A clinical primer

A guide to the rational use of cannabis-based medicines

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Contents

1. Foreword

The rational use of cannabis-based medicines

High-quality medicines are one of the health sector's greatest tools. They are used to treat or prevent disease and to promote health.

> *The rational use of medicines requires that 'patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community.'*
>
> *The rational use of medicines, WHO 2020*

Cannabis-based medicines are cannabis-derived, with a defined and standard cannabinoid content. They are typically administered by inhalation, by the oromucosal or the oral route. These medicines are still very new to most health professionals.

The rational use of cannabis-based medicines requires health professionals consider their clinical utility, with patient safety in mind.

This clinical primer text seeks to share knowledge of good prescribing, dispensing and administration practices. It aims to improve health professionals' ability to discuss the benefits and risks of cannabis-based medicines with their patients, family or carers, and to make clinical decisions that improve patient safety and treatment outcomes.

About the authors and editor

This text draws on clinical research, clinical observations, and professional experiences to provide useful, real-world insights to the rational use of cannabis-based medicines.

Author, Dr Jürgen Fleisch (MD, PhD) undertook a fellowship in pain medicine in Portland, USA. Since 2007 he has practised anaesthesiology and pain therapy at the Leiden University Medical Center (LUMC), the Netherlands. LUMC is an ESMO - a Designated Centre of Integrated Oncology and Palliative Care. Jürgen's close cooperation with the Department of Oncology means that he regularly treats pain and related symptoms in cancer patients using classic medications and interventional pain treatments. He also has considerable experience prescribing cannabis-based medicines.

Author, Martin Woodbridge (MPHC, DPH) trained and lectured at the University of Otago's Wellington School of Medicine, and worked for Medsafe, the medicines safety authority. In 2007, he wrote New Zealand's regulatory policy and clinical guidelines on the medicinal use of cannabis for the Ministry of Health.

Since then, he has advised on programmes in Oceania and Asia and for the United Nations International Narcotics Control Board's regulatory guidance on cannabis intended for medical and scientific use. He is also the author of the complimentary text 'A primer to medicinal cannabis'. Martin has worked with Carl and Jürgen on different projects relating to the rational use of medicines.

Editor, Professor Emeritus Dr Carl Burgess (MB ChB, MD, MRCP, FRACP, FRCP) is a member of the New Zealand Order of Merit for Services to Pharmacology. He taught internal medicine and clinical pharmacology from 1982 to 2013 at the University of Otago's Wellington School of Medicine, while also a consultant hospital physician to Capital and Coast Health, New Zealand. Carl has been involved in clinical pharmacology research since 1976. He provides deep knowledge of clinical pharmacology and the rational use of medicines, having investigated the clinical use of anti-depressives, anti-arrhythmic agents, anti-thrombotics, and bronchodilators, among other medicine classes. Carl is a former member of the Standing Committee on Therapeutic Trials (SCOTT), undertaking the scientific assessment of clinical trial applications for new pharmaceutical-type medicines.

Acknowledgements

The authors would like to thank health professionals from around the world for their valuable clinical contributions, drawing on their experiences as prescribers, pharmacists and nurses working with cannabis-based medicines (see section: insights from health professionals). Also thanks to Associate Professor Dr Simon Adamson for his advice on screening tools (see appendix: clinical evaluation tools).

Disclaimer

The clinical primer is produced by Woodbridge Research Ltd. It is a free-to-access educational resource funded under the policy of education without commercial bias. This project was made possible with funding provided by Bedrocan International. This booklet reflects published data, information and clinical insights as at the year 2025. It considers the rational use of cannabis-based medicines within a prescriber-pharmacy model of care.

While all efforts have been made to ensure the accuracy and scientific nature of information at the time of its production, the authors make no representations, implied or otherwise, as to the safety and efficacy of cannabis-based medicines and the methods of administration until such time that reliable clinical data is provided, nor to the contents of this booklet as certain information may have become outdated due to the rapid scientific and clinical developments in this field.

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2. The current situation

A glance at the past and a view to the future

Cannabis comprises a single species of dioecious plant, *Cannabis sativa* Linnaeus. Cannabis is one of the oldest known medicinal plants and has been in use in different parts of the world for centuries.

Cannabis originated in the Tibetan Central Plateau. The cultivated 'drug-type' cannabis likely moved with humans from Central Asia along the ancient Silk Route to various parts of the world. More recently, selective breeding and extensive hybridisation has led to numerous plant chemovars, with specific chemical constituents, being developed for medicinal use.

As early as the 1960s, the major biologically active cannabinoids delta-9-tetrahydrocannabinol (Δ-9-THC or THC) and cannabidiol (CBD) were identified in the cannabis plant. By the early 1990s the cannabinoid receptors CB1 and CB2 had been discovered. [1] Our understanding of the endocannabinoid system, the cannabinoid receptors, endogenous and plant-derived cannabinoids continue to increase with time.

In the last decade, significant advancements have been made in cultivation techniques, medicine quality, production standards, and safer administration methods. A pivotal development occurred in 2024 with the publication of the European Pharmacopoeia's cannabis flower monograph [2] which requires cannabis flower when prescribed to a patient is of pharmaceutical quality.

The accumulated credible research now demonstrates that cannabinoids have therapeutic applications in certain conditions. [3-6] Accordingly, cannabis-based medicines are now considered a potential therapeutic option.

Cannabis-based medicines

Cannabis-based medicines are cannabis-derived, with a defined and standard cannabinoid content. This class of medicine is increasingly being made available, globally.

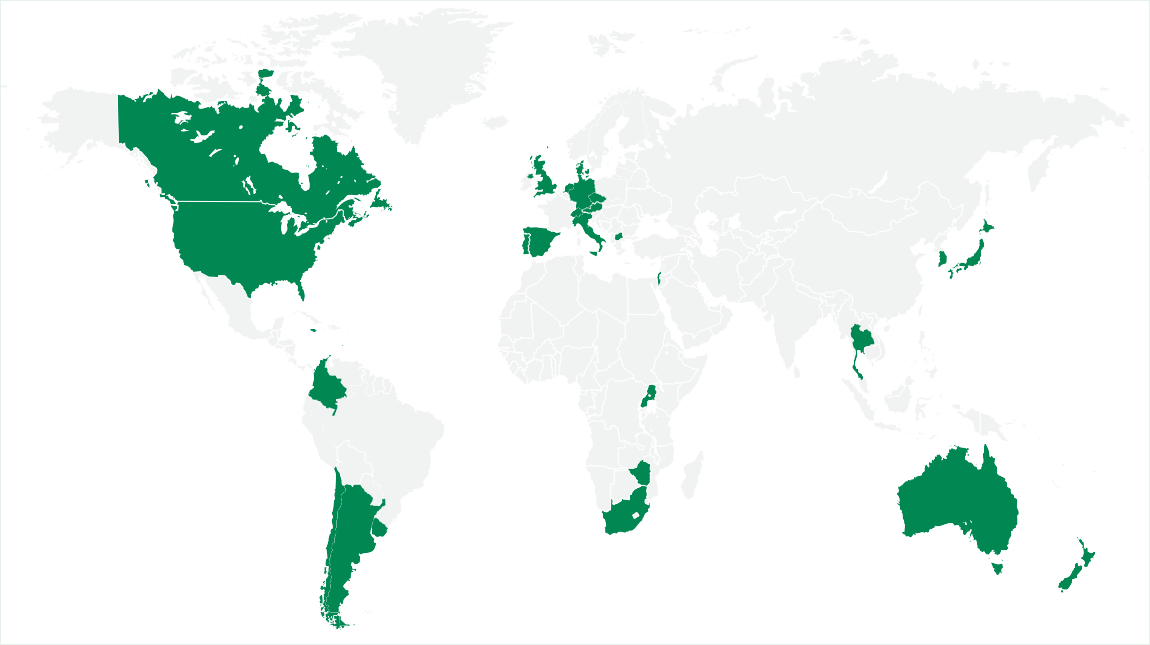
The regulatory situation varies by country: some countries permit cannabis solely for medical and scientific purposes, others allow both medical and adult-recreational use, while other countries have no legislation in place for either.

Within the medical field, there is a general perception that these medicines became available due to popular demand rather than through conventional medicine development. Indeed, the recent and rapid re-introduction of cannabinoids into modern medical practice indicates that there is still more to understand and discover.

Various strategies are used to provide and dispense cannabis-based medicines to patients. The prescriber-pharmacy model of care appears to offer the highest quality of care through continuity and patient co-management, in contrast to 'cannabis clinics,' 'cannabis dispensaries,' or 'courier mail' services.

Only a handful of cannabis-based medicines, like Sativex® and Epidiolex®, are approved and registered for specific indications, and only in a few countries. Others are unapproved medicines which, in many countries, are expected to meet a minimum quality standard. The safety or clinical efficacy of these formulations need to be determined through clinical trials. Alongside cannabis-based medicines, there are several approved synthetic cannabinoids including Marinol® (dronabinol, a synthetic THC) and Cesamet® (nabilone, a synthetic THC analogue).

Figure: countries cultivating the cannabis plant and producing cannabis for medical and scientific purposes



Countries cultivating the cannabis plant and producing cannabis for medical and scientific purposes are indicated on the above map: Argentina, Australia, Austria, Canada, Chile, Colombia, Czechia, Denmark, Germany, Israel, Italy, Jamaica, Japan, Lesotho, Netherlands, New Zealand, North Macedonia, Portugal, Republic of Korea, Saint Vincent and the Grenadines, Spain, Switzerland, Thailand, Uganda, United Kingdom, United States of America, Uruguay, Zimbabwe. [7]

Despite many technical advancements, several of these countries do not actually have access to medicines with a defined and standard cannabinoid content.

Utility

Cannabinoids have recently been introduced as a tool in the physician's 'toolbox'. Reflecting on this current situation, cannabis-based medicines are currently not a first-line treatment. Indeed, often they are third-line treatments, prescribed when other options (available registered medicines) have been trialled and failed or where those medicines' side effects are unacceptable for patients. Furthermore, cannabinoids elicit a range of clinical responses, some of which have no defined endpoint and make it difficult to measure changes in symptom control.

Among the many publications on the usage of cannabinoids, three stand out for their thorough investigation of both positive and negative aspects. These publications include:

- The US National Academies of Sciences, Engineering, and Medicine's (NASEM) 2017 comprehensive review on the health effects of cannabis and cannabinoids. [4]
- The European Pain Federation (EFIC) 2018 position paper on the appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. [8]
- The British National Institute for Health and Clinical Excellence (NICE) 2019 guideline on cannabis-based medicinal products. [3]

Tables: summary of key publications on the clinical utility of cannabis-based medicines and cannabinoids

NASEM
The US National Academies of Sciences, Engineering and Medicine Review

NASEM concluded in 2017 there is substantial evidence that cannabis-based medicines are effective for the treatment of:

- Chronic pain in adults
- Chemotherapy-induced nausea and vomiting
- Spasticity symptoms in multiple sclerosis (patient-reported improvement)

Moderate evidence for:

- Improving short-term sleep outcomes in individuals with sleep disturbance associated with obstructive sleep apnea syndrome (OSAS)
- Fibromyalgia
- Chronic pain
- Multiple sclerosis

Limited evidence for:

- Increasing appetite and decreasing weight loss associated with HIV/AIDS
- Improving clinician-measured spasticity symptoms in multiple sclerosis
- Improving anxiety symptoms
- Improving symptoms of post-traumatic stress disorder (PTSD)

There was no evidence for: cancer therapy; cancer-associated anorexia/cachexia syndrome and anorexia nervosa; irritable bowel syndrome (IBS); epilepsy; spasticity in patients with paralysis due to spinal cord injury; amyotrophic lateral sclerosis (ALS); chorea, and certain neuropsychiatric symptoms associated with Huntington's disease; motor system symptoms associated with Parkinson's disease; dystonia; achieving abstinence in the use of addictive substances; and, mental health outcomes in individuals with schizophrenia or schizophreniform psychosis.

EFIC
The European Pain Federation

EFIC summarised the evidence in 2018 per pain diagnosis, and provides practical advice on safe prescribing, including:

- Cancer pain: nabiximols oromucosal spray (plant-derived THC/CBD) can be considered as part of an add-on individual therapeutic trial for cancer pain without sufficient relief from opioids or other established analgesics.
- Chronic neuropathic pain: cannabis-based medicines can be considered as third-line therapy for chronic neuropathic pain.
- Chronic non-neuropathic non-cancer pain: in exceptional cases, cannabis-based medicines can be considered as an individual therapeutic trial, if all established treatments have failed and after careful analyses and multidisciplinary assessment.

A pain diagnosis is summarised as chronic abdominal pain, chronic low back pain, Crohn's disease, fibromyalgia, headaches and rheumatoid arthritis. There is insufficient evidence for the use of cannabis-based medicines in non-neuropathic 'benign' pain.

NICE
The British National Institute for Health and Clinical Excellence Guideline

The NICE recommendations in 2019 focus on four fields of medicine where cannabis-based medicines are mainly prescribed:

- Intractable nausea and vomiting: consider nabilone (synthetic THC) as an add-on treatment for adults (above 18 years) with chemotherapy-induced nausea and vomiting, which persists with conventional antiemetics.
- Spasticity: offer a four-week trial of THC:CBD spray to treat moderate to severe spasticity in adults with multiple sclerosis if other pharmacological treatments are not effective. After the trial period, continue THC:CBD spray if the person has at least a 20% reduction in spasticity related symptoms.
- Severe treatment-resistant epilepsy: cannabidiol (CBD) with clobazam is recommended as an option for treating seizures associated with Lennox–Gastaut syndrome in patients aged 2 years and older, only if the frequency of drop seizures is checked every 6 months, and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment.
- Chronic pain: do not offer cannabis-based medicines (including nabilone, dronabinol, THC, THC/CBD and cannabidiol) to adult patients with chronic pain.

NICE 'allows' the prescription of cannabis-based medicines 'when there is an unmet clinical need'. In general, NICE uses strong wording around who should prescribe cannabis-based medicines: '...initial prescription of cannabis-based medicines must be issued by a doctor on the specialist register with a special interest in the condition being treated. For children and young patients, the initiating prescriber should also be a tertiary paediatric specialist.'

Many cannabis-based medicines are unapproved. There are unknowns associated with 'unapproved medicines' or 'prescribing an approved medicine off-label.' Therefore, a strong clinical argument is necessary for such prescribing.

A limited number of healthcare professionals have experience in prescribing, dispensing or administering cannabis-based medicines. This includes specialists authorised to work with novel medicines. Meanwhile, published surveys of general practitioners (family doctors) indicate they would readily consider prescribing cannabis-based medicines for serious and terminal conditions where evidence shows efficacy. [9-11]

Current prescribing indicates that cannabis-based medicines containing THC or THC:CBD are mainly used in the context of pain, oncology, or palliative care settings. Clinical benefits are observed in conditions such as pain, nausea, and vomiting.

3. Pharmacology

This section focuses on pharmacology. It covers basic chemistry, the endocannabinoid system, dosing and dose forms, and the pharmacokinetic properties of pulmonary, oromucosal and oral administration routes.

Pharmacodynamics

Cannabis sativa L.

Cannabis sativa L., a plant, consists of hundreds of chemical compounds – at least 100 of these are cannabinoids. The difference between distinct cannabis varieties (cultivars) is determined by the cannabinoid and specific terpene content. Terpenes are the volatile aromatic compounds that give cannabis its characteristic aroma. [12]

Cannabinoids and terpenes are produced within the glandular trichomes, located on the entire surface of the plant. The largest concentration of trichomes is found on the flowering heads of the unfertilised female plant, the cannabis inflorescence (the flower).

