni et al., (2022)
	Most participants (51.0%) agreed**	Regarding drowsiness/sedation	Oldfield et al., (2020)
Gastrointestinal effects are a significant adverse effect of medicinal cannabis	Most participants (87.8%) agreed	Regarding nausea and vomiting	Di Giovanni et al., (2022)
	Most participants (87.8%) agreed	Regarding cannabis hyperemesis syndrome	Di Giovanni et al., (2022)
	Some participants (26.5%) agreed **	Regarding nausea	Oldfield et al., (2020)
	Most participants (19.7%) agreed	Regarding gastrointestinal and electrolyte disturbances	Abo Ziad et al., (2022)
	Some participants (18.4%) agreed**	Regarding weight gain/increased appetite	Oldfield et al., (2020)
Other adverse effects of medicinal cannabis	Most participants (73.2%) agreed	Regarding chronic cough	Di Giovanni et al., (2022)
	Most participants (67.1%) agreed	Regarding increased risk of COPD	Di Giovanni et al., (2022)
	Most participants (58.5%) agreed	Regarding rapid heart rate	Di Giovanni et al., (2022)
Medicinal cannabis has a role to play in the treatment of pain	Most participants (82.2%) agreed		Abo Ziad et al., (2022)
	Most participants (80.2%) agreed	Regarding chronic cancer pain	Karanges et al., (2018)
	Most participants (79.1%) agreed		Philpot et al., (2019)

Theme	Result	Notes	Reference
	Most participants (74.0%) agreed		Schauer et al., (2022)
	Most participants (67.8%) agreed	Regarding Intractable pain	Philpot et al., (2019)
	Most participants (63.5%) agreed		Crowley et al., (2017)
	Most participants (39.1%) agreed	Regarding chronic non-cancer pain	Karanges et al., (2018)
	Most participants (40.5%) neither agreed nor disagreed	Regarding neuropathic pain	Karanges et al., (2018)
Medicinal cannabis has a role to play in the treatment of cancer and palliative care	Most participants (84.2%) agreed	Regarding cancer	Abo Ziad et al., (2022)
	Most participants (78.8%) agreed	Regarding end of life/palliative care	Karanges et al., (2018)
	Most participants (79.1%) agreed	Regarding cancer	Philpot et al., (2019)
	Most participants (72.7%) agreed	Regarding cancer	Schauer et al., (2022)
	Most participants (68.5%) agreed	Regarding palliative care	Crowley et al., (2017)
	Most participants (59.7%) agreed	Regarding terminal illness	Philpot et al., (2019)
	Most participants (48.8%) neither agreed nor disagreed	Regarding anti-tumour effects	Karanges et al., (2018)
Medicinal cannabis has a role to play in the treatment of seizures and epilepsy	Most participants (70.3%) agreed	Regarding intractable epilepsy	Karanges et al., (2018)
	Most participants (53.6%) agreed		Schauer et al., (2022)
	Most participants (48.4%) agreed		Philpot et al., (2019)
	Most participants (41.9%) agreed		Philpot et al., (2019)
	Most participants (28.9%) agreed		Abo Ziad et al., (2022)
Cannabis has a role to play in the treatment of nausea and vomiting	Most participants (66.8%) agreed	Regarding nausea and/or vomiting	Philpot et al., (2019)
	Most participants (64.7%) agreed	Regarding CINV	Karanges et al., (2018)
	Most participants (59.7%) agreed	Regarding nausea	Schauer et al., (2022)

Theme	Result	Notes	Reference
Cannabis has a role to play in appetite promotion	Most participants (60.0%) agreed		Schauer et al., (2022)
	Most participants (39.5%) agreed		Abo Ziad et al., (2022)
	Most participants (56.7%) agreed	Regarding cachexia associated with severe illness	Karanges et al., (2018)
Cannabis has a role to play in the treatment of musculoskeletal disorders	Most participants (62.3%) agreed	Regarding multiple sclerosis	Crowley et al., (2017)
	Most participants (61.2%) agreed	Regarding spasticity in multiple sclerosis	Karanges et al., (2018)
	Most participants (55.2%) agreed	Regarding spasticity	Schauer et al., (2022)
	Most participants (54.8%) did not know	Regarding ALS	Philpot et al., (2019)
	Most participants (50.0%) agreed	Regarding severe and persistent muscle spasms, including those characteristic of Multiple Sclerosis	Philpot et al., (2019)
	Most participants (38.8%) agreed	Regarding muscle spasms	Philpot et al., (2019)
	Most participants (38.8%) agreed	Regarding fibromyalgia	Abo Ziad et al., (2022)
Cannabis has a role to play in the treatment of depression	Most participants (61.9%) disagreed	Regarding depression/anxiety	Schauer et al., (2022)
	Most participants (52.2%) disagreed	Regarding depression	Karanges et al., (2018)
	Most participants (50.0%) disagreed	Regarding depression	Philpot et al., (2019)
	Most participants (49.0%) disagreed	Regarding anxiety	Karanges et al., (2018)
	Most participants (58.1%) agreed	Regarding anxiety	Philpot et al., (2019)
Cannabis has a role to play in the treatment of insomnia	Most participants (66.7%) disagreed	Regarding sleep	Schauer et al., (2022)
	Most participants (49.8%) disagreed	Regarding insomnia	Karanges et al., (2018)
	Most participants (33.9%) agreed	Regarding sleeplessness	Philpot et al., (2019)
Cannabis has a role to play in the treatment of Post-Traumatic Stress Disorder	Most participants (57.5%) disagreed		Schauer et al., (2022)
	Most participants (56.0%) agreed		Abo Ziad et al., (2022)

Theme	Result	Notes	Reference
	Most participants (51.7%) agreed		Philpot et al., (2019)
	Most participants (41.1%) neither agreed nor disagreed	Regarding PTSD	Karanges et al., (2018)
Cannabis has a role to play in the treatment of anxiety	Most participants (61.9%) disagreed	Regarding depression/anxiety	Schauer et al., (2022)
	Most participants (49.0%) disagreed	Regarding anxiety	Karanges et al., (2018)
	Most participants (58.1%) agreed	Regarding anxiety	Philpot et al., (2019)
Cannabis has a role to play in the treatment of other conditions	Most participants (89.2%) disagreed	Regarding ADHD	Schauer et al., (2022)
	Most participants (88.9%) disagreed	Regarding Alzheimer's disease	Schauer et al., (2022)
	Most participants (70.8%) disagreed	Regarding opioid addiction	Schauer et al., (2022)
	Some participants (64.1%) disagreed	Regarding Parkinson’s disease	Schauer et al., (2022)
	Most participants (59.7%) agreed	Regarding autism	Philpot et al., (2019)
	Most participants (54.8%) agreed	Regarding Obstructive Sleep apnoea	Philpot et al., (2019)
	Most participants (50.5%) agreed	Regarding glaucoma	Schauer et al., (2022)
	Most participants (40.3%) neither agreed nor disagreed	Regarding dementia patients with agitation	Karanges et al., (2018)
	Most participants (53.2%) did not know	Regarding inflammatory bowel disease, including Crohn’s disease	Philpot et al., (2019)
	Most participants (53.2%) did not know	Regarding Tourette Syndrome	Philpot et al., (2019)
	Most participants (53.2%) did not know	Regarding tics	Philpot et al., (2019)
	Most participants (49.2%) did not know	Regarding glaucoma	Philpot et al., (2019)
	Most participants (48.4%) did not know	Regarding HIV/AIDS	Philpot et al., (2019)
	Most participants (35.5%) did not know	Regarding weight loss	Philpot et al., (2019)

Theme	Result	Notes	Reference
Medicinal cannabis is effective	Most participants (51.0%) agreed		Adler et al., (2022)
	Most participants (48.0%) neither agreed no disagreed		Karanges et al., (2018)
Medicinal cannabis is generally safer than prescription medications	Most participants (44.0%) agreed	Regarding chemotherapy drugs	Karanges et al., (2018)
	Most participants (51.3%) neither agreed no disagreed	Regarding antipsychotics	Karanges et al., (2018)
	Most participants (50.6%) neither agreed no disagreed	Regarding antidepressants	Karanges et al., (2018)
	Most participants (48.0%) neither agreed no disagreed	Regarding prescription opioids	Karanges et al., (2018)
	Most participants (47.2%) neither agreed no disagreed	Regarding benzodiazepines	Karanges et al., (2018)
	Most participants (46.3%) neither agreed no disagreed	Regarding statins	Karanges et al., (2018)
THC is generally safer than prescription medication	Most participants (41.0%) agreed	Regarding acetaminophen	Hordowicz et al., (2022)
	Most participants (39.9%) agreed	Regarding benzodiazepines	Hordowicz et al., (2022)
	Most participants (37.6%) agreed	Regarding non-steroid anti-inflammatory drugs	Hordowicz et al., (2022)
	Most participants (35.8%) agreed	Regarding Z-drugs	Hordowicz et al., (2022)
	Most participants (51.4%) neither agreed nor disagreed	Regarding gabapentinoids	Hordowicz et al., (2022)
	Most participants (48.6%) neither agreed nor disagreed	Regarding antipsychotics	Hordowicz et al., (2022)
	Most participants (47.4%) neither agreed nor disagreed	Regarding norepinephrine reuptake inhibitors	Hordowicz et al., (2022)
	Most participants (43.9%) neither agreed nor disagreed	Regarding selective serotonin reuptake inhibitors	Hordowicz et al., (2022)
	Most participants (42.8%) neither agreed nor disagreed	Regarding tramadol	Hordowicz et al., (2022)