Good cultivation practices allow for cannabis materials which meet medicine standards of quality and chemical consistency. [13-16]

Phyto-cannabinoids

Phyto-cannabinoids are synthesised by the cannabis plant. Cannabis initially produces CBG (cannabigerol) and then converts it into a specific phytocannabinoid acid via cannabinoid oxidocyclase.

The phytocannabinoid acid is the inactive form found in the fresh plant. The most abundant are tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA).

Heating to temperatures above 100°C causes decarboxylation (releasing CO_2), converting the acids into their bioactive forms, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). [17, 18]

THC is psychoactive, euphorigenic, and has intoxicating* effects at high doses. [19] In the body, THC is converted to a potent psychoactive metabolite, 11-hydroxy-THC (11-OH-THC). CBD is psychoactive but does not have intoxicating effects. Synthetic and semi-synthetic cannabinoids mimic the effects of phyto-cannabinoids, such as THC.

Cannabinoids, like opioids, act on specific receptors in humans. These are known as cannabinoid receptors.

* WHO. ICD-10: Intoxication is a transient condition that follows the administration of a psychoactive substance and results in disturbances in the level of consciousness, cognition, perception, judgement, behaviour, or other psycho-physiological functions and responses.

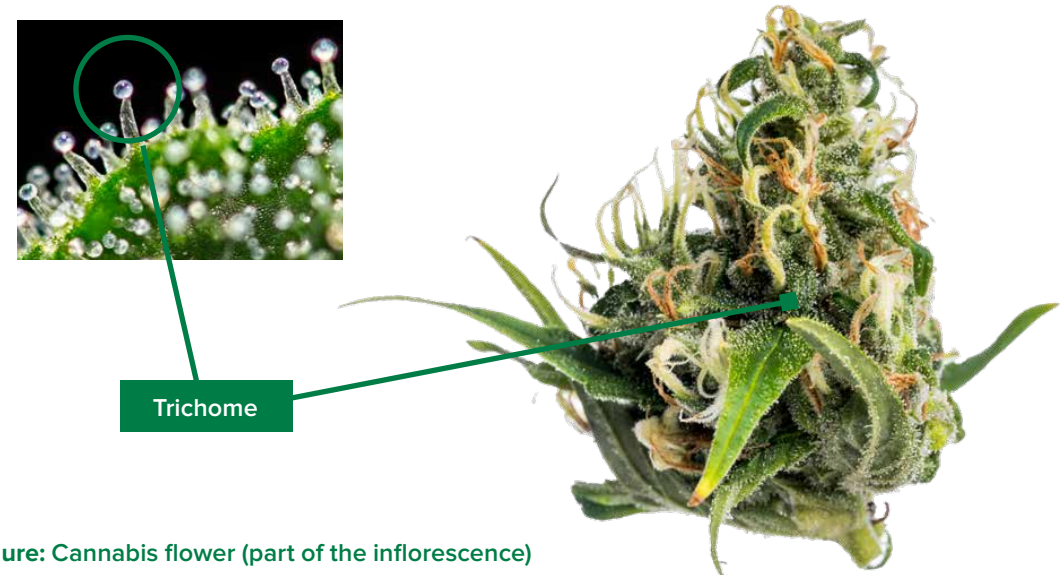


Figure: Cannabis flower (part of the inflorescence)

Figure: comparing opioids and cannabinoids

	
Papaver somniferum (opium poppy) Poppy straw	***Cannabis sativa* L. (cannabis)** Trichome / crude resin extract
Opioids: morphine, codeine	Cannabinoids: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)
Opioid receptor: μ receptor (G-protein coupled receptor) [20]	Cannabinoid receptor: CB1 and CB2 (G-protein coupled receptor) [21, 22]

The actions of THC

THC activates both CB1 and CB2 receptors (as a partial agonist with high affinity), which in turn influences the activity of various physiological systems. At the CB1 receptor, THC modulates neurotransmitter release, in particular gamma-aminobutyric acid (GABA) and glutamate. The response THC elicits is strongly influenced by both the expression level and signalling efficiency of cannabinoid receptors and by ongoing endogenous cannabinoid release.

The actions of CBD

CBD, by comparison to THC, has less affinity for the CB1 and CB2 receptors and works to partly block receptor activity (as a partial antagonist). CBD displays high potency as an antagonist of CB1 and CB2 receptor agonists in CB1- and CB2-expressing cells or tissues. Furthermore, CBD inhibits the uptake and hydrolysis of the endocannabinoid anandamide (AEA), thus increasing its concentration in the tissues where it is produced. CBD has been identified as a serotonin receptor (5-HT1A) agonist, which may be the basis of its purported anxiolytic and antipsychotic actions. [23-26]

Endocannabinoid system

The human endocannabinoid system

The human endocannabinoid system (ECS) contains cannabinoid (CB) receptors, which are activated by naturally produced endocannabinoids. Endocannabinoids identified and well-studied include N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonylglycerol (2-AG).

The ECS is involved in a host of homeostatic and physiologic functions. The ECS plays a critical role in the nervous system and regulates multiple physiological processes, including the adjustment of the response to pain, appetite, digestion, sleep, mood, and memory.

The ECS also influences seizure thresholds, coordination, sensory integration (touch, balance, sense of space), and other processes, such as the immune system and inflammation, heart function, fertility, bone physiology, the central stress response system, neural development, and eye pressure.

As the knowledge of the human ECS develops, so will the understanding of how the phyto-cannabinoids work. This understanding will lead to better medicines.

The cannabinoid receptors

Endocannabinoids are lipid-based retrograde neuro-transmitters which exhibit similar biological activities as phyto-cannabinoids. The phyto-cannabinoids of *Cannabis sativa* L. work in a similar way to the naturally produced endocannabinoids. However, unlike phyto-cannabinoids, endocannabinoids are rapidly degraded by FAAH (fatty acid amide hydrolase). Phyto-cannabinoids induce their pharmacological effects by binding to specific cannabinoid receptors. Cannabinoid receptors (CB) belong to the superfamily of the G-protein-coupled receptors that mediate the pharmacological effects of phyto-cannabinoids, endo-cannabinoids, and synthetic cannabimimetic compounds. [1, 21, 22]

Two types of cannabinoid receptors - CB1 and CB2 - have been identified with certainty.

CB1 receptor

The CB1 receptors are primarily located on nerve cells in the brain and spinal cord.

CB1 receptors mediate most, if not all, of the psychoactive effects of THC (and related compounds as analogues), being found in high concentration within the central nervous system – particularly within the cortex, hippocampus, amygdala, basal ganglia outflow tracts, and cerebellum.

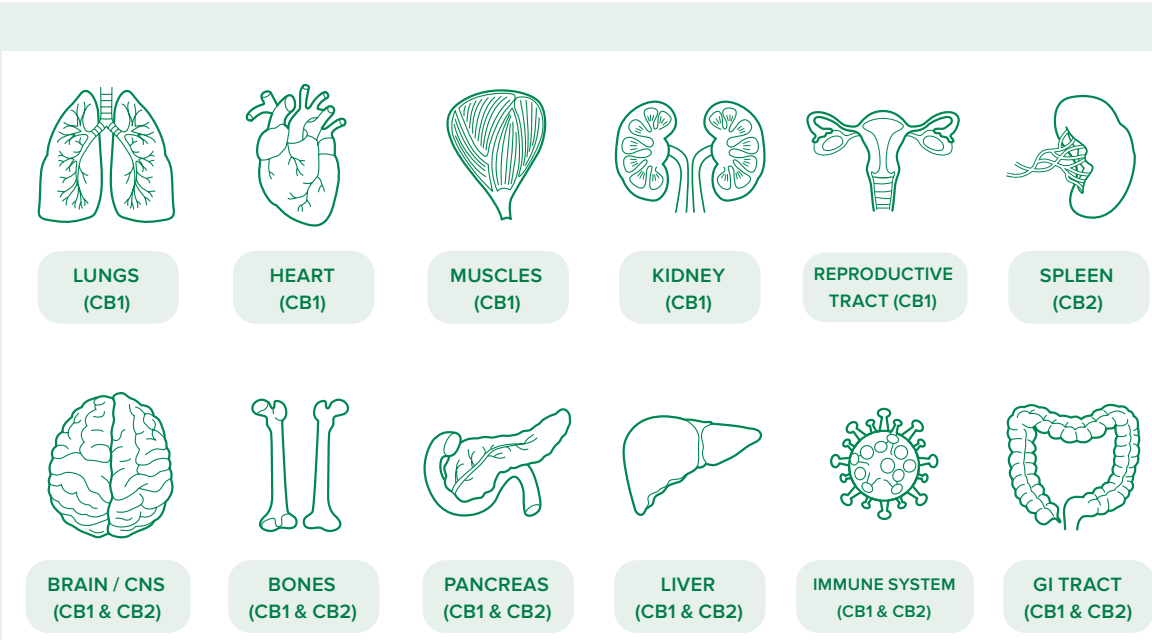
CB1 is also found in certain peripheral organs and tissues, such as the lungs, liver, white blood cells, endocrine gland and parts of the reproductive, gastrointestinal and urinary tracts.

The CB1 isoform is highly expressed in the central nervous system. It is thought to be the most widely expressed G-protein coupled receptor in the brain. Indeed, the CB1 receptors are concentrated in areas controlling pain, appetite, emotion and nausea, [27, 28] corresponding to the most prominent behavioural effects: (a) spinal cord – peripheral sensation, pain sensitivity; (b) hypothalamus – appetite; (c) cortex – higher cognitive and emotional functions; (d) medulla oblongata – nausea-vomiting centre, chemoreceptor emetic trigger zone.

CB2 receptor

CB2 is mainly found in peripheral and immune-related organs such as the spleen (splenic macrophages and B lymphocytes), tonsils, peripheral nerve terminals, the gastrointestinal tract, as well as in microglial and cerebral granule cells. [27] It is postulated that CB2 plays a role in the regulation of immune responses and inflammatory reactions. [29]

Figure: location of cannabinoid receptors



Dosing and administration

Dose forms

The management of the dose is critical to balance the desired therapeutic effects against the prevention of side effects.

The importance of dose form

The form in which cannabis-based medicines are administered determines the onset, intensity, and duration of effects. It also influences patient behaviour in different ways, including adherence to the daily regime (compliance), the time interval of usage, frequency of use, and total daily dosage.

The major factors which affect the safety and efficacy of a specific dose form is included in the table below:

Table: dosing summary by route of administration

Dose forms Factors to consider when selecting a dose form	
Accuracy of dosing	How precise the dosing method is to reach the desired dose, to avoid under-dosing, over-dosing and side effects.
Bioavailability	The available fraction of the dose that reaches the bloodstream to provide a therapeutic effect - typically, for cannabis-based medicines, pulmonary dose forms have the highest bioavailability, followed by sublingual, buccal, rectal and oral dose forms.
Onset of action	The length of time before the effects of the medicine are felt.
Duration of effect	The length of time the medicine is active.
Reproducibility	The degree to which the medicine can be given to achieve repeated effects, preferably with good precision.
Safety	The dose form is easy to use, of good quality and does not cause harm or intolerable side effects.

Route of administration

There are two major administration routes:

- By inhalation – pulmonary absorption, or
- By mouth – oromucosal solutions, sprays and wafers with sublingual or buccal absorption, or ingested oral solutions and capsules with small intestine absorption.

Cannabinoids can also be applied to the skin (transdermal), administered rectally (suppositories), or injected; these dose forms are much less common and rarely necessary. The therapeutic effect of non-standard products like 'cannabis teas' are unpredictable, with highly variable plasma levels. As a result, these dose forms are not considered in this text.

Different dose forms permit administration by various routes in order to meet the needs of the patient.

Table: dosing summary by route of administration

	Pulmonary (vapour inhalation)	Oromucosal (sublingual & buccal)	Oral (ingestion)
Delivery	A vapour is inhaled into the lungs.	Applied under the tongue (sublingual) or inside of the cheek (buccal).	Taken by mouth and swallowed.
Ingredients	Typically, a vapour of cannabinoids and terpenes from cannabis herbal material.	Isolated cannabinoids or extracts for cannabis herbal material. May contain diluents or suspending agents.	Isolated cannabinoids or extracts for cannabis herbal material. May contain suspending or bulking agents.
Absorption	Absorbed by the lungs. The large surface area of the lungs increases the rate of absorption. Part of the dose is inevitably swallowed. Bioavailability up to 40%.	Absorbed by soft tissues of the mouth, under the tongue (sublingual) or inside of the cheek (buccal). A good absorption rate is achieved in small-volume doses. A fraction of the dose is inevitably swallowed.	Absorbed in the gastrointestinal tract and metabolised in the liver. The absorption rate is affected by gut physiology, food, stomach health. Poor absorption, low bioavailability (< 10%), and difficult to titrate.
Distribution	Rapid onset of action.	Onset of action can vary based on absorption from the mouth lining.	Onset of action is slow due to gut absorption and metabolism.
Metabolism	Minimal first-pass liver metabolism.	Partial first-pass liver metabolism from swallowing part of the dose.	High level of first-pass liver metabolism creates a potent psychoactive metabolite, 11-hydroxy-THC (11-OH-THC).
Excretion	Dependent upon movement out of adipose tissues into the bloodstream. Is found in faeces and urine	Dependent upon movement out of adipose tissues into the bloodstream. Is found in faeces and urine	Dependent upon movement out of adipose tissues into the bloodstream. Is found in faeces and urine

Pharmacokinetics

Overview

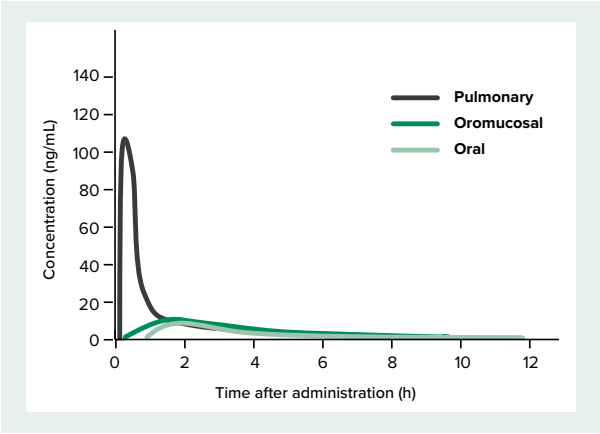
The pharmacokinetics of THC and CBD varies as a function of its route of administration.[30, 31] Following inhalation, peak blood THC and CBD levels are dose-dependent. THC plasma concentrations decrease rapidly after inhalation due to rapid distribution into tissues and metabolism in the liver. Administration by the sublingual, buccal, and oral routes reach maximum concentrations for THC, CBD, and 11-OH-THC slower, respectively. High intra- and inter-subject variability is noted for oral administration, in particular.

THC metabolism occurs mainly in the liver, catalysed by CYP450 enzymes, and, to a lesser degree, other tissues, like the heart and lungs. Metabolism of THC to 11-hydroxy-THC (11-OH-THC) and later to 11-nor-9-carboxy-THC (11-COOH-THC) contributes to the reduction of THC in blood.

Body storage of THC increases with increasing frequency and duration of use. THC is widely distributed, particularly in adipose tissue. The slow elimination of THC and metabolites is due to the slow re-diffusion/redistribution from body fat and other tissues into the blood. THC and metabolites are mainly excreted from the body in urine and faeces.