Theme	Result	Notes	Reference
	Most participants (40.5%) neither agreed nor disagreed	Regarding buprenorphine	Hordowicz et al., (2022)
	Most participants (37.6%) neither agreed nor disagreed	Regarding strong opioids (other than buprenorphine)	Hordowicz et al., (2022)
	Most participants (38.7%) neither agreed nor disagreed	Regarding tricyclic antidepressants including amitriptyline	Hordowicz et al., (2022)
There are contraindications to the use of medicinal cannabis	Most participants (97.6%) agreed	Regarding pregnancy	Di Giovanni et al., (2022)
	Most participants (97.6%) agreed	Regarding a history of psychosis	Di Giovanni et al., (2022)
	Most participants (92.7%) agreed	Regarding breastfeeding women	Di Giovanni et al., (2022)
	Most participants (92.7%) agreed	Regarding patients under 25	Di Giovanni et al., (2022)
	Most participants (96.3%) agreed	Regarding a history of substance use disorder	Di Giovanni et al., (2022)
	Most participants (89.0%) agreed	Regarding family history of psychosis	Di Giovanni et al., (2022)
Experience			
I have patients who use medicinal cannabis	Most participants (81.4%) agreed		Hachem et al., (2022)
	Most participants (68.6%) agreed**	Regarding recreational cannabis for a medical condition	Oldfield et al., (2020)
	Most participants (57.1%) agreed	Regarding increased enquiries about recreational cannabis since it was legalised	Hachem et al., (2022)
	Most participants (55.3%) agreed	Regarding received a request for medicinal cannabis	Oldfield et al., (2020)
Patients regularly ask me about medicinal cannabis	Most participants (90.5%) agreed**	Regarding medicinal cannabis requests (1 - 4 patients in the past 12 months)	Oldfield et al., (2020)
	Most participants (87.8%) agreed	Regarding medicinal cannabis enquiries (0 - 5 patients in the past 6 months)	Hordowicz et al., (2022)
	Most participants (54.0%) agreed	Regarding medicinal cannabis enquiries (1-5 patients in the past 3 months)	Karanges et al., (2018)
	Most participants (51.0%) agreed	Regarding medicinal cannabis enquiries (<10 patients in the past week)	Sajdeya et al., (2021)

Theme	Result	Notes	Reference
I have experience with prescribing medicinal cannabis	Most participants (93.1%) disagreed		Hordowicz et al., (2022)
	Most participants (93.1%) disagreed	Regarding prescribing	Hordowicz et al., (2022)
	Most participants (91.3%) disagreed	Regarding prescribing	Rosenbaek et al., (2023)
	Most participants (75.6%) disagreed	Regarding certifying patients for medicinal cannabis	Philpot et al., (2019)
	Most participants (72.7%) disagreed	Regarding recommending medicinal cannabis	Schauer et al., (2022)
	Most participants (74.2%) disagreed	Regarding certifying patients for medicinal cannabis	Philpot et al., (2019)
	Most participants (66.7%) disagreed**	Regarding attempting to prescribe medicinal cannabis	Oldfield et al., (2020)
I have experience with patients on recreational cannabis	Most participants (46.1%) selected 1-4 patients (whole population - or 68.6% subpopulation)	If you have patients using recreational cannabis for a medical condition, how many patients are there?	Oldfield et al., (2020)
	Most participants (57.9%) selected smoking (whole population or - 86.3% sub-population)	If you have patients using recreational cannabis for a medical condition, what is their preferred formulations?	Oldfield et al., (2020)
What are the most common indications that you have observed medicinal cannabis used for?	Most participants (77.2%) agreed**	Regarding neuropathic pain	Hachem et al., (2022)
	Most participants (66.7%) agreed**	Regarding insomnia	Hachem et al., (2022)
	Most participants (64.9%) agreed**	Regarding nociceptive pain	Hachem et al., (2022)
	Most participants (63.2%) agreed**	Regarding anxiety	Hachem et al., (2022)
	Most participants (59.6%) agreed**	Regarding other pain	Hachem et al., (2022)
	Most participants (53.6%) agreed**	Regarding intractable pain	Hachem et al., (2022)
	Most participants (51.8%) agreed**	Regarding cancer	Hachem et al., (2022)
	Most participants (47.4%) agreed**	Regarding loss of appetite	Hachem et al., (2022)
	Most participants (41.1%) agreed**	Regarding Terminal illness	Hachem et al., (2022)
	Some participants (40.4%) agreed**	Regarding nausea/vomiting	Hachem et al., (2022)

Theme	Result	Notes	Reference
	Some participants (39.3%) agreed**	Regarding HIV/AIDS	Hachem et al., (2022)
	Some participants (38.6%) agreed**	Regarding depression	Hachem et al., (2022)
	Some participants (35.7%) agreed**	Regarding Multiple Sclerosis	Hachem et al., (2022)
	Some participants (35.1%) agreed**	Regarding headaches	Hachem et al., (2022)
	Some participants (33.3%) agreed**	Regarding cachexia	Hachem et al., (2022)
	Some participants (30.4%) agreed**	Regarding Inflammatory bowel disease	Hachem et al., (2022)
	Some participants (22.8%) agreed**	Regarding muscle spasms	Hachem et al., (2022)
	Some participants (21.4%) agreed**	Regarding other	Hachem et al., (2022)
	Some participants (21.4%) agreed**	Regarding Epilepsy	Hachem et al., (2022)
	Some participants (17.5%) agreed**	Regarding other	Hachem et al., (2022)
	Some participants (15.8%) agreed**	Regarding tics	Hachem et al., (2022)
	Some participants (12.5%) agreed**	Regarding Tourette Syndrome	Hachem et al., (2022)
	Some participants (12.3%) agreed**	Regarding seizures	Hachem et al., (2022)
	Some participants (10.7%) agreed**	Regarding Graft vs. host disease	Hachem et al., (2022)
	Some participants (8.9%) agreed**	Regarding Glaucoma	Hachem et al., (2022)
	Some participants (8.9%) agreed**	Regarding Obstructive sleep apnoea	Hachem et al., (2022)
	Some participants (7.1%) agreed**	Regarding ALS	Hachem et al., (2022)
	Some participants (5.4%) agreed**	Regarding Asthma	Hachem et al., (2022)
	Some participants (5.4%) agreed**	Regarding COPD	Hachem et al., (2022)
	Some participants (1.8%) agreed**	Regarding Parkinson's disease	Hachem et al., (2022)
	Some participants (1.8%) agreed**	Regarding Chronic pain/mood disorder	Hachem et al., (2022)

Theme	Result	Notes	Reference
	Some participants (1.8%) agreed**	Regarding Cystic fibrosis	Hachem et al., (2022)
What indications do you recommend or prescribe medicinal cannabis for in your practice?	The top 3 indications included cancer, intractable pain and terminal illness	Regarding prescribing and recommending for 'conditions'	Hachem et al., (2022)
	The top 3 indications included pain, neuropathic pain and nausea/vomiting	Regarding prescribing and recommending for 'symptoms'	Hachem et al., (2022)
	The top 3 indications were chronic cancer pain, chronic non-cancer pain and neuropathic pain	Regarding prescribing in future	Hordowicz et al., (2022)
	The top 3 indications were chronic cancer pain, neuropathic pain and CINV and other cancer treatment complications	Regarding current prescribing	Hordowicz et al., (2022)
	The top 3 indications included 'dying patient', 'oncologic condition' and 'multiple sclerosis'	Regarding initiating treatment	Adler et al., (2022)
	The top 3 indications included 'dying patient', 'oncologic condition' and 'multiple sclerosis'	Regarding continuing treatment	Adler et al., (2022)
I make specific recommendations to medicinal cannabis patients	Most participants (77.0%) agreed	Regarding specific routes of administration	Sajdeya et al., (2021)
	Most participants (70.0%) agreed	Regarding educational about the endocannabinoid system	Sajdeya et al., (2021)
	Most participants (66.0%) agreed	Regarding education about specific medicinal cannabis products	Sajdeya et al., (2021)
	Most participants (62.0%) agreed	Regarding recommended specific CBD and THC dosages	Sajdeya et al., (2021)
	Most participants (50.0%) agreed	Regarding recommending a specific THC:CBD ratio	Sajdeya et al., (2021)
	Most participants (45.0%) agreed	Regarding providing a list of recommended websites about medicinal cannabis	Sajdeya et al., (2021)
	Most participants (40.0%) disagreed	Regarding recommending specific dispensaries	Sajdeya et al., (2021)
	Most participants (92.0%) agreed	Regarding conducting a physical exam	Sajdeya et al., (2021)

Theme	Result	Notes	Reference
I conduct regular health checks of medicinal cannabis patients	Most participants (86.0%) agreed	Regarding reviewing patient outside medical record	Sajdeya et al., (2021)
	Most participants (77.0%) agreed	Regarding asking patients about cannabis use	Schauer et al., (2022)
	Most participants (76.0%) agreed	Regarding advising of possible drug interactions	Sajdeya et al., (2021)
	Most participants (71.0%) agreed	Regarding enquiring about the specific products received from dispensaries	Sajdeya et al., (2021)
	Most participants (64.0%) agreed	Regarding screening for cannabis use disorder	Sajdeya et al., (2021)
	Most participants (61.3%) agreed	Regarding assessing patients for dependence	Schauer et al., (2022)
	Most participants (53.7%) neither agreed nor disagreed	Regarding screening for cannabis use disorder	Di Giovanni et al., (2022)
	Most participants (36.0%) either disagreed or neither agreed nor disagreed	Regarding communicating with patient's primary care physician or referring doctor	Sajdeya et al., (2021)
'Other' aspects of physicians' clinical practice	The top options included anxiety and mood disorders, the risk of addiction, cardiovascular disease and a family history of psychosis	Regarding precautions or contraindications that are assessed for when prescribing	Hachem et al., (2022)
	The top option included patients taking high doses of opioids, benzodiazepines or other sedating mediations	Regarding patient population prescribe to most often	Hachem et al., (2022)
	Top 3 types/formulations included oils, capsules and edibles	Regarding types/formulations most often recommend	Hachem et al., (2022)
Training/education			
I would like further training on medicinal cannabis	Most participants (79.0%) agreed	Regarding recreational cannabis use	Di Giovanni et al., (2022)
	Most participants (77.4%) agreed		Philpot et al., (2019)
	Most participants (75.0%) agreed		Adler et al., (2022)
	Most participants (57.3%) agreed	Regarding accessing information	Oldfield et al., (2020)

Theme	Result	Notes	Reference
	Most participants (50.7%) disagreed		Abo Ziad et al., (2022)
I have received adequate training in medicinal cannabis	Most participants (94.7%) disagreed	Regarding training during medical degree	Hachem et al., (2022)
	Most participants (90.8%) disagreed	Regarding practical training after medical degree	Hachem et al., (2022)
	Most participants (51.3%) disagreed	Regarding training other than medical degree or practical training	Hachem et al., (2022)
	Most participants (53.7%) neither agreed nor disagreed	Regarding recreational cannabis	Di Giovanni et al., (2022)
Specific medicinal cannabis topics that I would be most interested learning about	Most participants (72.0%) agreed	Regarding drug-drug interactions	Sajdeya et al., (2021)
	Most participants (72.0%) agreed	Regarding evidence for indications	Sajdeya et al., (2021)
	Most participants (67.0%) agreed	Regarding minimising use of opioids or other drugs	Sajdeya et al., (2021)
	Most participants (66.0%) agreed	Regarding updates on research findings	Sajdeya et al., (2021)
	Most participants (66.0%) agreed	Regarding specific modes of delivery	Sajdeya et al., (2021)
	Most participants (66.0%) agreed	Regarding the effects of phytocannabinoids and terpenes	Sajdeya et al., (2021)
	Most participants (60.0%) agreed	Regarding recommending ideal doses and ratios	Sajdeya et al., (2021)
	Most participants (57.0%) agreed	Regarding education about the endocannabinoid system	Sajdeya et al., (2021)
	Most participants (51.0%) agreed	Regarding safety	Sajdeya et al., (2021)
	Most participants (51.0%) agreed	Regarding comparing available products	Sajdeya et al., (2021)
	Most participants (50.0%) agreed	Regarding cannabis use disorder	Sajdeya et al., (2021)
I have a preference for accessing or receiving training around medicinal cannabis	Most participants (95.0%) agreed	Regarding previous use of research articles	Sajdeya et al., (2021)
	Most participants (93.0%) agreed	Regarding previous use of online sources (websites, videos, etc.)	Sajdeya et al., (2021)
	Most participants (84.0%) agreed	Regarding learning opportunities: online learning/training modules	Sajdeya et al., (2021)

Theme	Result	Notes	Reference
	Most participants (84.0%) agreed	Regarding previous use of discussions with other medicinal cannabis providers	Sajdeya et al., (2021)
	Most participants (84.0%) agreed	Regarding previous use of dispensary staff (e.g., sales representatives)	Sajdeya et al., (2021)
	Most participants (75.0%) agreed	Regarding learning opportunities: clinical education conference (single day)	Sajdeya et al., (2021)
	Most participants (73.0%) agreed	Regarding previous use of medicinal cannabis conferences	Sajdeya et al., (2021)
	Most participants (72.0%) agreed	Regarding preference for educational content: continuing medical education sessions	Oldfield et al., (2020)
	Most participants (67.0%) agreed	Regarding previous use of books	Sajdeya et al., (2021)
	Most participants (63.0%) agreed	Regarding learning opportunities: medicinal cannabis research conference	Sajdeya et al., (2021)
	Most participants (62.0%) agreed	Regarding previous use of magazines about cannabis	Sajdeya et al., (2021)
	Most participants (50.0%) agreed	Regarding usefulness of medicinal cannabis conferences	Sajdeya et al., (2021)
	Most participants (45.0%) agreed	Regarding learning opportunities: clinical education conference (multiple days)	Sajdeya et al., (2021)
	Some participants (44.0%) agreed	Regarding previous use of lectures	Kruger et al., (2018)
	Some participants (42.7%) agreed	Regarding preference for educational content: continuing medical education online modules	Oldfield et al., (2020)
	Some participants (38.0%) agreed	Regarding previous use of personal experience with medicinal cannabis	Sajdeya et al., (2021)
	Some participants (33.3%) agreed	Regarding preference for educational content: information sheets	Oldfield et al., (2020)
	Some participants (30.0%) agreed	Regarding previous use of your own research	Kruger et al., (2018)
	Some participants (30.0%) agreed	Regarding previous use of 'none'	Kruger et al., (2018)

Theme	Result	Notes	Reference
	Some participants (29.0%) agreed	Regarding previous use of continuing medical education	Kruger et al., (2018)
	Some participants (19.0%) agreed	Regarding previous use of grand rounds	Kruger et al., (2018)
	Some participants (5.0%) agreed	Regarding previous use of workshop	Kruger et al., (2018)
	Some participants (4.0%) agreed	Regarding previous use of formal course	Kruger et al., (2018)
	Most participants (74.0%) neither agreed nor disagreed	Regarding usefulness of magazines about cannabis	Sajdeya et al., (2021)
	Most participants (66.0%) neither agreed nor disagreed	Regarding usefulness of books	Sajdeya et al., (2021)
	Most participants (64.0%) neither agreed nor disagreed	Regarding usefulness of discussions with other medical marijuana providers	Sajdeya et al., (2021)
	Most participants (56.0%) neither agreed nor disagreed	Regarding usefulness of research articles	Sajdeya et al., (2021)
	Most participants (52.0%) neither agreed nor disagreed	Regarding usefulness of online sources (websites, videos, etc.)	Sajdeya et al., (2021)
	Most participants (51.0%) neither agreed nor disagreed	Regarding usefulness of personal experience with MC	Sajdeya et al., (2021)
	Most participants (50.0%) neither agreed nor disagreed	Regarding usefulness of staff from dispensaries (sales representatives, etc.)	Sajdeya et al., (2021)
I have awareness of tools and resources for medicinal cannabis use with my patients	Most participants (92.7%) disagreed	Regarding the Cannabis Use Disorder Identification Test Revised (CUDIT-R)	Di Giovanni et al., (2022)
	Most participants (72.0%) disagreed	Regarding assessment tools for cannabis overuse	Di Giovanni et al., (2022)

* Semi-structured interview

** Result represents the percentage of a sub-population (not the whole population) who were asked the question

Abbreviations - ADHD: Attentive deficit hyperactivity disorder, ALS: Amyotrophic lateral sclerosis, CBD: cannabidiol, COPD: Chronic obstructive pulmonary disease, CINV: Chemotherapy induced nausea and vomiting, GPs: general practitioners, HIV: Human immunodeficiency virus, MS: Multiple sclerosis, PTSD: Post traumatic stress disorder, and THC: Δ^9-tetrahydrocannabinol.