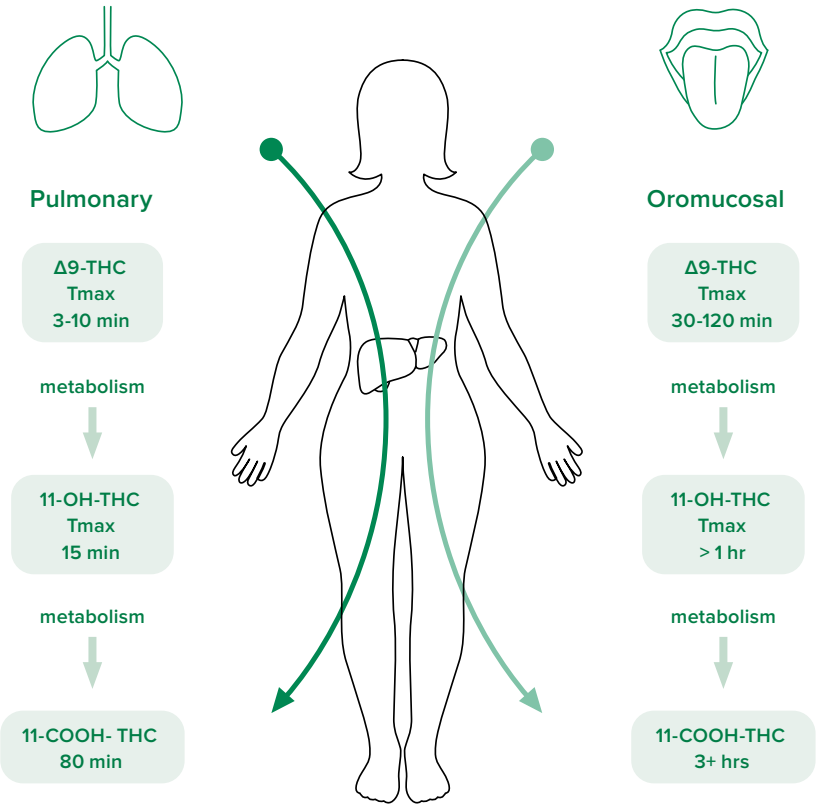
The metabolism of CBD largely follows the same route as THC. CBD is subjected to a significant first-pass effect; hydroxylated to 7-OH-CBD and 7-COOH-CBD by CYP450 enzymes. However, a large proportion of the dose is excreted unchanged in the faeces.

Figure: illustration of relative differences in Cmax and Tmax for THC, between dose format



Note to figure: Intra- and inter-patient variability is influenced by patient characteristics, dose form, total dose, and frequency of use (steady-state). Cmax is the maximum serum concentration achieved, and Tmax is the time taken to reach the maximum concentration. Reference dose: 20 mg THC.

Figure: comparative pharmacokinetics of THC by pulmonary and oromucosal administration



Pulmonary administration

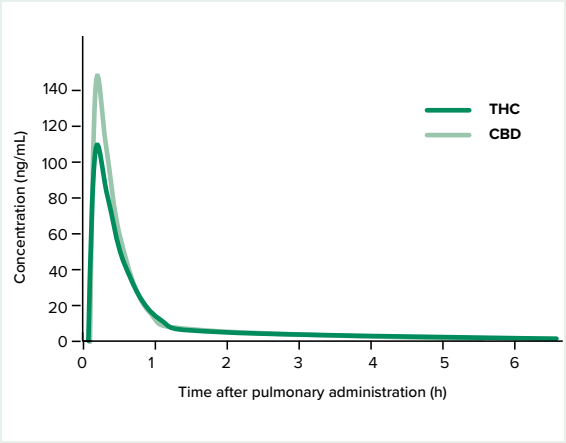
Administration via the pulmonary route can be a convenient, very rapid and efficient method of cannabinoid delivery, allowing self-titration to the desired therapeutic effect. [32-35] A vaporiser medical device is used to administer pharmaceutical-quality cannabis herbal material. The rapid onset of effects of inhaled cannabinoids enable easier titration to an optimal dose based on symptom severity, tolerability and avoidance of side effects. [32, 36]

Pulmonary pharmacokinetics profile	
Bioavailability	Up to 40%
Peak plasma concentration	3-10 minutes
Onset of clinical effects	5-10 minutes
Duration of action	1-3 hours

THC and CBD are lipophilic compounds rapidly absorbed and distributed by the lungs. The bioavailability of inhaled THC is upward of 40%. Following inhalation, THC and CBD plasma levels increase rapidly. The increase in plasma concentration of cannabinoids is dose-dependent.

Peak plasma concentrations typically occur 3-10 minutes after inhalation, resulting in onset of clinical effects after about 5-10 minutes and taper off within 1-3 hours. [32, 35] There is low inter-subject variability in THC plasma concentrations with pulmonary administration. Pulmonary administration of THC mostly avoids first-pass metabolism. THC is converted to its active metabolite, 11-OH-THC, and further metabolism occurs later.

Figure: approximate plasma concentrations after pulmonary administration of 20 mg THC or CBD



Variation in peak THC and CBD plasma concentrations after inhalation

The pharmacokinetic parameters (PK) of inhaled vapour containing THC, THC:CBD, and CBD administered by a quality vaporiser medical device (Storz & Bickel Volcano® Medic vaporiser) is described in the series of tables below. [35]

Table: pharmakokinetic parameters of inhaled vapour of pharmaceutical-quality cannabis herbal material containing 22% THC and < 1.0% CBD

Amount cannabis herbal material	Amount cannabinoids mg	Cmax ng/mL	Tmax minutes
100 mg	THC: 22 mg	THC: 82 ng/mL	5 min
	CBD: < 1 mg	CBD: 0.2 ng/mL	5 min

Table: pharmacokinetic parameters of inhaled vapour of pharmaceutical-quality cannabis herbal material containing 6.3% THC and 8.0% CBD

Amount cannabis herbal material	Amount cannabinoids mg	Cmax ng/mL	Tmax minutes
200 mg	THC: 12.6 mg	THC: 76 ng/mL	5 min
	CBD: 16 mg	CBD: 80 ng/mL	5 min

Table: pharmacokinetic parameters of inhaled vapour of pharmaceutical-quality cannabis herbal material containing 9.0% CBD and < 1% THC

Amount cannabis herbal material	Amount cannabinoids mg	Cmax ng/mL	Tmax minutes
200 mg	CBD: 18 mg	CBD: 155 ng/mL	5 min
	THC: < 1 mg	THC: 13 ng/mL	5 min

The pharmacokinetic parameters of inhaled aerosols of pharmaceutical-quality cannabis herbal material by a selective-dose vaporiser medical device (SyqeAir Inhaler) is described in the series of tables below [31, 33]

Table: pharmacokinetic parameters of inhaled vapour of pharmaceutical-quality cannabis herbal material containing 22% THC

Amount cannabis herbal material	Amount cannabinoids mg	Cmax ng/mL	Tmax minutes
16.0 mg	THC: 3.52 mg 0.5 mg THC released by device	14.3 ng/mL	3.7 min
16.0 mg	THC: 3.52 mg 1.0 mg THC released by device	33.8 ng/mL	4.4 min
15.1 mg	THC: 3.08 mg 1.0 mg THC released by device	38 ng/mL	3 min

Reducing variability in pulmonary dosing

Administration by smoking is never advised. The use of a quality vaporisor medical device eliminates exposure to toxic pyrolytic compounds of cannabis smoke and reduces variability in administered cannabinoid content with ≤ 35% of dose reaching the lungs. [31-33, 37-39] Highly functioning devices markedly reduce variability in the administered dose. [31]

Registered medical devices like the SyqeAir Inhaler or the Volcano Medic® are now available. Other reliable, affordable and portable devices are required to ensure that patients have access to these devices.

Figure: vaporisor medical device

A portable vaporiser by Storz & Bickel, compatible with cannabis herbal material. This company also manufactures the Volcano vaporiser.

A portable metered-dose vaporiser by Syqe Medical, with cartridges containing standardised cannabis herbal material.

Inter-patient and intra-patient variability in administered dose occurs from the depth of inhalation, duration of inhalation, and breath-holding time. The quality and consistency of the cannabis herbal material used and the quality of the thermal inhalation medical device will either increase or decrease variability. [31, 40]

Patients with COPD and/or asthma should be monitored when using such a device as the depth of breath and breath-hold time will impact the total dose.

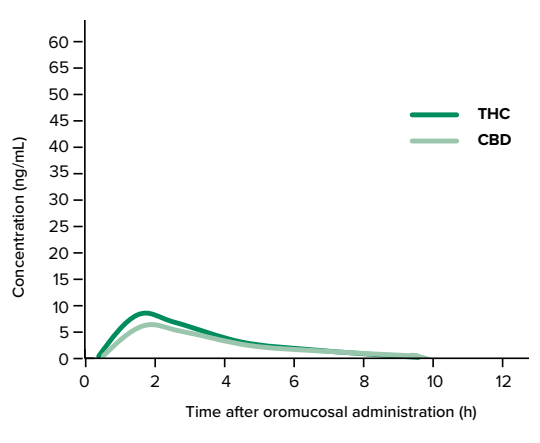
Oromucosal administration

Oromucosal dose forms are relatively easy to administer. The ease of dosing and rapid onset of action means oromucosal administration, via the sublingual or buccal surface, is the preferred choice for many physicians and patients. [41]

Oromucosal pharmacokinetic profile	
Bioavailability	Up to 20%
Peak plasma concentration	30-120 minutes
Onset of clinical effects	30-90 minutes
Duration of action	6-8 hours

THC and CBD are highly lipophilic compounds, which are rapidly absorbed by the oromucosa (in particular, the sublingual surface), entering the bloodstream and bypassing the liver. [42-47] Bioavailability generally ranges between about 5% and 20% and varies according to the dose form (viscous solutions, sprays, wafers), the vitality of mucosa, and the accuracy of dosing by the patient. Inevitably some of the administered doses will be swallowed, resulting in first-pass metabolism.

Figure: approximate plasma concentrations after oromucosal administration of 20 mg THC or CBD



Peak plasma concentrations vary according to the dose form and concentration, and may be reached between 30-120 minutes minutes, resulting in onset of clinical effects after about 30-90 minutes and taper off within 6-8 hours.

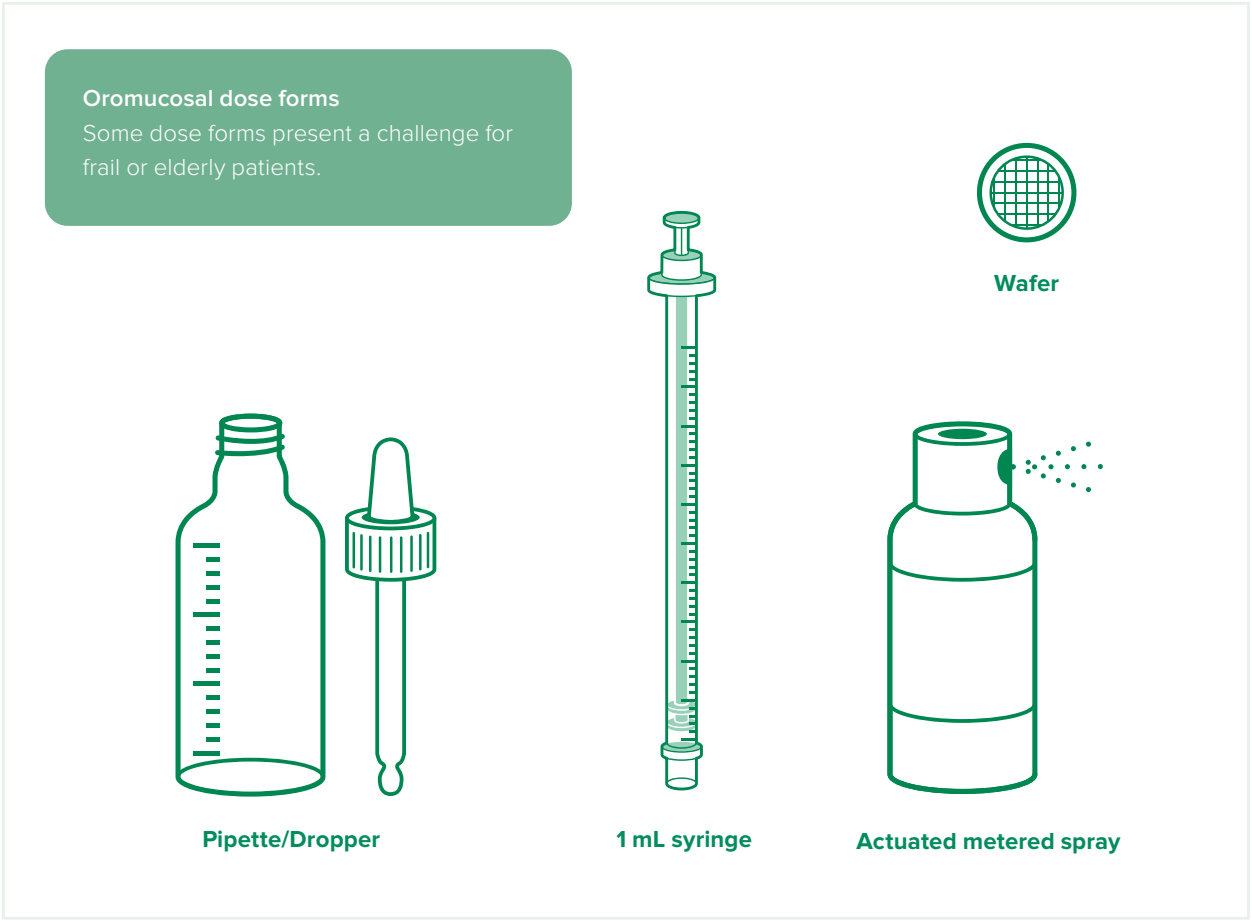
Spray, sublingual drops and then wafer dose forms, respectively, appear to increasingly reduce variability in Tmax and to reach higher Cmax with similar doses. Plasma concentrations of THC tend to be higher than corresponding CBD after administration of CBD:THC medicines. The plasma increase of cannabinoids is dose-dependent.

Reducing variability in oromucosal dosing

The dose format can introduce or reduce variability in the taken dose, for example:

- Actuated, metered dose sprays are a precise dosing format, with a specific dose per spray. A 10.8 mg THC and 10 mg CBD dose may reach a Cmax of 5.5 ng/mL and 2.5 ng/mL, respectively, after 1.6 hours. [44, 48] Formulations may contain alcohol in the solution, which can be unpleasant for patients or cause mild site-specific ulceration.
- Sublingual wafers provide highly consistent dosing and rapidly dissolve with a good absorption rate. A 50 mg CBD dose may reach a Cmax of 19.84 ng/mL after 3.3 hours. [42]
- With sublingual solutions, frail or elderly patients may find it hard to squeeze a dropper under the tongue, and under or over-dose may occur. A syringe helps the accuracy of dose amount but may be fiddly for frail or elderly patients. Some oromucosal solutions contain chlorophyll, which may cause an unpleasant taste. Post-administration, consuming a banana or boiled sweet may help.

Figure: oromucosal administration formats



Oral administration

Oral preparations are familiar dose forms. They are similar to other medicines patients already take and are easy to administer for patients who can swallow. The ease of dosing is offset by intra- and inter-patient variability. While there is a positive dose-concentration relationship for most dose forms (solutions, tablets, capsules), oral THC and CBD have a highly variable pharmacokinetic profile, which differs between formulations.