Results

1.1 Subjective Knowledge

Nine studies investigated physicians' 'subjective' or perceived knowledge in relation to medicinal cannabis (Table 3). Overall, participants had poor self-assessed knowledge of medicinal cannabis. However, self-assessed knowledge was high in particular areas such as regional or regulatory requirements around medicinal cannabis and the cannabis product, Sativex.

Six of these did so by asking participants whether they thought they had sufficient knowledge of medicinal cannabis 'in general' [2, 4, 8-10, 13]. All six of these studies found that most participants disagreed and two out of seven questions in this topic had high disagreement levels (≥ 80%).

Three studies asked physicians about their perceived knowledgeable regarding the different types and formulations of medicinal cannabis products [8, 11, 12]. Overall, results were mixed, other than one study that demonstrated that participants had a high perceived knowledge (≥ 80% agreement level), around specific products, that is, Sativex [11].

Finally, three studies investigated perceived knowledge around the regional and regulatory requirements of medicinal cannabis [4, 5, 8]. While results were mixed, there was a greater level of agreement (i.e., 97.2% - 72.9% across three out of six questions) [4, 5] than disagreement (i.e., 78.9% - 70.0% across two out of six questions) [8] by most participants in these studies.

1.2 Objective Knowledge

Three studies explored physicians' 'objective' knowledge in relation to medicinal cannabis (Table 3). Overall, participants' objectively-assessed knowledge of medicinal cannabis was good.

Physicians' objective knowledge around 'specific topics' including the effective doses [9], cannabinoid content [9, 11], associated risks [9], efficacy [9] and harm reduction strategies [9] of medicinal cannabis products was investigated. Most participants reflect a good level of knowledge around the associated risks, efficacy and harm reduction strategies associated with medicinal cannabis in 20 out of 30 questions in these topics. Participants were

particularly knowledgeable around harm reduction strategies and achieved high scores (≥ 80% answered correctly) in 12 associated questions.

In contrast, most participants had low knowledge around the effective doses and cannabinoid content of medicinal cannabis products. Six out of seven questions relating to these topics were answered incorrectly or as 'unsure'.

1.3 Beliefs

Sixteen studies investigated physicians' beliefs around medicinal cannabis (Table 3).

Overall, participants appeared cautiously supportive of medicinal cannabis and believed they had an important role in prescribing and recommending products to their patients. However, there was a general unwillingness to prescribe medicinal cannabis and participants were not overly comfortable with medicinal cannabis therapy. The top barriers to prescribing included abuse and diversion and a lack of evidence. Participants were particularly mindful of the adverse effects associated with medicinal cannabis therapy, particularly around psychosis. Participants were most supportive of the use of medicinal cannabis products for pain, cancer/palliative care and seizures.

1.3.1 Support for Medicinal Cannabis

Eight studies explored physicians' support of medicinal cannabis. Seven of these asked participants if they were supportive of medicinal cannabis 'in general' [1, 6, 8, 12, 13, 15, 16]. Overall, most participants agreed in seven out of nine questions in this topic, however support was conservative (i.e., agreement levels 65.2% - 38.7%). Four studies also queried if participants were supportive of the legalisation of medicinal cannabis [1, 3, 6, 16]. Participants were largely undecided, indeed most participants in four out of six questions in this topic 'neither agreed nor disagreed'.

1.3.2 The Role of the Physician in Medicinal Cannabis

Three studies explored physicians' role in the use of medicinal cannabis as a treatment for their patients. Two studies explored whether participants believed they played an important role in prescribing [8] and recommending [1] medicinal cannabis to their patients.

There was unanimous agreement from most participants in all nine questions in these topics. Particular support (agreement levels ≥ 80%) was given for the role of pain specialists and oncologists in recommending medicinal cannabis products [1].

Three studies explored physicians' willingness to prescribe medicinal cannabis to their patients [1, 8, 10]. Results were mixed. Overall, most participants in these studies demonstrated an unwillingness to prescribe in two out of three questions and 'neither agreed nor disagreed' in the final question in this topic.

1.3.3 Comfort with Medicinal Cannabis

Five studies explored physicians' 'comfort' towards medicinal cannabis [4, 8, 9, 11, 12]. Three queried participants' comfort with counselling on medicinal cannabis [4, 8, 12]. Most participants 'agreed' in three out of four questions, however, agreement levels were low (i.e., 50.0% - 42.7%). Three asked participants whether they were comfortable using medicinal cannabis to treat their patients [4, 9, 11]. Most of the participants in these studies 'disagreed' in three of the four questions in this topic and only 'agreed' (i.e., 46.3%) regarding the identification of contraindications [4].

Overall, participants demonstrated greater comfort counselling patients rather than treating patients with medicinal cannabis.

1.3.4 Factors Influencing use of Medicinal Cannabis

Eleven studies explored factors influencing physicians when considering medicinal cannabis for their patients. One study did so by asking participants whether there were factors influencing medicinal cannabis recommendations 'in general' [14]. Most participants agreed in all seven questions in this topic area with particular emphasis (agreement levels ≥ 80%) on safety concerns, comorbidities, the medical condition in question and patient's preference.

Ten studies asked participants about their beliefs around 'specific' influencing factors when considering medicinal cannabis for their patients including the risks [3, 10, 12, 16], benefits [6, 8], quality of life effects [12], barriers [1, 5, 11] and required research [7].

Four queried participants on whether there were risks associated with medicinal cannabis use. Overall, most participants 'agreed' in five out of six questions in this topic.

Two studies asked participants if medicinal cannabis could provide health benefits to patients. Most participants in these studies agreed, however agreement levels were low (i.e., 49.7 - 44.0%).

One study queried whether medicinal cannabis could improve patients' quality of life. Participants were uncertain. Indeed, most participants either 'did not know' or 'neither agreed nor disagreed' in six out of seven questions in this topic.

Three studies queried physicians around the barriers to prescribing medicinal cannabis to their patients. The top reasons included abuse and diversion [1], the lack of evidence [5, 11], dosing uncertainty [5] and the need for additional approvals [11].

One study explored whether medicinal cannabis was a research priority. Participants agreed. The top choices regarding 'clinical conditions' were chronic pain, regarding 'safety' was dosing and product choice, regarding 'formulations' was the different THC/CBD ratios and regarding 'patient populations' was middle aged or older adults.

1.3.5 Adverse Effects of Medicinal Cannabis

Seven studies explored physicians' beliefs around the adverse effects of medicinal cannabis. All seven asked physicians' whether the use of medicinal cannabis is associated with significant adverse effects 'in general' [1-4, 6, 8, 11, 12, 15]. Most of the participants in these studies agreed across the eight questions in this topic and a high level of agreement (≥ 80%) was expressed regarding 'mental health'.

One study asked participants whether the use of THC, in particular, was associated with significant adverse effects [6]. Most participants in this study agreed in seven out of ten questions in this topic and the highest level of agreement related to 'psychosis and psychotic disorders' (61.3%). Interestingly, most participants 'disagreed' regarding the significance of 'euphoria or high' (51.5%).

Three studies also investigated participants' beliefs around the significance of specific adverse effects including psychosis [1, 4, 11], anxiety and depression [1, 4], neurological effects [1, 4], sedation [4, 11], gastrointestinal effects [1, 4, 11] and 'other' adverse effects [4]. Most participants in these studies agreed in all 22 questions relating to these topics.

Particular importance (agreement levels ≥ 80%) was expressed around psychosis, anxiety, sedation, neurological effects (i.e., feeling high, disorganised thoughts and memory loss) and gastrointestinal effects (i.e., nausea and vomiting and cannabis hyperemesis syndrome).

1.3.6 Indications of Medicinal Cannabis

Five studies investigated physicians' beliefs on the role medicinal cannabis has in treating specific indications. The indications queried included pain [1, 3, 8, 12, 15], cancer and palliative care [1, 3, 8, 12, 15], seizures [1, 8, 12, 15], PTSD [1, 8, 12, 15], nausea and vomiting [8, 12, 15], appetite promotion [1, 8, 15], musculoskeletal disorders [1, 3, 8, 12, 15], anxiety [8, 12, 15], depression [8, 12, 15] insomnia [8, 12, 15] and 'other' conditions [8, 12, 15].

Most participants in these studies 'agreed' regarding pain, cancer and palliative care, seizures, nausea and vomiting, appetite promotion and musculoskeletal disorders. Indeed, agreement was noted in 30 out of 33 questions in these topics with particular agreement (≥ 80%) regarding pain 'in general', chronic cancer pain and cancer.

Conversely, most participants in these studies tended to 'disagree' regarding depression and insomnia in six out of eight questions in this topic. Furthermore, there was no clear direction for support regarding PTSD and anxiety.

When 'other' indications were considered, there was a high level of disagreement (≥ 80%) regarding ADHD and Alzheimer's disease and participants reflected a lack of knowledge around less common indications such as inflammatory bowel disease, Tourette's Syndrome and glaucoma.

1.3.7 Pharmacological Considerations

Four studies explored physicians' beliefs around the pharmacology of medicinal cannabis. These included contraindications [4], safety [6, 8] and efficacy [2, 8]. One study explored if participants believed there were contraindications to the use of medicinal cannabis [4]. Most participants in these studies agreed in all six questions in this topic and there was a high level of agreement (≥ 80%) regarding certain contraindications i.e., pregnancy, a history of psychosis or substance use disorder, breastfeeding women and patients under the age of 25 years.

Two studies explored the safety of 1) medicinal cannabis 'in general' [8] and 2) THC [6] by asking participants if these were safer than other prescription medications. Most participants in these studies 'neither agreed nor disagreed' in 13 out of 18 questions. Furthermore, most participants in these studies believed that medicinal cannabis was safer than chemotherapy drugs [8] and that THC was safer than acetaminophen, benzodiazepines, non-steroid anti-inflammatory drugs and Z-drugs [6].

Two studies queried participants whether they believed medicinal cannabis had medical efficacy [2, 8]. Results were mixed - most participants in one study agreed (i.e., 51.0%) [2] but 'neither agreed nor disagreed' in the other study [8].

1.4 Experiences

Overall, it was found that participant received a high level of interest around medicinal cannabis but did not have a great deal of prescribing experience.

1.4.1 Previous Experiences

Eight studies explored physicians' previous experiences with medicinal cannabis (Table 3).

Two asked participants if they had patients who use medicinal cannabis [5, 11]. Most participants in these studies 'agreed' in all four questions in this topic and there was a high level of agreement (≥ 80%) in one of these questions. Four asked participants if they were regularly queried about medicinal cannabis [6, 8, 11, 14]. Most participants in these studies 'agreed' in all four questions and expressed a high level of agreement (≥ 80%) in two of these questions. Five asked participant if they had prescribed medicinal cannabis [6, 11-13, 15]. Most of the participants in these studies 'disagreed' in all seven questions in this topic and had a high level of disagreement (≥ 80%) in three of these questions. Finally, one study asked participants about their previous experiences with recreational cannabis [11]. Most participants in this study noted having between one to four patients who currently use recreational cannabis. Furthermore, the preferred formulation used by recreational patients was 'smoking'.

In summary, physicians' generally do not have prescribing experience with medicinal cannabis despite considerable use by and queries from their patients.

1.4.2 Experiences around Medicinal Cannabis Indications

Three studies investigated physicians' experiences around the indications of medicinal cannabis. One explored which indications physicians had observed patients using medicinal cannabis for [5]. The most common indications included neuropathic pain, insomnia and nociceptive pain. Three also asked participants what indications they had personally recommended prescribed medicinal cannabis for [2, 5, 6]. The top option regarding a 'condition' was cancer, regarding a 'symptom' was pain and regarding 'initiating' or 'continuing' treatment was for a dying patient.

1.4.3 Typical Practices around Medicinal Cannabis

Five studies asked physicians about their typical clinical practises around medicinal cannabis therapy. One asked if physicians' make specific recommendations to their medicinal cannabis patients [14]. Most participants 'agreed' in six out of seven questions in this topic. When participants 'disagreed', this related to recommending specific cannabis dispensaries to patients.

Two studies explored if physicians conducted regular health checks on their medicinal cannabis patients [4, 14]. Most of the participants in these studies agreed in seven out of nine questions in this topic with particular emphases (i.e., agreement level ≥ 80%) on physical examinations and reviewing patients outside of their medical record. Participants 'neither agreed nor disagreed' in the final two questions regarding screening for cannabis use disorder and communicating with the patients' referring doctor.

'Other' aspects of physicians' clinical practice regarding medicinal cannabis were also assessed [5]. Regarding 'assessing for contraindications', the most common option was anxiety and mood disorders. Regarding 'patient population prescribed to', the most common option included patients taking high doses of opioids, benzodiazepines or other sedating mediations. Regarding 'types and formulations of medicinal cannabis recommended' the most common option included oils, capsules and edibles.

1.5 Training and Education

Eight studies explored physicians' training and education around medicinal cannabis (Table 3).

Overall, participants did not have comprehensive training or education around medicinal cannabis and noted the need for this in their practice. Five did so by asking participants if they would like further training around medicinal cannabis [1, 2, 4, 11, 12]. Most participants in four out of 5 questions in this topic agreed.

Two asked participants whether they had received adequate training around medicinal cannabis [4, 5]. Most participants in these studies 'disagreed' in three out of four questions in this topic and there was particular disagreement (≥ 80%) around 'training during a medical degree' and 'practical training after a medical degree'.

One study asked participants about specific topics they would be interested in learning about [14]. The most common options included drug-drug interactions, evidence of efficacy and minimising the use of opioids or other drugs.

Three studies asked participants if they had a preferred mode of training and education activities [9, 11, 14]. Most participants in these studies 'agreed' in 23 out of 30 questions in this topic and there was particular emphasis (agreement ≥ 80%) around the use of research articles, online training and discussions with other medicinal cannabis providers or dispensary staff.

Finally, one study asked participants if they had an awareness of supporting tools and resources for medicinal cannabis patients [4]. Most participants disagreed in both questions in this topic, particularly (disagreement ≥ 80%) around the Cannabis Use Disorder Identification Test Revised (CUDIT-R).

1.6 References

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Appendix 4

Primary Outcomes

VAS Nervous

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: log(Nervous + 0.01)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	153.495	1	< 2e-16	***
Treatment	1.360	1	0.244	
Timepoint	124.472	10	< 2e-16	***
Gender	4.915	2	0.086	
Treatment x Timepoint	10.090	10	0.433	

Unadjusted pre-plan post-hocs comparisons

Timepoint	contrast	estimate	SE	df	t.ratio	p.value
VR1 perform	CBD - Placebo	-0.285	0.349	280.04	-0.816	0.415
VR2 perform	CBD - Placebo	-0.234	0.351	284.17	-0.669	0.504

Dunn-Sidak adjusted 3rd post-hoc comparison

Timepoint	contrast	estimate	SE	df	t.ratio	p.value	
R1	CBD - Placebo	-0.834	0.346	271.61	-2.414	0.049	*

Dunn-Sidak adjusted 9 post-hoc comparisons

Scenario	Timepoint	contrast	estimate	SE	df	t.ratio	p.value
VR1	Baseline	CBD - Placebo	0.154	0.347	275.750	0.443	1.000
	VR1 start	CBD - Placebo	-0.137	0.351	284.700	-0.389	1.000
VR2	VR2 start	CBD - Placebo	-0.415	0.347	275.770	-1.195	0.908
	R2	CBD - Placebo	-0.286	0.346	271.610	-0.827	0.991
VR3	VR3 start	CBD - Placebo	-0.430	0.346	271.610	-1.246	0.886
	R3	CBD - Placebo	-0.043	0.346	271.610	-0.125	1.000

Dunn-Sidak adjusted 3rd post-hoc comparison

contrast	estimate	SE	df	t.ratio	p.value	
VR1 start - VR1 perform	-0.786	0.187	668.780	-4.192	0.0001	***
VR2 start - VR2 perform	-0.781	0.187	669.020	-4.183	0.0001	***
R3 - VR3 start	0.099	0.184	668.620	0.539	0.931	

Means

Timepoint	Mean	SE
VR1 start	32.077	2.671
VR1 perform	57.455	2.988
VR2 start	19.463	2.551
VR2 perform	33.323	3.276
VR3 start	20.618	2.651
R3	24.250	3.098

VAS Nauseous

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: Log
Response: (Nauseous + 0.01)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	52.441	1	0.000	***
Treatment	0.549	1	0.459	
Timepoint	396.959	10	< 2.2e-16	***
Age	0.667	1	0.414	
Treatment x Timepoint	9.823	10	0.456	

Unadjusted pre-plan post-hocs comparisons

Timepoint	contrast	estimate	SE	df	z.ratio	p.value
R3	CBD - Placebo	0.089	0.337	Inf	0.263	0.793
Study close	CBD - Placebo	0.438	0.342	Inf	1.283	0.200