Oral pharmacokinetic profile	
Bioavailability	Up to 10%
Peak plasma concentration (Cmax)	60-180 minutes
Onset of clinical effects	60-180 minutes
Duration of action	6-12 hours

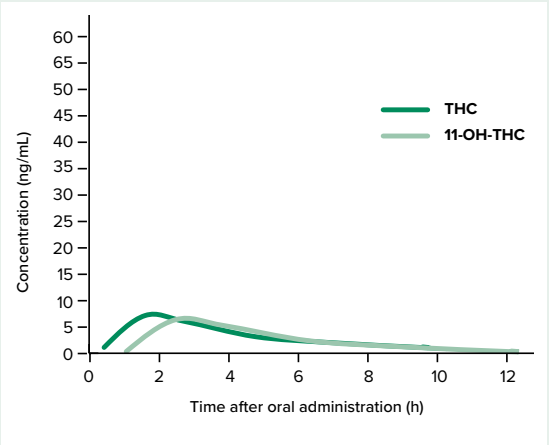
Absorption is slow and erratic within the gastrointestinal tract. Significant first-pass hepatic metabolism and high lipid solubility means 5-10% of the administered dose reaches the systemic circulation.[49, 50]

THC is metabolised in the liver to the major pharmacologically active metabolite 11-OH-THC, which occurs in approximately the same concentration in the blood as the parent compound, THC.[51-53] Therefore, the bioavailability of parent and metabolite, which are both active, result in an elevated bioavailability.

The high variability in the THC and CBD absorption of oral formulations results in delayed peak plasma concentrations compared to other routes of administration.[54, 55] Therefore, the accuracy of determining a therapeutic dosage is reduced for individual patients.

Following oral ingestion, THC maximal plasma concentrations are reached after 60-180 minutes, reaching maximal clinical effects after 60-180 minutes and tapers off after 6-12 hours, depending on the dose.

Figure: approximate plasma concentrations after oral administration of 20 mg THC



An oral THC dose is typically lower than a CBD dose, resulting in different pharmacokinetic profiles. For example, a 20 mg THC oral dose may reach a Cmax of 7.9 ng/mL after approximately 135 minutes, [53] while a 1500 mg CBD oral dose may reach a Cmax of 541 ng/mL after approximately 150 minutes. [55]

THC metabolism occurs mainly in the liver, catalysed by CYP450 enzymes. THC undergoes extensive first-pass metabolism, primarily by hydroxylation to 11-OH-THC, which is an active metabolite. Both THC and 11-OH-THC are present in approximately equal concentrations in plasma. [53] As would be expected, CBD is also subjected to significant first-pass metabolism.

THC and CBD are widely distributed, particularly in adipose tissue. Body storage of THC increases with increasing frequency and duration of use.

Reducing variability in oral dosing

The absorption rate is affected by gut physiology, diet, and general stomach health. The low bioavailability (< 10%) makes it difficult to titrate doses.

Patients should be advised to take their medicine consistently, with regard to time and dietary intake, to reduce variation.

For THC, an appreciable food effect is observed with high-fat, high-calorie meals, resulting in an up to a 4-hour delay in mean Tmax, while Cmax is not significantly changed. [50]

Administration of high-dose CBD with high-fat/high-calorie meals markedly increases Cmax and reduces the total variability compared with the fasted state. [56]

4. Prescribing

This section focuses on prescribing practices. Drawing on lessons learnt from various jurisdictions, it provides advice on developing a robust clinical strategy.

Clinical strategy

Patient suitability

Consistent with the rational use of medicines, [57] suitable patients are those who meet the criteria for prescribing when the cannabis-based medicine is appropriate for a patient's needs at a cost that is acceptable to them.

Medicine cost and accessibility need to be considered within clinical decision-making.

- Will patients be able to pay for their medicine?
- Will they have access to it at all times, in sufficient amounts, and at an affordable price?
- Can patients afford to initiate and maintain therapy for the duration of treatment?

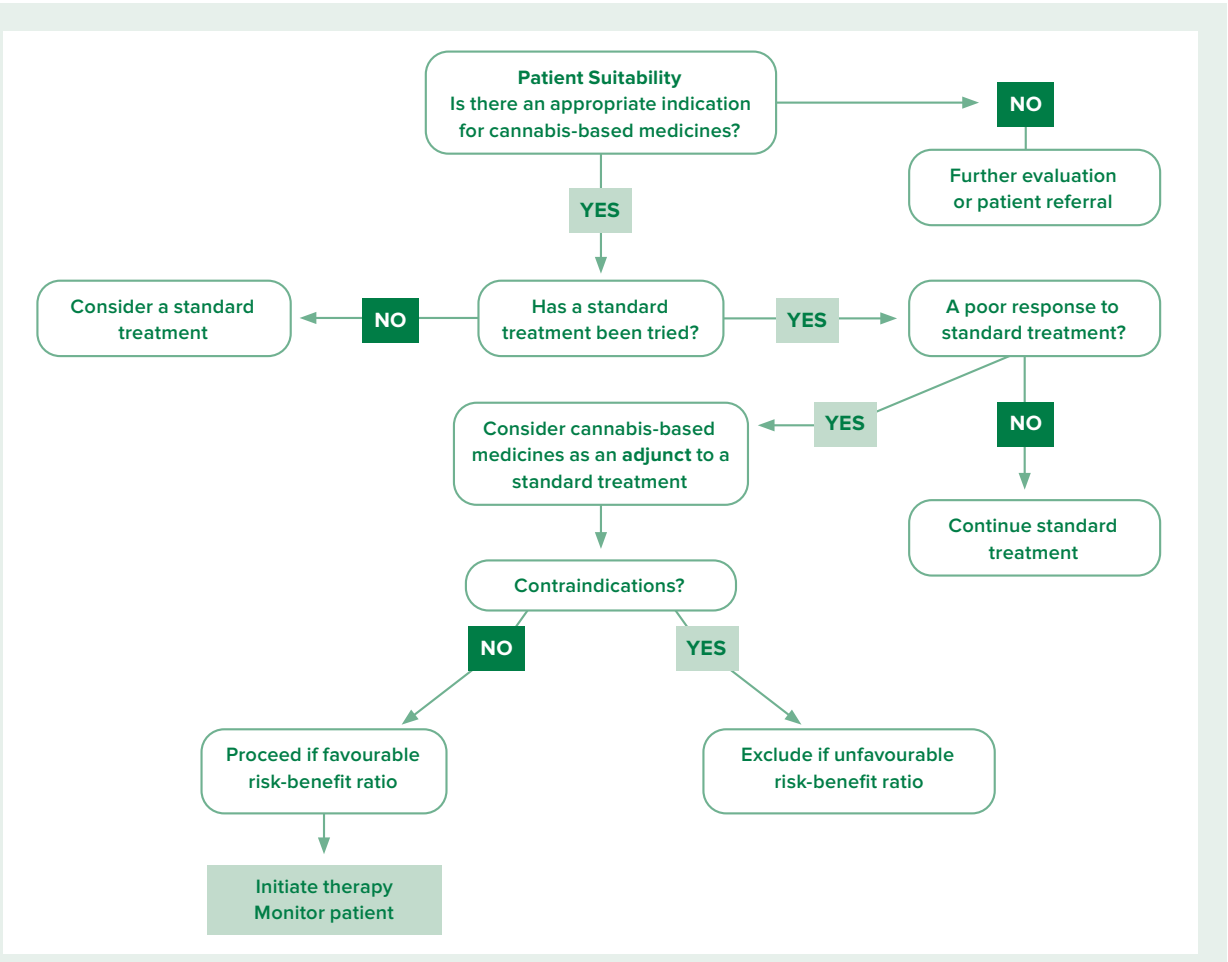
Prescribers need to know how to engage in an effective exchange of information with patients to discuss if cannabis-based medicines are appropriate.

Unlike other medicines, many patients will have an opinion about cannabis-based medicines. Some patients will be armed with information about why it is appropriate for them, whereas other patients will be naïve about the medicine topic. Some patients may have experience using cannabis recreationally and emphasise its clinical benefits over other medicines.

During a first consult, the main question is: 'Is this patient suitable to receive a cannabis-based medicine?' If the indication to prescribe seems appropriate, then cannabis-based medicines can be raised as a possible therapy.

See the patient suitability flow chart.

Figure: Patient suitability flow chart



The potential benefits

It is only recently that research has expanded the evidence base for the use of cannabis-based medicines. This has resulted in the use of these agents in a number of clinical settings or disease states.

Different countries permit cannabis-based medicines for specific indications. In sum, these indications include:

- Chronic pain, specifically neuropathic pain [4, 6, 8]
- Chemotherapy-induced nausea and vomiting; and anorexia associated with weight loss in patients with HIV/AIDS [3, 4, 50]
- Spasticity associated with multiple sclerosis [3, 4, 44]
- Seizures associated with refractory epilepsy (Dravet syndrome or Lennox-Gastaut syndrome) [3, 56]
- In particular, cannabinoids have been used in palliative care to enhance the quality of life of patients during the course of the illness (appetite stimulation, improving sleep, and relief of nausea), and to influence the affective qualities of pain. [34, 58-60]

Balancing the potential risks

Most patients tolerate cannabis-based medicines well. Side effects are generally dose-dependent.

Some patients will not respond well to typical doses, experiencing unwanted side effects. Some patients may experience medicine-medicine interactions. While in some patients, cannabis-based medicines are contraindicated.

Cannabinoids are often an adjunct treatment. Many patients will be co-prescribed with a number of other medicines. Like many other medicines, cannabinoids are metabolised by the liver's cytochrome P450 enzymes (CYP450). The potential for drug-drug interactions will increase when taken together with other medicines metabolised by the CYP450 system. [61]

Some patients have had worsened symptom control and new adverse effects such as sleepiness, abnormal liver function, and diarrhoea with high doses. In particular, large doses of Δ-9-THC may result in anxiety, tachycardia, psychomotor impairment, sedation, or pose a risk of harm (e.g. rapid orthostatic (postural)-hypotension which may result in a fall in the elderly). However, tolerance to the cardiovascular and psychological effects of Δ-9-THC tends to occur rapidly. [61] The known adverse effects of CBD include fatigue, diarrhoea, decreased appetite, and weight loss. [56, 62] However, there are many unknowns with long-term use of large doses of CBD [63, 64].

The medicine initiation age impacts on the long-term risk of cannabinoids. The long-term negative effects of THC are well described for illegal, recreational use in youth, [27, 65-69] but this is sparsely described when cannabis-based medicines are used. In patients under 25 years THC should only be considered if the benefits outweigh the risks. [69-71] There are still concerns with the use of high-dose CBD in young people. [56, 63, 69, 72, 73] High-dose CBD has been associated with an increased risk of hepatocellular injury, fatigue, decreased appetite, weight loss, somnolence and sedation. [10, 11] There is also a low risk of suicidal behaviour and ideation. [49, 56, 63, 73]

'Problematic cannabis use'

THC is euphorigenic and can lead to problematic use. [74] Some patients may currently use cannabis recreationally or have a history of having done so. [75] While there is a lower risk of misuse in a therapeutic context, some patients may self-escalate their dose or misuse prescribed cannabis-based medicines.

Risk factors for problematic cannabis use include:

- High dosages of THC
- Previous abuse of substances (controlled drugs or alcohol or tobacco)
- Males, especially 18 – 30 years
- Misuse of controlled drugs at an early age
- Current or previous major depression
- Childhood or current anxiety and depression

"When prescribing, the key things to keep in mind are compliance, contraindications and patient history."

Dr Patrick Welsch – on prescribing cannabis-based medicines

Patient history and shared decision making

Before initiating cannabis-based medicines, it is necessary to document a patient's medical history, which should comprise the following information:

- General medical history
- Medication history and previous treatments
- Co-morbidities
- Substance use or abuse history
- Screen for anxiety and depression (risk reduction with THC)

Prescribers should discuss:

- Diagnosis – the specific indication for which the cannabis-based medicine is being prescribed.
- Clinical justification for using a cannabis-based medicine, and if applicable, the reasons for using an unapproved medicine rather than an approved, registered medicine (standard treatment).
- Treatment options – possible costs, dose and route of administration, possible effects, side effects, possible medicine interactions.
- Treatment plan – the treatment timeframe and trial period, maximal effect, titrating the dose, monitoring of safety and efficacy.

Clinical evaluation tools

Clinical evaluation tools are used to support decision-making by health professionals prior to prescribing and during treatment. Some useful screening and assessment tools are discussed below and are recommended for use.

Be aware that self-reported health measures are based on an individual patient's perception of their health status and functioning.

Refer to Appendix 1 for full tables: **Clinical evaluation tools**.

Screening tools – risk of dependence

Substance dependence screening tools are developed for recreational drug use and misuse. The patient's age, gender and ethnicity, the dose, dose form and route of administration, prescribing and medical oversight, all significantly affect the potential for an individual to experience substance dependence. Therefore, the tools used to assess recreational cannabis dependence are slightly less relevant to measure cannabis-based medicine dependence. Their use in a medical setting should take into account these differences. [70, 75, 76]

If appropriate, consider screening for substance dependence before prescribing medicines containing THC. The assessment should include a personal and family history of alcohol or drug substance dependence.

CAGE – substance dependence

Screening with the 'CAGE' questionnaire is a fast way to check for signs of possible psychoactive substance (drug) dependency. The questions are designed to be less obtrusive than directly asking a patient if they have a problem with psychoactive substances. [77] Keep in mind the CAGE questionnaire was initially developed for alcohol misuse.

CUDIT-R – cannabis use disorder

The Cannabis Use Disorder Identification Test – Revised (CUDIT-R) is an 8-item test suited to the task of screening for problematic cannabis use or as a brief routine outcome measure. The CUDIT-R provides a severity rating, patterns of consumption, and a rough idea of where the individual is experiencing an actual or a risk of harm. The screen offers an opportunity to start a discussion on the potential for change with people who 'misuse' cannabis-based medicines. It can be used to measure changes over time. Another option is the CUDIT-Short Form (CUDIT-SF), a rapid screening tool administered in a clinical setting to identify individuals who likely meet the criteria for DSM-5 Cannabis Use Disorder. [78-80]

Screening tools – anxiety and depression

The most common mental disorders in outpatient settings and the general population are anxiety and depression, which frequently coexist. If relevant, consider screening for anxiety and depression before prescribing medicines containing THC. The PHQ-4 and HADS are described below.

Patient Health Questionnaire 4 (PHQ-4)

The PHQ-4 is an ultra-brief tool for detecting both anxiety and depressive disorders. Using four-point 'Likert-type' scale, the two-item depression measure (PHQ–2) and anxiety measure (GAD–2) identify the respective core symptoms. The PHQ–4 total score complements the subscale scores as a measure of symptom burden, functional impairment, and disability. A high PHQ–4 score indicates further clinical inquiry is warranted. [81, 82]

Hospital Anxiety and Depression Scale (HADS)

The HADS is widely used in medical settings to screen for anxiety or depressive disorders and is valid and reliable in various patient populations. HADS is a 14-item measure designed to assess anxiety and depression symptoms, with emphasis on reducing the impact of physical illness on the total score. The HADS produces two scales, one for anxiety (HADS–A) and one for depression (HADS–D). Using a 4-point severity scale, scores of greater than or equal to 11 on either scale indicate a definitive case. [83]

Assessment tools – quality of life

Edmonton Symptom Assessment System (ESAS)

ESAS is a simple and rapid quantitative symptom assessment to document multiple patient-reported symptoms at the same time. Patients with an advanced terminal illness, such as cancer patients, experience a significant burden of multiple symptoms, which often increase in intensity over time. Patients may report a cluster of symptoms, including fatigue, pain, anorexia, appetite, cachexia, dyspnea, anxiety and depression, which can negatively impact patients' quality of life and function. ESAS has been widely used in the oncology and palliative care setting to assess patient well-being. [84]

Short Form Survey (SF-12)

To establish a baseline measure of health-related quality of life, SF-12 may be used. [85]

Widely used in a patient and population-level analysis, the 12-item Short Form Survey (SF-12) tool provides insight into an individual's physical, mental and well-being components of health. SF-12 has been validated across a number of chronic diseases and conditions.