Dunn-Sidak adjusted 3rd post-hoc comparison

contrast	ratio	SE	df	null	z.ratio	p.value	
VR1 start / VR1 perform	0.784	0.120	Inf	1	-1.596	0.2961	
VR2 start / VR2 perform	0.676	0.102	Inf	1	-2.594	0.0282	*
R3 / VR3 start	20.878	3.161	Inf	1	20.071	<.0001	***

Means

Timepoint	Mean	SE
VR1 start	5.369	1.262
VR1 perform	7.712	1.508
VR2 start	5.403	2.054
VR2 perform	6.446	1.813
VR3 start	5.971	2.094
R3	46.529	4.171

Secondary Outcomes

Mean GSR Finger

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Inverse
Response: Mean_GSR_Finger

	Chisq	Df	Pr(>Chisq)	
(Intercept)	76.069	1	< 2.2e-16	***
Treatment	2.318	1	0.128	
Timepoint	91.170	9	0.000	***
Test group	0.414	1	0.520	
Treatment x Timepoint	6.136	9	0.726	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	z.ratio	p.value	
Baseline - Pretreatment	-0.006	0.011	Inf	-0.574	1.000	
VR1 Speech Preparation - Pretreatment	-0.055	0.008	Inf	-6.790	<.0001	***
VR1 Speech Delivery - Pretreatment	-0.060	0.008	Inf	-7.413	<.0001	***
VR1 Mental Arithmetic - Pretreatment	-0.060	0.008	Inf	-7.496	<.0001	***
R1 - Pretreatment	-0.056	0.008	Inf	-6.945	<.0001	***
VR2 Walk Plank - Pretreatment	-0.065	0.008	Inf	-8.135	<.0001	***
R2 - Pretreatment	-0.060	0.008	Inf	-7.475	<.0001	***
VR3 Roller Coaster - Pretreatment	-0.065	0.008	Inf	-8.041	<.0001	***
R3 - Pretreatment	-0.062	0.008	Inf	-7.714	<.0001	***

Mean GSR Forehead

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: Identity
Response: sqrt(Mean_GSR_Forehead)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	133.303	1	<2e-16	***
Treatment	0.122	1	0.727	
Timepoint	172.043	9	<2e-16	***
Test group	2.601	1	0.107	
Treatment x Timepoint	3.066	9	0.962	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	z.ratio	p.value	
Baseline - Pretreatment	-0.159	0.071	Inf	-2.222	0.026	
VR1 Speech Preparation - Pretreatment	0.069	0.078	Inf	0.887	0.375	
VR1 Speech Delivery - Pretreatment	0.343	0.087	Inf	3.966	0.000	***
VR1 Mental Arithmetic - Pretreatment	0.635	0.095	Inf	6.706	<.0001	***
R1 - Pretreatment	0.743	0.098	Inf	7.611	<.0001	***
VR2 Walk Plank - Pretreatment	0.754	0.099	Inf	7.644	<.0001	***
R2 - Pretreatment	0.866	0.101	Inf	8.599	<.0001	***
VR3 Roller Coaster - Pretreatment	0.907	0.102	Inf	8.932	<.0001	***
R3 - Pretreatment	1.106	0.106	Inf	10.388	<.0001	***

Mean Heart Rate

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: Inverse Response:log(Mean_HR_P)

	Chisq	Df	Pr(>Chisq)
(Intercept)	15880.639	1	<2e-16
Treatment	2.318	1	0.128
Timepoint	680.108	9	<2e-16
Test group	0.181	1	0.671
Treatment x Timepoint	11.536	9	0.241

Dunn-Sidak adjusted post-hoc comparisons

contrast	response	SE	df	null	z.ratio	p.value	
Baseline - Pretreatment	2.713	0.001	Inf	2.718	-3.972	0.001	**
VR1 Speech Preparation - Pretreatment	2.692	0.001	Inf	2.718	-20.437	<.0001	***
VR1 Speech Delivery - Pretreatment	2.687	0.001	Inf	2.718	-24.507	<.0001	***
VR1 Mental Arithmetic - Pretreatment	2.694	0.001	Inf	2.718	-18.739	<.0001	***
R1 - Pretreatment	2.712	0.001	Inf	2.718	-4.436	0.000	***
VR2 Walk Plank - Pretreatment	2.704	0.001	Inf	2.718	-11.110	<.0001	***
R2 - Pretreatment	2.716	0.001	Inf	2.718	-1.460	0.754	
VR3 Roller Coaster - Pretreatment	2.716	0.001	Inf	2.718	-1.456	0.757	
R3 - Pretreatment	2.717	0.001	Inf	2.718	-0.635	0.999	

Dunn-Sidak adjusted 5rd post-hoc comparison

contrast	response	SE	df	null	z.ratio	p.value	
VR1_Speech_Prep - Baseline_Measures	2.697	0.001	Inf	2.718	-16.503	<.0001	***
VR1_Speech - Baseline_Measures	2.692	0.001	Inf	2.718	-20.574	<.0001	***
VR1_Mental_Arith - Baseline_Measures	2.699	0.001	Inf	2.718	-14.816	<.0001	***
VR2_Walk_Plank - Baseline_Measures	2.709	0.001	Inf	2.718	-7.246	<.0001	***
VR3_RollerCoaster - Baseline_Measures	2.722	0.001	Inf	2.718	2.429	0.0734	

Stage	Mean	SE
Baseline_Measures	78.694	1.106
VR1_Speech_Prep	92.501	1.692
VR1_Speech	96.206	1.792
VR1_Mental_Arith	90.962	1.607
R1	79.067	1.142
VR2_Walk_Plank	84.710	1.445
R2	76.808	1.118
VR3_RollerCoaster	77.233	1.384

SD Skin conductance finger

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: sqrt
Response: (SD_GSR_Finger + 0.1)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	65.529	1	0.000	***
Treatment	0.062	1	0.803	
Timepoint	83.799	9	0.000	***
Age	0.080	1	0.778	
Treatment x Timepoint	15.492	9	0.078	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	z.ratio	p.value	
Baseline - Pretreatment	-0.027	0.084	Inf	-0.327	1.000	
VR1 Speech Preparation - Pretreatment	-0.603	0.074	Inf	-8.193	<.0001	***
VR1 Speech Delivery - Pretreatment	-0.605	0.075	Inf	-8.123	<.0001	***
VR1 Mental Arithmetic - Pretreatment	-0.453	0.080	Inf	-5.647	<.0001	***
R1 - Pretreatment	-0.075	0.089	Inf	-0.840	0.990	
VR2 Walk Plank - Pretreatment	-0.451	0.081	Inf	-5.586	<.0001	***
R2 - Pretreatment	-0.131	0.088	Inf	-1.480	0.740	
VR3 Roller Coaster - Pretreatment	-0.430	0.081	Inf	-5.345	<.0001	***
R3 - Pretreatment	-0.154	0.088	Inf	-1.760	0.521	

SD Skin conductance forehead

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: log(SD_GSR_Forehead + 0.1)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	0.001	1	0.972	
Treatment	0.006	1	0.937	
Timepoint	94.688	9	< 2e-16	***
Age	2.393	1	0.122	
Test group	4.562	1	0.033	* Higher for participants in the late group
Treatment x Timepoint	4.271	9	0.893	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	t.ratio	p.value	
Baseline - Pretreatment	-0.042	0.136	591	-0.308	1.000	
VR1 Speech Preparation - Pretreatment	-1.371	0.138	593	-9.962	<.0001	***
VR1 Speech Delivery - Pretreatment	-0.241	0.138	593	-1.751	0.530	
VR1 Mental Arithmetic - Pretreatment	-0.405	0.138	593	-2.941	0.030	*
R1 - Pretreatment	-0.178	0.137	593	-1.296	0.859	
VR2 Walk Plank - Pretreatment	-0.952	0.140	593	-6.820	<.0001	***
R2 - Pretreatment	-0.526	0.138	593	-3.822	0.001	**
VR3 Roller Coaster - Pretreatment	-0.554	0.138	593	-4.011	0.001	**
R3 - Pretreatment	-0.276	0.138	593	-2.009	0.340	

SD Heart Rate

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: Identity
Response: SD_HR_BPM