It uses the same eight dimensions to assess physical and mental health, including: four physical health-related dimensions (1) General Health (GH), (2) Physical Functioning (PF), (3) Role Physical (RP), and (4) Body Pain (BP), and four mental health-related dimensions (5) Vitality (VT), (6) Social Functioning (SF), (7) Role Emotional (RE), and (8) Mental Health (MH).

Responses to each of the SF-12 items are scored and expressed on a scale of 0–100 for each of the eight health dimensions. Interpretation of the SF-12 is based on the mean average scores.

Administration options

Choice of route of administration

Consider what dose form is most practical and effective? Pharmaceutical-quality cannabis-based medicine assure purity and dose consistency.

Table: administration method considerations [36-40]

	Pulmonary (vapour inhalation)	Oromucosal (sublingual & buccal)	Oral (ingestion)
Onset	5-10 minutes	30-90 minutes	60-180 minutes
Duration	1-3 hours	6-8 hours	6-12 hours
Bioavailability	≤ 40%	≤ 20%	≤ 10%
Positives	Rapid onset of action, advantageous for acute or episodic symptoms, easy to titrate to an optimal dosage. A vaporisor medical device harms from smoking.	Fast absorption and onset of action, long duration of action. Various dose forms – droppers, metered dose sprays, wafers.	Convenient and easy to administer.
Negatives	Up front expense and knowledge of the device, plus a high level of dexterity, is required for preparing a dose for some devices. Cannabis odour is possible. Potential for misuse.	Part of the dose may be swallowed, absorbed and metabolised. A high level of dexterity is required for some administration devices (droppers).	Titration is challenging due to delayed onset, first-pass metabolism, the psychoactive 11-OH-THC metabolite, and variability due to gut contents (high-fat meals).

Dosing

Practical considerations in dosing

The correct dose of any cannabis-based medication is the lowest possible dose that achieves the desired clinical effect with a minimal side effect profile.

A conservative dosing protocol should be used when managing frail and elderly patients, those with comorbidities, or those taking multiple medicines – especially medicines known to interact with cannabinoids.

See the patient suitability flow chart above and the appendix for tables of medicine interactions.

The dose form will impact on bioavailability, and hence the actual dose administered. As an example, therapeutic doses in the pain setting range from 5 to 40 mg THC per day when oromucosal administration is used. Similarly, for pulmonary administration, therapeutic doses may range from 20 -220 mg THC per day (equivalent to 100 mg to 1000 mg of a 20% cannabis herbal material).[86] The quantity per day of herbal material reflects the variability in the amount of cannabinoids vaporised by the device. This may yield ≤ 50% of the total available cannabinoids. [31, 33, 35, 87]

While there is no evidence that a pulmonary dose is better than a sublingual dose, the administration format does offer the advantage of more rapid onset of action.

Choosing a cannabis-based medicine

Prescribers are confronted with the question 'which type of cannabis-based medicine to start with?' In the field of pain medicine, or in the oncology or palliative care setting, should the patient start with a THC containing medicine or a combination of THC:CBD?

Keep in mind that THC and THC:CBD medicines are psychoactive and intoxicating at higher doses. CBD-predominant medicines are psychoactive, but non-intoxicating. CBD, in contrast to THC, is less potent and may require much higher doses for its adjunctive benefits.

Often CBD is prescribed to attenuate the psychotropic side effects of THC – such as acute anxiety or intoxication. [23, 35, 48, 88-93] However, it appears that CBD does not influence any of the cognitive impairments or psychological symptoms. [94, 95] Neither does CBD attenuate any of the other acute effects of THC, including behaviour, subjective experiences, and cognition.

Additionally, the co-administration of CBD appears to have no influence on Tmax, metabolites 11-OH-THC or 11-COOH-THC, or to total systemic exposure (AUC). [96] It has been demonstrated that CBD, after a 450 mg oral dose, can increase the acute effects of THC, which is likely explained by CBD inhibiting cytochrome P450-mediated metabolism of THC. [97]

Most prescribing occurs for patients with pain. This may include patients in an oncology or palliative care setting. THC is euphorigenic - giving rise to a feeling of well-being. Euphoria may be a desired clinical outcome of the prescribed medication to enhance the well-being of the patient. Feelings of euphoria are a dose-response event. This will require careful dose titration to the optimal daily dose. Caution is advised with frail and elderly patients who are more sensitive to the neurological, psychoactive and postural-hypotensive (orthostatic hypotension) effects of cannabinoids.

Titration

A titration period is required to reach a patient's personalised dose. Depending upon the indication, it is suggested that during initial titration, doses are evenly spread out over the day and according to individual response and tolerability. Patients may gradually increase the dose until they achieve an optimal daily dosage. It is important that the dosage is titrated slowly.

Start with a low dose - start low

Titrate slowly - go slow

Keep at the lowest effective dose - stay low

Most unwanted side effects may be prevented by following these guidelines:

- **Low dose** – it is better to take several small doses in a day that add up to the required dose, rather than to experiment with one single large dose. Stay at a low daily dosage, administered over multiple doses.
- **Patience** – cannabinoids may have a different effect on each patient. Wait for the effect, if any, to appear. It is best to use the same low dose for several days, and monitor any effects that may occur.
- **Increase the dose slowly** – after a few days, the patient can increase the dosage. Take a few days after each increase to monitor progress. Advise patients that it might take between one to two weeks to achieve the optimal dosage (the greatest medicinal effects with minimum side effects).

Regular monitoring is recommended in the early stages of clinical use.

Educate the patient to stop titrating up when experiencing unwanted effects.

Pulmonary administration

Practical considerations in administration

Cannabis-based medicines should never be administered by smoking. A vaporisor medical device offers patients an effective, safe, and easy-to-use delivery system. [31, 34, 38, 98]

There are particular variables which can influence the dose, including the:

- Quality of the vaporiser device
- Content of cannabinoids in the cannabis herbal material
- Size of the device chamber containing cannabis herbal material
- Depth of inhalation by patient, breath-hold time
- Vitality of lung tissue for the absorption of cannabinoids

Pulmonary administration is recommended only in patients with the capacity to produce a minimum airflow of 10 L/minute, at rest.

During initiation of titration:

- Patients should take the dose, by single-dose inhalations, with a minimum 10-15 minute break between inhalations until the patient achieves an optimal dosage.

To maximise consistency of inhaled doses:

- Upon administration, patients should be instructed to inhale up to five seconds of vapour from the device and hold their breath for up to five to ten seconds after each inhalation.

- Inhalations must be constant and soft. If the inhalation is too fast or too strong, the patient may start coughing, may feel burning in the soft palate, or become dizzy.

Reducing or eliminating second-hand exposure to exhaled vapour:

- Inhaled cannabis-based medicines should be administered in a well-ventilated space/room.
- Use around children should be strictly avoided.

Case example – pulmonary dosing – pain

Cannabis herbal material containing 22% THC, administered by a vaporisor medical device:

- Dosing starts with 100 mg (22 mg THC) three times daily – depending upon the indication. Start dosing in the evening.
- After two days, according to effect and possible side effects, a dose increase/decrease may occur.
- With THC, dosing is self-limiting. Individual response and side effects will establish an upper limit for the dosing of this medicine. It has been noted that increasing the THC content of inhaled doses results in an increased effect in reducing pain. [44, 56]
- After the patient reaches the upper limit dose, there should be a patient encounter.
- From there, the prescriber decides to further escalate the dose to the total daily recommended dose.

Cannabis herbal material

Pharmaceutical-quality cannabis herbal material contains consistent, measurable quantities of cannabinoids to assure repeatability of dose, and the ability to effectively adjust dose by titration. Minimum quality specifications should ensure standard cannabinoid and moisture content, and that the material is free of contaminants such as microbes, pesticides and heavy metals. [16, 99-103]

Table: content of cannabinoids in standardised cannabis herbal material

Cannabinoid % in herbal material	Content per 100 mg	Content per 1.0 g
THC: 22% CBD: < 1.0%	THC: 22 mg CBD: < 1.0 mg	THC: 220 mg/g CBD: < 10 mg/g
THC: 6.3% CBD: 8.0%	THC: 6.3 mg CBD: 8.0 mg	THC: 63 mg/g CBD: 80 mg/g
CBD: 9.0% THC: < 1%	CBD: 9 mg THC: < 1.0 mg	CBD: 90 mg/g THC: < 10 mg/g

Oromucosal administration

"...sublingual cannabis oil is easy to titrate [given] standardised preparations are available."

Dr Ruben van Coevorden - emphasising the importance of standardised preparations

Practical considerations in administration

Administration via the oral mucosa (sublingual and buccal) offers a faster onset of action compared to oral doses. A healthy mucosa will absorb these lipophilic medicines more promptly. Some dose formats require a medical device, such as a dropper or syringe. Wafers or sprays increase the rate of absorption. [42, 46]

The dose size impacts the rate of absorption and the risk of swallowing a dose. A swallowed dose will be poorly absorbed and extensively metabolised.

Case example – sublingual dosing – pain

A 1.3% THC and 2.0% CBD sublingual in a 10 mL solution (containing 13 mg/mL THC and 20 mg/mL CBD) administered by pipette/dropper:

- Dosing starts with two drops (0.05 mL) three times daily. Start dosing in the evening.
- After two days, according to effect and possible side effects, increase the dose to three drops three times daily.
- Recommended maximum dose ten drops (0.25 mL) 3 times daily. If the patient is taking 0.25 mL, then the patient is taking 9.75 mg THC and 15 mg CBD per day in total, respectively.
- After the patient reaches that dose, there should be a patient encounter.
- From there, the prescriber decides to further escalate the dose to the total daily recommended dose.

Table: content of cannabinoids in sublingual dose forms by syringe or pipette/dropper

10 mL solution	Content per mL	0.05 mL (2 drops)
THC: 2.0%	THC: 20 mg	THC: 1 mg
THC: 1.3% CBD: 2.0%	THC: 13 mg CBD: 20 mg	THC: 0.65 mg CBD: 1 mg
CBD: 2.0%	CBD: 20 mg	CBD: 1 mg
CBD: 10%	CBD: 100 mg	CBD: 5 mg

Table: oromucosal dosing by syringe and pipette/dropper [104]

Day	Using a syringe	Using a pipette/dropper
1-2	0.05 mL, 3 times per day	3 times per day, 2 drops (in elderly 1 drop)
3-4	0.1 mL, 3 times per day	3 times per day, 3 drops
6-5	0.15 mL, 3 times per day	3 times per day, 5 drops
7-8	0.2 mL, 3 times per day	3 times per day, 7 drops
9 - on	To a maximum 0.25 mL, 3 times per day	To a maximum 10 drops, 3 times per day

Oral administration

Practical considerations in administration

Oral administration is a less precise dosing format, resulting in delayed onset, varying magnitude of effect and duration of desired effects.[30, 50, 56]

Oral administration offers a slow onset of action. The absorption rate is affected by gut physiology, food (especially high-fat diets), and general stomach health. Cannabinoids are absorbed in the gastrointestinal tract and metabolised in the liver. First-pass metabolism creates 11-OH-THC, a potent metabolite of THC with intoxicating effects in high doses.

The low bioavailability (< 20%) makes it difficult to titrate doses.

The dose range for oral THC varies from 2.5 mg to 40 mg per day, while for CBD, the range extends upward from 750 mg per day in adults.

Special note - dosing in epilepsy

"When prescribing CBD, I have not observed any psychiatric side effects. When prescribing THC, I have observed psychotropic side effects in one child. After stopping THC, the side effects improved. When prescribing CBD, it is important to consider possible interactions with Clobazam; possibly get a blood concentration if the child becomes drowsy or sedated. Rarely there is also interaction with valproic acid from an increase of liver enzymes. Usually, this is uncomplicated. But this has to be considered in children with Lennox-Gastaut syndrome. CBD does not create any interactions with fenfluramine, which is prescribed for children with Dravet syndrome."

Professor Dr Gerhard Kurlemann - elaborating on a specific time frame for a CBD trial

Oral dosing often occurs with CBD in the treatment of epilepsy. Epidiolex®, a CBD oral solution (100 mg/mL), received US-FDA approval in 2018 and subsequently in other jurisdictions for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older.

Figure: dosing with a CBD oral solution

Dose type	Dose range	Maximum dosage
Oral solution	2.5-10 mg/kg/day	maximal dose of 20 mg/kg/day

- The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day).
- After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
- Based on individual clinical response and tolerability, it can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).
- Oral administration is recommended. Consistent dosing with respect to meals is recommended, given food may affect blood plasma levels.

See full prescribing information for Epidiolex® online.[56]

Precautions

The complete understanding of the safety profile of cannabis-based medicines is confounded by variations in study design, specific indications studied, the medicine quality and the chosen dose and administration form. [3, 4, 8, 64, 71, 105, 106]

As the cannabis-based medicine market develops, many new medicinal products and administration devices are becoming available. This rapid development presents an exponential potential for adverse drug reactions, medicine interactions, and medicine misuse in specific populations.

Adverse drug reactions, medicine quality, or safety concerns should always be reported as part of ongoing pharmacovigilance activities. It is important to distinguish between side effects, adverse effects and adverse drug reactions. An adverse effect is an unfavourable effect and may form part of the side effect profile, whereas an adverse drug reaction is an unexpected or unintended noxious effect suspected to be caused by or associated with the use of a medicine.

Consultation with a regional poison control centre and a medical toxicologist is encouraged for all symptomatic 'toxic' exposures.

Side effects

A side effect is a documented primary or secondary effect, whether therapeutic or adverse, that occurs when treatment goes beyond the desired effect and is secondary to the one intended. The side effect profile depends upon the specificity of the drug – THC and CBD might be considered 'dirty' drugs, i.e. they have multiple actions.

Δ-9-THC and CBD are generally well tolerated by patients with few serious side effects. Cannabinoids have a wide therapeutic index, and there have been no fatal incidents reported due to overdose. [71, 107] However, the soporific effects of anticonvulsants should not be mistaken for the potential overdose effect of CBD. Likewise, declines in attention and psychomotor performance from THC overdose should not be mistaken for side effects of benzodiazepines.

Common side effects of THC and CBD are listed in the tables below. In adult patients, most side effects are mild and transient in nature, and resolve within a few hours in line with blood serum levels of THC, depending upon the dose and route of administration. The risk is eliminated if the substance is slowly titrated. [48, 108, 109] Importantly, side effects should not be mistaken for effects of concomitant medications.

THC side effects

Side effects of THC (described as common to rare) depend upon the mode of administration, cannabinoid content, and total dose taken. [48, 50, 56, 108]. The most common side effects occur with high doses of THC with an incidence greater than placebo. Dizziness, drowsiness, reddened eyes from micro-vascular dilatation, a dry mouth, and appetite stimulation are the most common.

CBD side effects

A number of mechanisms of action have been described for CBD. [49, 110] Based on the limited available clinical research data, CBD seems to be potentially safe as a medication. [49, 73] In contrast to THC, CBD does not affect heart rate or blood pressure under normal conditions. In adults, administration of high doses does not usually lead to the emergence of significant side effects. [111] However, CBD's ability to influence the hepatic metabolism of other medications has the potential to cause adverse effects. [101, 111, 112]

There remain many unknowns with large and long-term doses of CBD [63, 64]. In paediatrics, some patients have had worsened symptom control and adverse effects such as sleepiness, abnormal liver function, and diarrhoea (especially in high doses). Other known adverse effects from CBD include fatigue, decreased appetite, and weight loss. [56, 63, 71, 73, 101, 113, 114]

For difficult-to-treat epilepsy in paediatric patients, high doses of CBD (20 mg/kg/day) are prescribed in addition to their stable antiepileptic drug regimens. These patients appear more vulnerable to adverse gastrointestinal effects and elevated liver transaminase levels. Additionally, the soporific effects of anticonvulsants should not be mistaken for the potential overdose effect of CDB.

When discontinuing high-dose CBD, the dose should be decreased gradually. In cases when used as an antiepileptic medicine, abrupt discontinuation should be avoided when possible to minimise the risk of increased seizure frequency and status epilepticus. [56]

When treating patients with CBD, obtain serum trans-aminases and total bilirubin levels prior to starting treatment. Patients should be monitored if they develop clinical signs or symptoms suggestive of hepatic dysfunction serum transaminases, and total bilirubin levels should be promptly measured. Treatment should be interrupted or discontinued if warranted. [56]

Table: side effects of THC

Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%
Dizziness	Euphoria (with high dose)	Orthostatic hypotension
Drowsiness	Blurred vison	Paranoia / Toxic psychosis
Dry mouth and reddened eyes	Headache	Depression
Appetite stimulation (may be beneficial in some patients)	Nausea (high doses)	Ataxia / Dyscoordination
Intoxication (with high dose)	Anxiety (THC naïve patients and with high doses)	Tachycardia (after titration)
	Nausea and vomiting (with high doses)	Cannabis hyperemesis [109]
	Diarrhoea (with high doses)	

Table: side effects of CBD (in particular with high doses)

Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%
Drowsiness	Fatigue	Infections
Somnolence	Malaise	
Decreased appetite	Asthenia	
Diarrhoea (high dose CBD)	Diarrhoea	
Anxiety	Weight loss	
Nausea	Rash	
Cognitive effects	Insomnia	
Pyrexia	Sleep disorder	
Abnormal liver function Transaminase elevations	Poor quality sleep	

Maximum dosing

Defining a maximum dose

While daily dosage recommendations are made, there is no fixed maximum dose for THC.

Defining a maximum dose is difficult, given variability introduced by administration route (dose type), bioavailability, patient response, and the length of time receiving treatment. For THC in particular, dosing is self-limiting, with an individual response and side effects establishing an upper dose limit.

Cannabinoids have a wide therapeutic index, with side effects from high doses being nuanced, time and dose-dependent, and typically transitory in nature.

During the titration period, undesirable, usually mild, side effects may occur. Side effects typically resolve in a few days.

Most side effects are the result of large doses and are influenced by the frequency of dosing, route of administration, and concomitant medicines. [71, 100]

The clinical features of high doses of THC

THC is responsible for a range of effects. [57, 58]

- An intoxicating dose refers to a transient, physiological and neurological sequelae of effects, including impairment of attention, memory, psychomotor performance, short-term memory, and an increase in heart rate.
  THC-naïve patients may be more sensitive and experience intoxication at lower doses. Paediatric patients are likely to experience more severe symptoms, including negative cardiac, CNS and gastrointestinal effects.
- With large doses of THC, bursts of uncontrolled laughter, the feeling of being happy and energised, and changes in the awareness of the patient's surroundings (colours, sounds) may also occur but are less clinically significant. Some patients may experience acute feelings of anxiety. Large oral doses of THC may heighten intoxication reactions from 11-OH-THC, a potent psychoactive THC metabolite.
- As time passes, intoxication changes to feelings of being content and relaxed (> 30 minutes post inhalation and > 3 hours post an oral dose, depending upon the total dose taken). In most patients, these symptoms are mild and appreciated.

Strategies to mitigate THC side effects

The patient's prior experience with THC, expectations and attitudes towards the regimen, and the environment in which the medicine is taken affect the patient's response.

In cases of a THC overdose, most often, it is sufficient for the patient to sit or lie down in a calm and comfortable location, preferably with someone familiar to talk to.

If side effects are unpleasant for the patient, prescribers should:

- Keep the THC total daily dosage low.
- Slowly titrate the dose upward to promote tolerance to psychoactive sequelae of THC, especially in THC-naïve patients. Titrate slower in elderly and frail patients.

If THC tolerance occurs, consider a cannabinoid free period of at least 48 hrs – preferably longer.

Medicine interactions

Refer to **Appendix: Medicine Interactions** for tables listing known and potential interactions.

Cannabis-based medicines can interact with other medicines, and the risk increases if a patient is taking several medicines at once. Most patients are likely to be co-prescribed another medicine.

Existing studies have demonstrated toxicity and/or loss of effect of concomitant medications. Medicine interactions with THC and CBD can occur through both pharmacokinetic and pharmacodynamic interactions.

While clinically significant medicine interactions exist, there is no medicine that cannot be used with cannabinoids, if necessary.

Pharmacokinetic interactions

Both THC and CBD are substrates for the CYP450 enzymes primarily found in the liver and small intestine. THC is metabolised by CYP2C9, CYP3A4 and CYP2C19. CBD is a substrate for CYP3A4 and CYP2C19. This implies that other medicines that either induce or inhibit these enzymes may affect plasma levels of THC and/or CBD, and, therefore, either potentiate or reduce the activity of cannabinoids [109, 117, 118]

In a similar fashion, THC and CBD can inhibit the enzymes that metabolise medicines through CYP3A4 (primarily CBD); CYP2C9 (both THC and CBD); 2C19 (primarily CBD); CYP2B6 (THC and CBD).

Cannabinoids may also increase the clearance of medicines that undergo CYP1A2 metabolism (clozapine, olanzapine and theophylline). CBD may inhibit p-glycoprotein (drug transporter), resulting in an increased risk of toxicity of these substrates (overlap with CYP3A4 substrates). THC-COO-glucoronide (inactive THC) is also an inhibitor of P450 enzymes. [119]

Pharmacodynamic interactions

The most common interactions occur with other sedatives or agents that have sedative activity; examples are alcohol, opioids, benzodiazepines, tricyclic antidepressants, antihistamines, etc. There will be added cognitive and psychomotor impairment. THC may cause added tachycardia, hypertension and fluid retention with agents, such as amphetamines, cocaine, noradrenergic agents and agents with potent anticholinergic activity. The soporific effects of high dose CBD may be increased with anti-convulsants. [71, 109]

Therefore, the prescriber ought to show caution if they wish to commence cannabinoids in patients who are taking these or other similar agents. In particular, prescribers should closely monitor the responses of frail or elderly patients and patients with chronic conditions, including liver and kidney disease. [71, 109]

Contraindications

There are some absolute and relative contraindications to cannabinoid use. Cannabinoids do have a number of important drug interactions, which can result in altered pharmacokinetics or pharmacodynamics.
As a result, cannabis-based medicines are contra-indicated in the context of pregnancy, psychiatric, sub-stance dependence, renal or hepatic disease, cardio-vascular disease, and in frail and elderly patients. [71]

Table 1: contraindications

Contraindication	Clinical reasoning
Initiation age	THC-containing medicines should be avoided in young patients, given the potential developmental risk. [69, 76] However, it may be appropriate to prescribe THC for patients aged < 25 years if the benefits outweigh the risks. [69-71]
Pregnancy and during the lactation period	THC and CBD, and metabolites are present in placental fluid and breast milk. Intake of cannabinoids during pregnancy may affect the development of the fetus. The use of cannabis-based medicines is not advised pre-conception and during breastfeeding. A reliable contraception is advised for the duration of and several months after treatment.
Psychosis familial or personal history	Avoid the use of THC containing medicines, as they may potentiate psychosis or other psychiatric conditions (schizophrenia or depression). The potential of cannabinoids to indirectly affect brain dopamine levels may negatively impact the functioning of patients with psychosis. Anxiety and depression are possible in the case of non-predisposed individuals, especially when very high doses of THC are taken. A direct link between cannabinoids and psychosis has not yet been established.
Dependency substance misuse, including cannabis	THC is euphorigenic and may result in drug-seeking behaviour in some patients. [65, 69] THC-containing medicines should be prescribed with particular care if patients have prior problematic substance use. The evidence suggests that the risk of developing an addiction to cannabis when taken as a medicine is minimal. The recommended dose for medicinal use is often lower than that of a recreational user, and a medical professional should always be involved in medicating and monitoring the patient. High doses of medicinal cannabis, taken over long periods, may lead to dose escalation and misuse. The abrupt cessation may then cause withdrawal symptoms, such as mild forms of restlessness, irritability, insomnia, vivid dreams, and decreased appetite.

Table 2: contraindications

Contraindication	Clinical reasoning
Hepatic and Renal disease	Hepatic and Renal disease can result in significant alterations in drug handling, and dose reductions may be required. The effects of THC and CBD may be significantly different in patients with liver disease. While cannabinoids are also linked to the progression of fibrosis in hepatitis C. If cannabinoids are included in the therapeutic regimen, continuous monitoring is warranted for these patients to ensure the dosage taken does not exceed the metabolic capacity.
Cardiac conditions angina, cardiac arrhythmias, Brugada syndrome	It is possible that a THC overdose will result in acute hypertension and/or tachycardia. THC can result in an elevated risk of myocardial infarction (MI), thought to be secondary to a combination of tachycardia and an increase in blood pressure leading to a dangerous combination of increased cardiac output and cardiac oxygen demand. [120] Immediately post inhalation, there is an increased risk of myocardial infarction within 1 hour of inhalation of THC, with the risk rapidly decreasing with time.
Hypersensitivity	Patients with known or suspected hypersensitivity to cannabinoids or any medicine ingredients should not be prescribed that medicine. If a patient develops hypersensitivity reactions after treatment initiation, the medicine should be discontinued.
Elderly patients	In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or therapies (polypharmacy). Elderly patients are more sensitive to the neurological, psychoactive and postural-hypotensive (orthostatic hypotension) effects of cannabinoids. This is especially applicable to elderly patients who are prone to falls and those with dementia.

Cessation

If unacceptable adverse reactions occur, then the dose should be reduced and potentially tapered off or ceased. If medicine cessation is required, slow downward dose titration may be applicable.

Patients using higher doses of THC may be titrated off THC-containing products when discontinuing their use. Stopping the use of THC abruptly may cause withdrawal symptoms like restlessness, irritability, mild sleep and appetite disturbances. A desire for more cannabinoids and emotional lability may occur. These reactions may occur during the 'wash out' period, given fluctuations in levels of THC and its active metabolite (11-OH-THC) as they are released from fatty tissues.

In cases when used as an adjunct to antiepileptic medicine, abrupt discontinuation should be avoided, when possible, to minimise the risk of increased seizure frequency and status epilepticus. When discontinuing high dose CBD, the dose should be decreased gradually. [56]

General considerations

Medicine costs

Few health insurances or national pharmaceutical schemes subsidise cannabis-based medicines. This is related to the fact that they are not first-line treatments, are not identified as essential medicines, and are typically unapproved medicines. While clinical evidence is increasing rapidly, only a few have supporting clinical data which show them as equal to or better than currently available treatments in these subsidy schemes.

In this situation, patients must pay out-of-pocket for cannabis-based medicines. Medicine affordability, therefore, may have implications for a patient's treatment plan.

Driving and operating machinery

Any substance that interferes with cognitive and psychomotor functions can be deleterious for a complex task like driving. The effects of THC on driving are modest, comparable to a low dose of alcohol. Impairment is more pronounced in THC-naïve patients and when combined with alcohol or sedative-type drugs (benzodiazepines, antipsychotics).

Prescribers and pharmacists should be cognisant of all possible medicine interactions that may cause drowsiness or sedation.

Patients receiving THC-containing medicines remain at risk of positive tests for cannabis in oral fluid even if they are not impaired. There are countries where it is illegal to drive cars or to operate machinery when traces of THC may be found in the urine/blood. Therefore, patients using THC-containing medicines should be advised about driving, and to avoid operating machinery during treatment initiation and in the hours immediately following each dose. [121]

The European Pain Federation (EFIC) suggests health professionals advise "patients not to drive at all if therapy with cannabis-based medicines is started or modified until a stable dosage for 5-7 days is reached. And, patients should not drive while under the influence of cannabis-based medicines and not drink alcohol. Do not prescribe cannabis-based medicines to patients with professional driving occupations (taxi drivers, truck drivers, ambulances). A medical assessment - for working ability of patients in jobs where there is a potential for harm to oneself or to others - is recommended." [5]

Travel

The regulatory situation differs across the globe. Some countries allow cannabis-based medicines, while others have strongly worded legislation prohibiting it.

Enquiries should be made at the Embassy of the country of transit and final destination before travel. Additionally, the International Narcotics Control Board has information on international agreements governing the transportation of medicines across borders, available from: https://www.incb.org/incb/en/travellers/index.html

Co-management

Across the globe, prescribing occurs predominantly in an outpatient setting. Some patients may bring cannabis-based medicines from home into the hospital or hospice setting, raising important considerations for co-medicine management and continuity of care.

"When prescribing cannabis-based medicines, I always give a hand-out to the patient about the correct use of these medicines. The same instruction is placed at the digital patient chart and is communicated with the general practitioner of the patient in order to facilitate transparency."

Nurse Metta Bunk - on the importance of thorough communication

Perioperative use

Patients treated with cannabis-based medicines require special attention during the perioperative period.

In the perioperative period, anaesthesiologists should be aware of all medications the patient is currently taking. The acute effects of cannabinoids, in particular THC, can affect the pulmonary, cardiovascular, and central nervous systems. [8, 122] There are currently no clear-cut recommendations of when to stop cannabis-based medicines before surgery - published recommendations range between 6-8 hours up to ten days before surgery.

The question of cannabis-based medicine use (including recreational use) should be discussed by the anaesthesiologist during the pre-anaesthesia encounter. Information should be gathered about the duration of use, frequency, route of administration and medicine type (THC, THC:CBD, CBD), and total daily dose.

For the intra-operative phase, some studies have suggested that there were antagonistic effects between propofol and cannabinoids, requiring increased propofol dosages for the induction of anaesthesia. [123] Chronic cannabinoid administration may increase the patient's risk of bradycardia, sinus arrest and coronary vasospasm. Inhaled cannabinoids administered pre-operatively may increase airway reactivity and can cause increased cough, sputum and wheezing.

During the post-operative period, there should be awareness of a potential cannabiswithdrawal syndrome. [124] Within 1 week of abruptly discontinuing cannabinoids, such as THC, patients manifesting any three or more of the following symptoms are regarded as being in withdrawal: irritability, nervousness or anxiety, sleep difficulty, decreased appetite or weight loss, depressed mood, and any physical symptom, namely abdominal pain, shakes/tremors, sweating, fever, chills, or headache.

Post-operatively, patients administered cannabinoids, such as THC, appear to have higher pain scores and experience poor sleep, although this could also represent a manifestation of THC withdrawal syndrome. Some patients may bring their cannabis-based medicine for post-operative usage. However, cannabis-based medicines do not appear to be effective for the prevention or treatment of post-operative nausea and vomiting, nor for the management of acute post-operative pain.

Refer to the Appendix for tables: **Medicine interactions**.