	Chisq	Df	Pr(>Chisq)	
(Intercept)	133.326	1	< 2.2e-16	***
Treatment	0.000	1	0.994	
Timepoint	40.006	9	0.000	***
Gender	5.245	2	0.073	
Age	6.803	1	0.009	**Lower for older participants
Treatment x Timepoint	9.840	9	0.364	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	z.ratio	p.value
Baseline - Pretreatment	0.782	0.242	Inf	3.234	0.011
VR1 Speech Preparation - Pretreatment	0.276	0.233	Inf	1.183	0.912
VR1 Speech Delivery - Pretreatment	-0.022	0.219	Inf	-0.102	1.000
VR1 Mental Arithmetic - Pretreatment	0.006	0.226	Inf	0.027	1.000
R1 - Pretreatment	1.706	0.277	Inf	6.147	<.0001
VR2 Walk Plank - Pretreatment	0.604	0.254	Inf	2.376	0.147
R2 - Pretreatment	0.791	0.245	Inf	3.228	0.011
VR3 Roller Coaster - Pretreatment	-0.131	0.221	Inf	-0.593	0.999
R3 - Pretreatment	0.667	0.243	Inf	2.747	0.053

Max Skin conductance finger

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: sqrt
Response: (Max_GSR_Finger - min(Vital$Max_GSR_Finger) + 0.1)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	179.778	1	<2e-16	***
Treatment	1.504	1	0.220	
Timepoint	114.297	9	<2e-16	***
Age	0.148	1	0.701	
Treatment x Timepoint	5.079	9	0.827	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	z.ratio	p.value	
Baseline - Pretreatment	-0.024	0.100	Inf	-0.243	1.000	
VR1 Speech Preparation - Pretreatment	0.462	0.107	Inf	4.334	0.000	***
VR1 Speech Delivery - Pretreatment	0.603	0.109	Inf	5.522	<.0001	***
VR1 Mental Arithmetic - Pretreatment	0.706	0.110	Inf	6.397	<.0001	***
R1 - Pretreatment	0.757	0.110	Inf	6.911	<.0001	***
VR2 Walk Plank - Pretreatment	1.125	0.116	Inf	9.730	<.0001	***
R2 - Pretreatment	0.976	0.112	Inf	8.677	<.0001	***
VR3 Roller Coaster - Pretreatment	1.121	0.115	Inf	9.786	<.0001	***
R3 - Pretreatment	1.127	0.114	Inf	9.876	<.0001	***

Max Skin conductance forehead

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: sqrt(Max_GSR_Forehead)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	154.369	1	< 2e-16	***
Treatment	0.026	1	0.872	
Timepoint	146.334	9	< 2e-16	***
Gender	5.622	2	0.060	
Test group	5.117	1	0.024	*Higher for participants in the late group
Treatment x Timepoint	3.201	9	0.956	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	t.ratio	p.value	
Baseline - Pretreatment	-0.376	0.128	589	-2.934	0.031	*
VR1 Speech Preparation - Pretreatment	-0.249	0.130	590	-1.909	0.409	
VR1 Speech Delivery - Pretreatment	0.337	0.130	590	2.585	0.086	
VR1 Mental Arithmetic - Pretreatment	0.569	0.130	590	4.368	0.000	***
R1 - Pretreatment	0.866	0.130	590	6.681	<.0001	***
VR2 Walk Plank - Pretreatment	0.741	0.131	590	5.640	<.0001	***
R2 - Pretreatment	0.857	0.130	590	6.580	<.0001	***
VR3 Roller Coaster - Pretreatment	0.877	0.131	590	6.702	<.0001	***
R3 - Pretreatment	1.107	0.130	590	8.502	<.0001	***

Dunn-Sidak adjusted 5rd post-hoc comparison

contrast	estimate	SE	df	t.ratio	p.value	
VR1_Speech_Prep - Baseline_Measures	0.128	0.130	588.000	0.978	0.864	
VR1_Speech - Baseline_Measures	0.713	0.130	588.000	5.467	<.0001	***
VR1_Mental_Arith - Baseline_Measures	0.945	0.130	588.000	7.248	<.0001	***
VR2_Walk_Plank - Baseline_Measures	1.118	0.132	588.000	8.491	<.0001	***
VR3_RollerCoaster - Baseline_Measures	1.253	0.131	588.000	9.566	<.0001	***

Stage	Mean	SE
Baseline_Measures	15.194	2.327
VR1_Speech_Prep	15.591	2.200
VR1_Speech	19.970	2.223
VR1_Mental_Arith	21.580	2.082
R1	25.541	2.642
VR2_Walk_Plank	23.614	2.742
R2	24.734	2.424
VR3_RollerCoaster	24.289	2.366

Max Heart Rate

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: log(Max_HR_BPM)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	44885.908	1	<2e-16	***
Treatment	2.378	1	0.123	
Timepoint	226.056	9	<2e-16	***
Gender	3.457	2	0.178	
Treatment x Timepoint	4.333	9	0.888	

Dunn-Sidak adjusted post-hoc comparisons

contrast	ratio	SE	df	null	t.ratio	p.value
Baseline / Pretreatment	1.079	0.013	590.000	1.000	6.277	<.0001
VR1 Speech Preparation / Pretreatment	1.153	0.014	591.000	1.000	11.538	<.0001
VR1 Speech Delivery / Pretreatment	1.197	0.015	591.000	1.000	14.611	<.0001
VR1 Mental Arithmetic / Pretreatment	1.144	0.014	591.000	1.000	10.888	<.0001
R1 / Pretreatment	1.095	0.013	591.000	1.000	7.369	<.0001
VR2 Walk Plank / Pretreatment	1.061	0.013	591.000	1.000	4.722	<.0001
R2 / Pretreatment	1.030	0.013	591.000	1.000	2.408	0.138
VR3 Roller Coaster / Pretreatment	0.986	0.012	591.000	1.000	-1.120	0.936
R3 / Pretreatment	1.032	0.013	591.000	1.000	2.551	0.095

VAS Tense

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: Log
Response: (Tense + 0.01)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	109.332	1	< 2.2e-16	***
Treatment	0.000	1	0.999	
Timepoint	85.728	10	0.000	***
Gender	8.173	2	0.017	*Higher for women compared to men
Test group	2.967	1	0.085	
Treatment x Timepoint	5.796	10	0.832	

Dunn-Sidak adjusted post-hoc comparisons

contrast	ratio	SE	df	null	z.ratio	p.value	
Baseline / Pretreatment	1.310	0.204	Inf	1	1.740	0.575	
VR1 start / Pretreatment	1.860	0.291	Inf	1	3.935	0.001	**
VR1 perform / Pretreatment	3.650	0.576	Inf	1	8.197	<.0001	***
R1 / Pretreatment	3.330	0.532	Inf	1	7.506	<.0001	***
VR2 start / Pretreatment	1.250	0.196	Inf	1	1.438	0.804	
VR2 perform / Pretreatment	2.100	0.338	Inf	1	4.640	<.0001	***
R2 / Pretreatment	1.870	0.297	Inf	1	3.949	0.001	**
VR3 start / Pretreatment	1.070	0.167	Inf	1	0.434	1.000	
R3 / Pretreatment	2.530	0.402	Inf	1	5.812	<.0001	***
Study close / Pretreatment	1.160	0.186	Inf	1	0.956	0.984	

Dunn-Sidak adjusted 3rd post-hoc comparison

contrast	ratio	SE	df	null	z.ratio	p.value	
VR1 start / VR1 perform	0.508	0.080	Inf	1	-4.32	<.0001	***
VR2 start / VR2 perform	0.595	0.094	Inf	1	-3.283	0.0031	**
R3 / VR3 start	2.360	0.371	Inf	1	5.464	<.0001	***

Means

Timepoint	Mean	SE
VR1 start	26.554	2.813
VR1 perform	46.212	3.328
VR2 start	19.403	2.607
VR2 perform	29.923	3.107
VR3 start	17.103	2.324
R3	35.074	3.522

VAS Calm

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: scaled (Calm)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	4.054	1	0.044	*
Treatment	0.015	1	0.903	
Timepoint	115.736	10	< 2e-16	***
Gender	12.332	2	0.002	**Women scored lower than men
Treatment x Timepoint	16.627	10	0.083	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	t.ratio	p.value	
Baseline - Pretreatment	-0.263	0.129	669	-2.038	0.349	
VR1 start - Pretreatment	-0.581	0.130	669	-4.466	0.000	***
VR1 perform - Pretreatment	-1.438	0.129	669	-11.116	<.0001	***
R1 - Pretreatment	-0.913	0.128	669	-7.113	<.0001	***
VR2 start - Pretreatment	-0.233	0.129	669	-1.805	0.524	
VR2 perform - Pretreatment	-0.858	0.130	669	-6.600	<.0001	***
R2 - Pretreatment	-0.561	0.128	669	-4.371	0.000	***
VR3 start - Pretreatment	-0.159	0.128	669	-1.237	0.913	
R3 - Pretreatment	-0.985	0.128	669	-7.676	<.0001	***
Study close - Pretreatment	-0.12	0.129	669	-0.931	0.987	