Prescribing summary

Patients should understand the risks and benefits of cannabis-based medicines. Following that, prescribing should be guided by the pharmacokinetic properties of the selected dose form, the influence of patient comorbidities and potential medicine interactions, alongside regular monitoring to assess the clinical benefit. [59]

Key things to keep in mind

- Clear and consistent communication – explain the patient's regimen thoroughly.
- Review all medication use beforehand.
- Do not prescribe THC-containing medicines to patients taking high doses of opioids or benzodiazepines. Consider tapering down high doses of opioids (> 90 mg morphine equivalent/day) and benzodiazepines if prescribing cannabis-based medicines containing Δ-9-THC (especially high doses).
- The sedative effects of high-dose CBD may be increased when co-administered with anti-convulsants; these patients should be monitored during treatment.
- Extra caution is advised in patients with a history of mental illness, cardiovascular disease, kidney and liver illness, the elderly and frail, and those with dementia.
- Patients are aware that the treatment may be discontinued if the benefit has not been established.

Treatment plan

Once a thorough clinical assessment is completed, a treatment plan should be established with the patient and their family members or carers as appropriate.

A treatment plan provides information about the goal of the treatment and its expected length, and the documented evidence for the medicines used. It also provides patients with advice on how to find an optimal daily dosage and how to maintain it, changes in their other medication, ways to reduce the risk of side effects and possible medicine interactions, how safety and efficacy are to be measured and assessed, and a plan to stop treatment if required.

It should be clear to the patient that the initial trial of the cannabis-based medicine will be no longer than twelve weeks (for in-patient trials, four weeks may be appropriate). At the end of the trial period, it will be determined if the cannabis-based medicine is efficacious enough with only minor side effects. After that period, a decision may be taken for longer-term treatment.

Coordination between prescribers, pharmacists and nurses will enable an effective service for complex patients, especially at the outset.

A suggested treatment plan

The treatment plan should be laid out in the patient's chart and should include the nine points in the following table.

Treatment plan	
1 **Informed consent**	Informed consent has been obtained – this includes that the patient has received information about the cannabis-based medicine, the (possible) out-of-pocket costs for patients, treatment goals, and possible side effects, and consequences of non-compliance (risks and harms) have been discussed. Patients are aware the treatment may be discontinued if the benefit has not been established.
2 **Treatment goals**	Treatment goals should: • Be clearly stated and measurable – for example, by using symptom checklists (e.g. a brief pain inventory). A test phase of up to three months after initiating therapy should be considered. • Incorporate suitable diagnostic and measurement technique(s) which are used to assess the safety and efficacy of the recommended regimen. • Include a plan to reassess the condition and determine over time if the desired effect has been obtained and maintained. • Cannabinoids are typically an adjunct medicine. Detail the procedure for reducing concurrent medicines, if applicable, or tailing off concurrent medicines and other treatments that may be redundant for specified condition(s). In general, avoid high doses of Δ-9-THC and very high doses of CBD. Specifically, discourage patients from smoking cannabis-based medicines or the recreational use of cannabis during treatment. If patients start using cannabis recreationally, the prescription should be ceased.
3 **Treatment agreement**	A treatment agreement may be appropriate in some settings. This is a formal treatment agreement signed by the patient, typically given the risks associated with an unapproved medicine or prescribing an approved medicine off-label.
4 **Patient guidance**	For a particular dose type or dose form, guidance is provided for: • The starting dose • The frequency of dosing • Titration up and down to adjust to the optimal effective dosage The frequency of dispensing the medicine should be clearly stated. Short dispensing intervals are useful to improve compliance if there are concerns around safe use. Storage requirements to minimise the risk of diversion and misuse – cannabis-based medicines should be stored in a cool, dry place, safely and away from children.
5 **Monitoring**	Monitoring arrangements and regular reviews and appointments should be clearly laid out in the initial treatment plan.
6 **Driving**	The risks of driving a car and operating machinery should be clearly stated – it is forbidden in many countries to use cannabis-based medicines containing THC and to drive.
7 **Travelling**	Some countries prohibit the use of cannabis-based medicines – enquiries should be made with the country of (transit and) destination before travel. Typically, a certificate should be provided if your patient is travelling with a cannabis-based medicine prescription for a duration of up to 30 days.
8 **Cessation/Exit strategy**	An exit strategy for situations where treatment goals were not reached should be clearly stated. A plan to stop treatment at a particular dosage if no significant effect has been seen, or if intolerable side effects have occurred, or if dependence or diversion has been identified. A protocol for returning unwanted or unused medicine, and if required and necessary, the medical device used to administer the medicines.
9 **Information leaflets**	Provide easy to read information leaflets which inform the patient of the potential benefits and risks of cannabis-based medicines.

5. Pharmacy

Medicines review and dispensing protocols enhance patient safety and improve medicine adherence. This section focuses on pharmacy practice. It provides advice for pharmacists, including lessons learnt from other jurisdictions, which help to establish good pharmacy practices.

Cannabis as a medicine

The medicine status – a controlled drug, a prescription medicine, or over-the-counter – will impact on pharmacy practice (the medicine may require being stored in a locked cabinet or refrigerator).

In some countries, CBD products are prescription medicines and may contain only trace amounts of THC. While a product containing THC is a controlled drug, on prescription. This includes finished products such as cannabis flowers for pulmonary administration or cannabis extracts for oral administration. Only a few cannabis-based medicines are officially approved medicines (e.g. Sativex® buccal spray). Most are unapproved medicines.

The prescription of unapproved medicines, or prescribing an approved medicine off-label, requires a good clinical argument. It then becomes the dispensing pharmacists' role to:

- Ensure that the medicines prescribed to patients are suitable
- Advise patients about the medicine (how to take them, what reactions may occur)
- Answer patients' questions

"For a successful and safe therapy with cannabis-based medicines, physicians and pharmacists should be in a close exchange."

Pharmacist Dennis Stracke – on working closely with prescribers

The big issues for pharmacy practice

Two very important points are often raised about cannabis-based medicines:

- The full cost of medicine is privately funded (out-of-pocket payments) in many countries.
- There may be an unmet need for effective, accessible therapy, and therefore, there may be an interest in the use of cannabis-based medicines in a range of, often complex, conditions.

The unmet need and full cost to the patient have implications for prescribing and dispensing cannabis-based medicines. Firstly, patients self-fund the medication for the duration of that prescribed treatment. Secondly, patients are likely to present with complex health conditions, on multiple medications, at various stages of disease progression. For Pharmacists, this raises issues around:

- Dealing with potential medicine-medicine interactions
- Managing medicine initiation and titration to an optimal dosage
- Potentially, cessation of that medicine

Patients may wish to stop taking a cannabis-based medicine due to ongoing cost, lack of efficacy of the medicine, or occurrence of intolerable side effects. Remember that the rational use of medicines requires that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community".

Important considerations when dispensing

Pharmacists can assist patients with managing their medicine-use behaviours and ensuring their safety. When introducing cannabinoids into a patient's therapeutic regimen, pharmacists should consider the following:

1. At-risk patients

Assess the potential risks with the elderly (e.g. postural hypotension), in those with cardiac risk factors (cardio-pulmonary disease), in those with a history of psychosis or depression, and with young persons (given the potential risk to the developing brain).

Absolute contraindications include acute psychosis and other unstable psychiatric conditions. Relative contraindications include severe cardiovascular disease (may exacerbate arrhythmia or a history of arrhythmias), immunological, liver, or kidney disease, especially during an acute illness.

2. Potential medicine interactions

Several medicines potentially interact with cannabis-based medicines. Pharmacists should be aware of potential medicine-medicines interactions, and how these will be identified and treated. A full medicine regimen review should be undertaken, in particular for those medicines which interact with the CYP-450 metabolic enzymes.

3. Potential side effects

In general, patients seem to tolerate cannabis-based medicines well. However, some patients taking cannabinoids have had worsened symptom control and new side effects such as sleepiness and diarrhoea, or have altered liver function. In particular, large doses of THC have been shown to pose a risk of harm (e.g. postural hypotension resulting in a fall).

Side effects mainly occur after taking high doses or when used in combination with other substances. For THC dominant medicines, these include:

- Dry mouth
- Redness of the eyes
- Heightened appetite (which may be desirable)
- Mild euphoria (which may be desirable)
- Hallucinations (at very high doses)
- Reduction of alertness of the user, especially in the few hours directly after consumption.
- Increased heart rate
- Lowering of blood pressure and dizziness

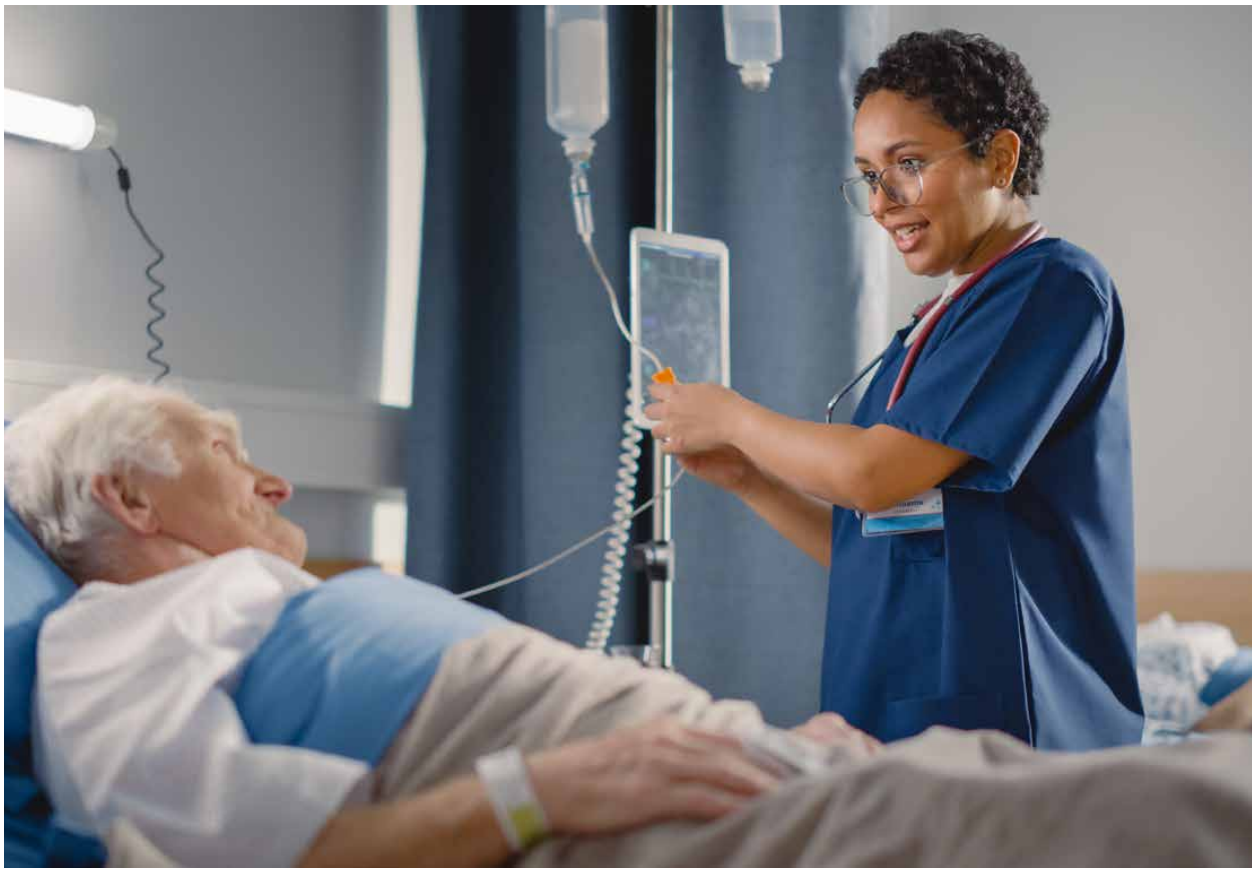
In general, side effects will slowly decrease and then disappear within a few hours. This depends upon the dose and mode of administration.

There are also many unknowns with large doses of CBD – indeed, the US-FDA continue to monitor their use, given "there are many unanswered questions about the science, safety, and quality of products containing CBD". [72] Some patients have had worsened symptom control and new side effects such as:

- Sleepiness
- Abnormal liver function
- Diarrhoea (especially in high doses)
- Fatigue
- Decreased appetite
- Weight loss

4. Titration of dose to the optimal daily dosage

Like with other medicines, individual patients will respond differently to cannabis-based medicines. Their response depends on the cannabis product used, the condition being treated, the duration of treatment, how it is administered, and genetic predisposition.



A patient's doctor generally provides advice regarding dose titration (dose adjustments to a desired effect) to achieve an optimal daily dosage. Titration helps patients to obtain the desired therapeutic effect/s and minimises undesired effects.

Many patients will titrate their dose in the first weeks of therapy. Pharmacists should provide guidance, as per the prescription, on:

- The starting dose, and for titration up and down (minimum and maximum dose) – how dosage adjustments would be made based on the dose form
- How to find an optimal daily dosage based on the severity of the patient's condition and changes in their other medication
- How to maintain their daily dosage

Keep in mind that the pharmacological effects are dose-related and subject to interpatient variability. Systemic absorption will be different in intensity and timing based on the route of administration.

5. Assessing medicine safety and reporting adverse drug reactions

Be cognisant of typical side effects, possible medicine and food interactions, and potential for adverse drug reactions.

Discuss possible side effects based on the patient's total medicine regimen. Discuss ways to reduce the risk of side effects occurring. Explain that these are novel medicines, and there may be yet unknown potential adverse reactions to these medicines, which should be reported.

Encourage your patient to tell you about adverse effects. Report these immediately to your domestic pharmacovigilance centre for adverse drug reactions monitoring. The more details, the better: the medicine name and dose suspected of causing the reaction, alongside a list of symptoms, signs, laboratory results, and past medical history.

6. Assessing medicine efficacy

Request feedback from your patient regarding side effects and determine if the desired effect has been obtained and maintained over time. In direct consultation with the prescribing doctor, discuss a plan to modify or stop treatment at a particular dosage if no significant effect has been seen, if intolerable side effects have occurred, or if dependence has been identified.

7. Safe medicine storage, driving, foreign travel

Cannabis-based medicines should be stored in the official pharmacy container, in a safe and secure place where young children cannot reach it, and away from heat and direct sunlight (in accordance with label storage conditions).

Patients should avoid driving, operating machinery or engaging in any potentially hazardous activity under the influence of cannabis-based medicines. THC and CBD may produce undesirable effects such as drowsiness which will impair judgement and driving performance.

Remind patients to check that it is legal for them to take cannabis-based medicines into any countries they are travelling through and travelling to. Its legal status will vary between countries.

8. Returns protocol

Confirm a protocol for returning unwanted or unused cannabis-based medicine and, if required and necessary, the device used to administer it (e.g. a medical device). Out-of-date or unwanted medicine should be taken back to the pharmacy for safe disposal.

Hurdles for dispensing in hospitals and hospices

The different patient medicine use settings (hospital, hospice and home) each present pharmacists with unique challenges. For a public hospital or hospice pharmacy, in particular, there are a number of logistical hurdles with the introduction of cannabis-based medicines; these might include:

Cost of dispensing – The cannabis-based medicine may be privately funded, which, if dispensed by a publicly funded hospital pharmacy, may mean the cost of dispensing falls on the pharmacy without remittance.