Dunn-Sidak adjusted 3rd post-hoc comparison

contrast	estimate	SE	df	t.ratio	p.value	
VR1 start - VR1 perform	0.858	0.130	668.880	6.574	<.0001	***
VR2 start - VR2 perform	0.625	0.130	669.240	4.809	<.0001	**
R3 - VR3 start	-0.827	0.128	668.630	-6.467	<.0001	***

Means

Timepoint	Mean	SE
VR1 start	67.738	2.506
VR1 perform	46.576	2.883
VR2 start	76.284	2.405
VR2 perform	60.538	3.293
VR3 start	77.765	2.185
R3	58.103	3.276

VAS Excited

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: sqrt
Response: Excited + 0.01

	Chisq	Df	Pr(>Chisq)	
(Intercept)	131.972	1	< 2.2e-16	***
Treatment	0.655	1	0.418	
Timepoint	56.698	10	0.000	***
Age	0.348	1	0.555	
Treatment x Timepoint	10.597	10	0.390	

Dunn-Sidak adjusted post-hoc comparisons

contrast	estimate	SE	df	z.ratio	p.value	
Baseline - Pretreatment	-0.029	0.020	Inf	-1.407	0.824	
VR1 start - Pretreatment	-0.041	0.021	Inf	-1.981	0.386	
VR1 perform - Pretreatment	-0.061	0.021	Inf	-2.906	0.036	*
R1 - Pretreatment	-0.041	0.020	Inf	-2.015	0.362	
VR2 start - Pretreatment	0.030	0.020	Inf	1.533	0.738	
VR2 perform - Pretreatment	0.054	0.019	Inf	2.797	0.050	
R2 - Pretreatment	0.025	0.020	Inf	1.285	0.891	
VR3 start - Pretreatment	0.058	0.019	Inf	3.033	0.024	*
R3 - Pretreatment	-0.068	0.021	Inf	-3.251	0.011	*
Study close - Pretreatment	-0.1549	0.0228	Inf	-6.792	<.0001	***

VAS Bored

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gamma
Link: Identity
Response: (Bored + 0.01)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	17.239	1	0.000	***
Treatment	0.485	1	0.486	
Timepoint	3.578	10	0.964	
Age	0.810	1	0.368	
Treatment x Timepoint	18.174	10	0.052	

Salivary Cortisol

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: log(Cortisol)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	50.820	1	0.000	***
Treatment	0.076	1	0.783	
Timepoint	22.424	4	0.000	***
Gender	5.432	2	0.066	
Age	7.252	1	0.007	**Lower for older participants
Time	2.718	1	0.099	
Treatment x Timepoint	2.189	4	0.701	

Dunn-Sidak adjusted post-hoc comparisons

contrast	ratio	SE	df	null	t.ratio	p.value	
Baseline / Pretreatment	0.938	0.077	322.000	1	-0.773	0.902	
Rest 1 / Pretreatment	1.296	0.120	254.000	1	2.817	0.021	*
Rest 2 / Pretreatment	1.404	0.139	218.000	1	3.434	0.003	**
Rest 3 / Pretreatment	1.271	0.135	189.000	1	2.269	0.094	

Dunn-Sidak adjusted 3rd post-hoc comparison

contrast	ratio	SE	df	null	t.ratio	p.value	
Rest1 / Baseline	1.380	0.094	302.000	1	4.731	<.0001	***
Rest2 / Baseline	1.500	0.106	331.000	1	5.674	<.0001	***
Rest3 / Baseline	1.350	0.101	349.000	1	4.065	0.0002	***

Means

Timepoint	Mean	SE
Baseline	7.091	0.423
Rest1	9.907	0.670
Rest2	10.515	0.731
Rest3	9.665	0.871

Tertiary Outcomes

Eye Openness

Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: Eye_Openness

	Chisq	Df	Pr(>Chisq)	
(Intercept)	490.294	1	< 2e-16	***
Treatment	0.218	1	0.641	
Timepoint	8.646	4	0.071	
Gender	4.286	2	0.117	
Treatment x Timepoint	1.460	4	0.834	

Eye Gazing

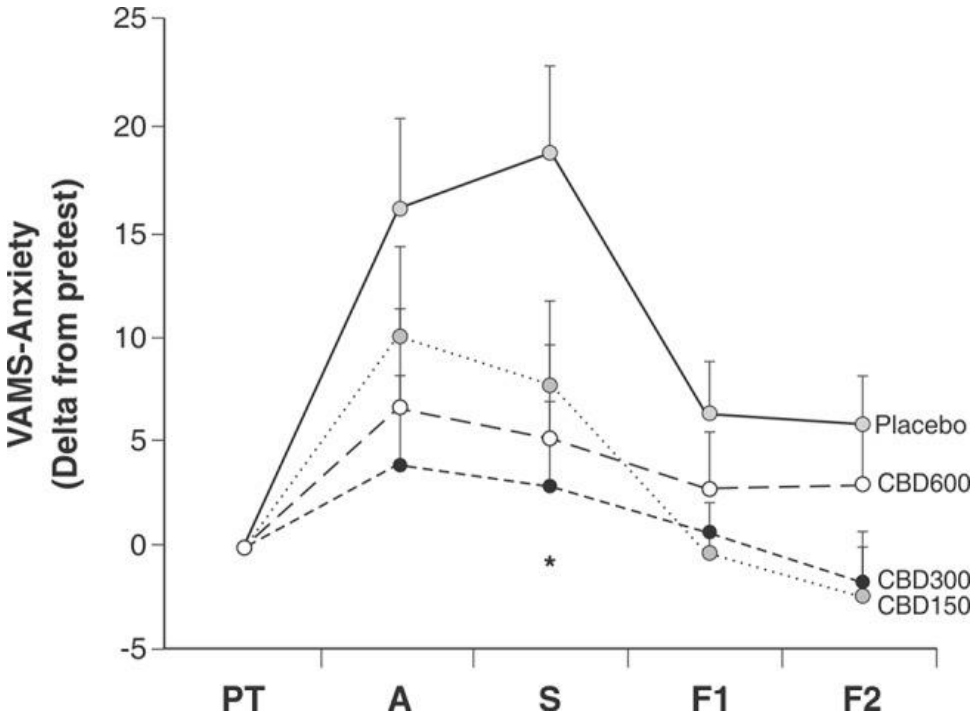
Analysis of Deviance Table (Type III Wald chisquare tests)
Distribution: Gaussian (Normal)
Link: Identity
Response: (Gaze duration/total duration)

	Chisq	Df	Pr(>Chisq)	
(Intercept)	67.009	1	0.000	***
Test group	0.000	1	1.000	
Treatment x Target	776.937	5	< 2.2e-16	***
Target x Timepoint	188.096	9	< 2.2e-16	***
Treatment x Target x Timepoint	4.646	9	0.864	

Dunn-Sidak adjusted post-hoc comparisons

Target	Timepoint	contrast	estimate	SE	df	t.ratio	p.value	
Floor	.	CBD - Placebo	-0.001	0.038	380.220	-0.018	1.000	
Nothing	.	CBD - Placebo	0.007	0.038	380.220	0.195	1.000	
Target	.	CBD - Placebo	-0.007	0.038	380.220	-0.177	1.000	
.	VR1_Mental_Arith	Floor - Nothing	-0.671	0.053	634.470	-12.550	<.0001	***
.		Floor - Target	-0.001	0.053	634.470	-0.020	1.000	
.		Nothing - Target	0.670	0.053	634.470	12.530	<.0001	***
.	VR1_Speech_Prep	Floor - Nothing	-0.235	0.053	634.470	-4.433	0.000	***
.		Floor - Target	-0.657	0.053	634.470	-12.410	<.0001	***
.		Nothing - Target	-0.422	0.053	634.470	-7.977	<.0001	***
.	VR1_Speech	Floor - Nothing	-0.963	0.053	634.470	-18.004	<.0001	***
.		Floor - Target	-0.025	0.053	634.470	-0.466	1.000	
.		Nothing - Target	0.938	0.053	634.470	17.538	<.0001	***
.	VR2_Walk_Plank	Floor - Nothing	-0.945	0.055	634.470	-17.147	<.0001	***
.		Floor - Target	-0.004	0.055	634.470	-0.065	1.000	
.		Nothing - Target	0.941	0.055	634.470	17.082	<.0001	***

Appendix 5



Reproduced from Linares *et al,.* (2019). Visual Analogue Mood Scale (VAMS) anxiety factor scores in each phase of the simulated public speaking test (SPST) for groups treated with cannabidiol (CBD) 150, 300, and 600 mg or placebo (points in the curve refer to mean scores and vertical lines refer to mean standard errors).* Lower anxiety levels in the group treated with CBD 300 mg relative to the placebo phase (p = 0.042). **Abbreviations:** PT = pre-test; A = anticipatory anxiety; S = speech; F1= post-test 1; F2 = post-test 2.