Dispensing methods – Standard medicine dispensing methods and audits are difficult to employ. This includes how these medicines are disposed of or destroyed because cannabis-based medicines are not always presented in standard dose formats. As a result, it is difficult to evaluate dispensing efficiency compared with/alongside other dispensed medicines

Medicine usage – Recording medicines usage (as specific doses) is difficult because medicines may not be presented in standardised formats (e.g. oils in re-sealable dropper bottles/dose taken by syringe from a resalable dropper bottle containing an oil; and inhaled doses as a granulated cannabis flower, with non-specific unpackaged dose weights), or are brought into a hospital setting and presented to the pharmacy open and partially used. This makes it difficult to measure/quantify the amount of medicine available and used.

Inhaled dose forms – Inhaled dose forms (pulmonary administration via a vaporiser medical device) is a hurdle because there is currently no standardised dose (a disposable pad containing mg dose for insertion into a medical device), which makes it difficult to audit administration and usage. The medicine's primary container is likely to contain loose cannabis flower or granulate, making it difficult to account for the total volume of the medicine remaining

For all pharmacists, including community pharmacists:

- Oral dose forms may require a cold chain supply, and storage in a locked pharmacy refrigerator if a controlled drug. This is both a cost and storage compliance burden

- Inhaled dose forms may require storage in a locked cabinet. Administration should be by an inhalation device for administration - such as the SyqeAir Inhaler and Volcano Medic vaporisers. Knowledge of vaporiser medical device technology by pharmacy staff means upskilling will be required

Forget the hype

Cannabis-based medicines are not a panacea or a cure for the disease. Focus on providing good advice to patients – they need a supportive but critical view of the risks and benefits of cannabis-based medicines.

For pharmacists, dispensing cannabis-based medicines is similar to other medicines. However, many patients will have an opinion about 'cannabis' and 'cannabis-based medicines'. Some patients will be armed with information, whereas others will be naïve to the topic.

A solid understanding of these medicines and clear communication is really important. In particular, pharmacists must be able to:

- Promote patient medicine compliance and share patient-friendly medicine information
- Assist in identifying adverse drug reactions and reporting them.
- Encourage patients and carers to inform their doctors
- Help support prescribers in decision-making and with medicine regimen review
- Answer tricky medicine queries

Talking with patients

- First, ask the patient what they already know about cannabis-based medicines
- Inform them about the mechanism of action, how to use it, the dosage regimen, possible side effects, how to safely store it
- Provide patients with an information sheet which includes a table of interactions and side effects
- Make sure that the patient takes notice of possible interactions with other medicines or contra-indications – there are certain conditions where cannabis-based medicines should not be used
- In a follow-up discussion, ask the patient about their experience with the use of the medicine, with extra attention to potential side effects and the medicine's effectiveness

For patients prescribed an inhaled dose form, talk about:

- The differences between 'vaping cannabinoids' and 'vaporising cannabis herbal material', and help them to fully understand why smoking should be avoided
- Explain the benefits of using a vaporiser medical device compared with smoking
- Explain what makes a good vaporiser – what quality aspects to look for

Key things to keep in mind

The pharmacist's role includes screening the patient's medicine regimen to assess the risk of medicine interactions or contraindications given the patient's condition. Pharmacists need to start planning for the future now, including thinking about:

- What role will you play in patient care, given these are new, often untested medicines?
- How will cannabis-based medicines impact your service, and how will you adapt to meet that need?
- What innovations will be required in your pharmacy practice to promote the well-being of patients using cannabis-based medicines?

A variety of standardised cannabis-based medicines and modes of administration are available globally. It is likely prescribers will have access to these and similar medicines. As such:

- Pharmacists need to work collaboratively with prescribers as cannabis-based medicines are introduced into clinical practice.
- Pharmacists should be cognisant of prescribing protocols on starting dose, assessment of efficacy and safety, risk mitigation, treatment cessation, and medicine return.

Cannabis-based medicines will often be a third- or fourth-line adjunctive therapy. These patients may have multiple indications and contraindications. There is the potential for medicine interactions and adverse effects to occur.

With new clinical data, health professional insights, and products becoming available, it is important that practical, evidence-based health professional guidance and education are taken up by pharmacists to support decision-making.

Forget the hype. Focus on providing good advice to patients – they need a supportive but critical view of the risks and benefits of cannabis-based medicines. A pharmacist must provide proper, easy-to-understand information, describing potential side effects, and preparing the patient or carer on what to do if a problem occurs when using cannabis-based medicine.

6. Nursing

Administration protocols enhance patient safety and improve medicine adherence. This section focuses on nursing practice. It provides advice for nurses, including lessons learnt from other jurisdictions which help to establish good nursing practices.

Assessment, monitoring, and collaboration

Most prescribing of cannabis-based medicines occurs in an outpatient setting; some patients may bring their medicines into the hospital or hospice setting, or already be using them at home.

- **Assessment**: Understand the risks of the treatment before initiation – especially medicine-medicine interactions and side effects from overdosing.
- **Monitoring**: At follow-up care, assess safety and effectiveness. Dose adjustments can be made in consultation with the prescriber. Talk with patients about the safe use of cannabis-based medicines as part of their therapeutic regimen

"If there aren't side effects, but there isn't a significant relief, it is possible to raise the dosage. If there are intolerable side effects, we stop the usage and report that to the treating doctor."

Nurse Miriam Ogintz – on communication with prescribers

- **Collaboration**: Nurses have a direct channel to communicate with doctors who prescribe medicines. This is a quick and convenient way to communicate any medicine problems or possible dose adjustments. Nurses should talk with pharmacists about the total dosage, the potential for medicine interactions, or the co-use of other sources of 'cannabis medicines' (especially those of dubious quality)

Administration by inhalation

Inhaled dose forms

Vaporiser medical devices contain cannabis herbal material or an extract of cannabis. They offer rapid onset of action and patient control of the inhaled amount via breath timing and depth. This method of administration provides high concentrations of cannabinoids rapidly when needed.

Second-hand exposure

Outside of pandemic conditions, public or private hospitals or hospices may have a policy of 100% occupancy. Administration by a vaporiser medical device would, therefore, occur in rooms with a minimum dual occupancy, while low-risk, second-hand exposure to exhaled vapours may present an issue for nursing staff, especially if pregnant or those who become pregnant. [125]

In many health settings, pulmonary administration poses a potential low-risk safety issue for staff and patients from exposure to second-hand vapours. [125] Nonetheless, reducing second-hand exposure to exhaled vapour is important. Inhaled cannabis-based medicines should be administered in a well-ventilated space/rooms, and use around children should be strictly avoided.

Dispensing a granulate of cannabis herbal material

Each vaporiser medical device will have specific instructions and documentation which should be consulted. Generally, hands should always be thoroughly washed before dispensing the granulated cannabis herbal material. Dispensing the granulate into the vaporising basket should be done using a thoroughly clean dispensing spatula. Physical contact with the granulate should be avoided to reduce microbial burden and to maintain product sterility. When dispensed, the granulate dose will be contained within the basket which sits within the vaporiser. Some devices are 'fiddly' and may be difficult to fill for elderly and frail patients.

Extraction of cannabinoids from cannabis herbal material

Each vaporiser medical device will have specific instructions and documentation which should be consulted. Generally, before an initial administration, patients should be given instructions on safe and effective inhalation, as follows:

- In the device 'off mode', ask the patient to try inhaling through the mouthpiece a few times
- Be sure that the patient is able to take deep breaths through the inhalation mouthpiece
- Instruct patients to exhale completely before inhalation

During initiation of titration, patients take the dose, by single-dose inhalations, with a minimum 10-15 minute break between inhalations, until the patient achieves optimal dosage, as directed in the prescription.

To maximise the consistency of inhaled doses, upon administration, patients should be instructed to inhale up to five seconds of vapour from the device and hold their breath for up to five to ten seconds after each inhalation. Inhalations must be constant and soft. If the inhalation is too fast or too strong, the patient may start coughing, and may feel burning in their lips or palate, or become dizzy.

Patients, if they are able to swallow, should be provided water, if requested. This may help with throat irritation and minimise coughing and, therefore, loss of the administered dose.

Disposal of spent material

With many vaporisers, the extraction of the active compound, THC, is never totally complete. Current vaporiser medical device technology is capable of up to 90% extraction. Therefore, spent material should be disposed of safely and responsibly.

Cleaning and maintenance

Each vaporiser medical device will have specific instructions. See documentation for detailed information on cleaning and maintenance.

Safety measures

To assure safety, the vaporiser medical device is recommended to be used as follows:

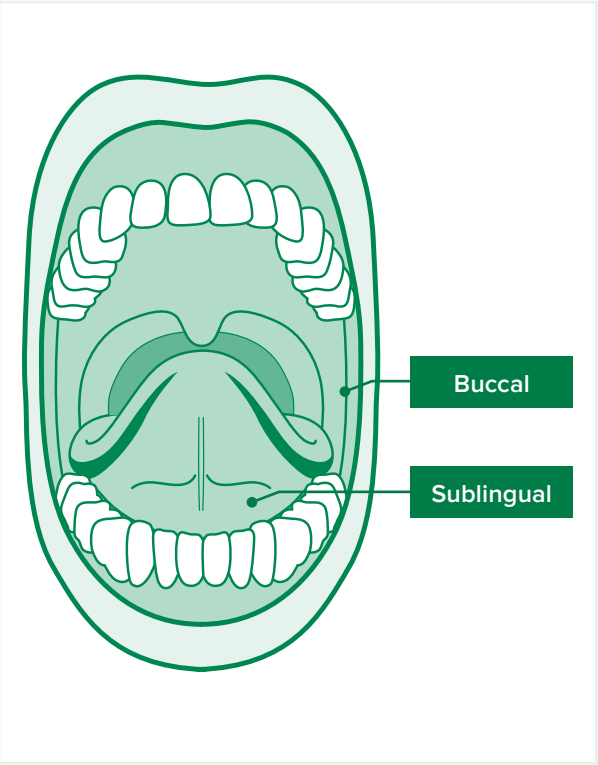
- Use and store the device in a cool, dry place
- Never cover/store the device when it is turned on
- Place the device and electronic dock on a flat smooth surface away from heat and humidity sources
- Never exhale into the vaporiser; this causes overheating, battery explosion and dirt accumulation in the inner chamber
- Never clean the vaporiser when it is connected to the battery or charging dock or when it is hot (the battery should not need cleaning)
- Use the cleaning tools provided
- Never leave the vaporiser running without supervision
- Keep out of reach of children

Oromucosal administration

Administration via the oral mucosa offers a faster onset of action compared to oral doses. A healthy mucosa will absorb these lipophilic medicines more promptly.

The dose size impacts the rate of absorption, and the risk of swallowing a dose. A swallowed dose will be poorly absorbed and extensively metabolised.

Figure: buccal and sublingual administration



Some dose formats require a medical device, such as a pipette/dropper, syringe or spray.

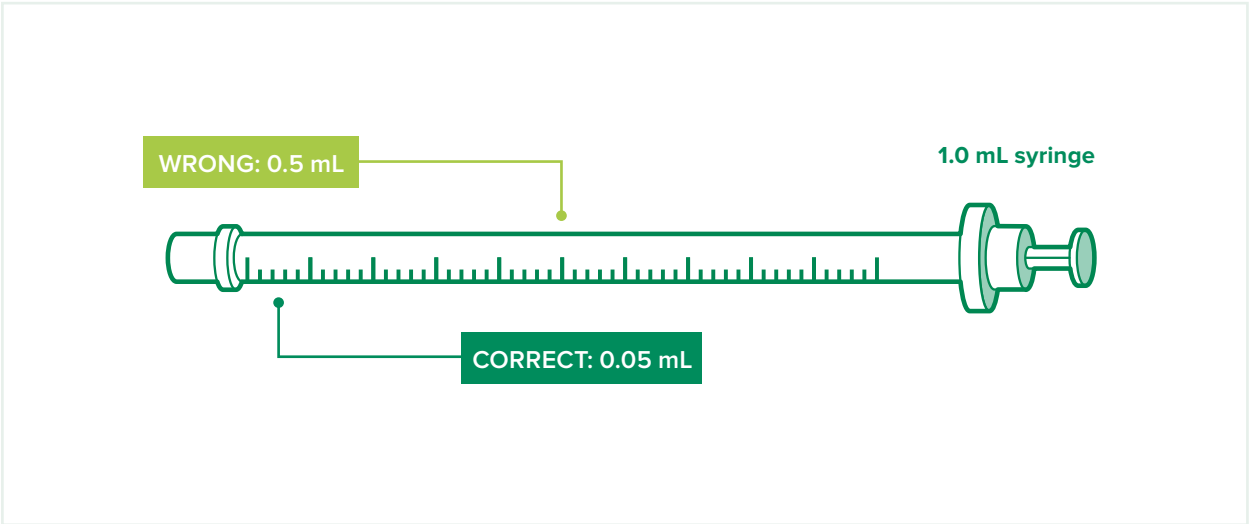
Pipettes/droppers or syringes can present a challenge for some patients – frail, elderly or limited mobility patients may find it hard to squeeze a dropper, deliver it under the tongue, with a consequent risk of under- or over-dose. Alternatively, put the dose in a teaspoon and take it into the mouth under the tongue.

A pipette/dropper or syringe helps increase the accuracy of the dose given but may be difficult or 'fiddly' for some patients. The correct use of a pipette/dropper or syringe should be provided to patients to prevent errors when dosing. For example, do not mistake doses of 0.05 mL for 0.5 mL, as shown below.[104]

An actuated, metered dose spray is a reliable administration format, with a specific dose per spray. Spray formulations may contain alcohol to suspend the solution, which can be unpleasant for patients.

Some oro-mucosal solutions may contain chlorophyll when extracted from the plant material, which may have an unpleasant taste. If a patient complains of taste, they might consume a piece of banana, an olive, or a boiled sweet, for example.

Figure: to administer 0.05 ml is sometimes challenging



Oral administration

The low bioavailability makes it difficult to titrate doses.

Oral administration offers a slow onset of action. The absorption rate is affected by gut physiology, food (especially high-fat diets), and general stomach health.

An appreciable food effect is observed with high-fat diets or when a food bolus is present in the stomach. Patients should be advised to take their medicine consistently, with regard to time and dietary intake, to reduce variation.

Remember, the metabolism of oral doses of THC creates 11-OH-THC, a potent metabolite with intoxicating effects. Patients should be monitored to prevent risks from intoxication.

Key things to keep in mind

Nurses have the most frequent contact with patients, carers and family. Whether in hospital, in clinic, or in-home, there is an opportunity to observe medicine use and/or to discuss safe and effective medicine use. For cannabis-based medicines, a nurse's role might include assessing medicine efficacy and side effects, and identifying adverse drug reactions and reporting these.

Nurses may also care for patients with an advanced illness to the end-of-life-care, and may encounter cannabis-based medicine use. At that point, nurses are instrumental in patient, carer and family education – talking about the care plan, and helping them understand and successfully implement the treatment options applicable to local laws, policies and procedures.

Clear, consistent guidance on how to administer cannabis-based medicines by the pulmonary, oromucosal and oral route, as necessary:

- Check the patient's understanding of their regimen
- Ask whether they have any questions or any concerns

"There are some patients who still think that cannabinoids can cure cancer – if these patients do not receive enough or correct information, they might miss the standard prescribed cancer treatment".

Nurse Niramon Pojdoung – on communicating accurate information to patients

Be aware of the indications, benefits and harms.

Keep up-to-date with trends in social media postings of 'fake' information. This is part of a nurse's toolkit in being able to prevent the use of 'underground medical cannabis products' which have no quality standards and which are expensive for the patient.

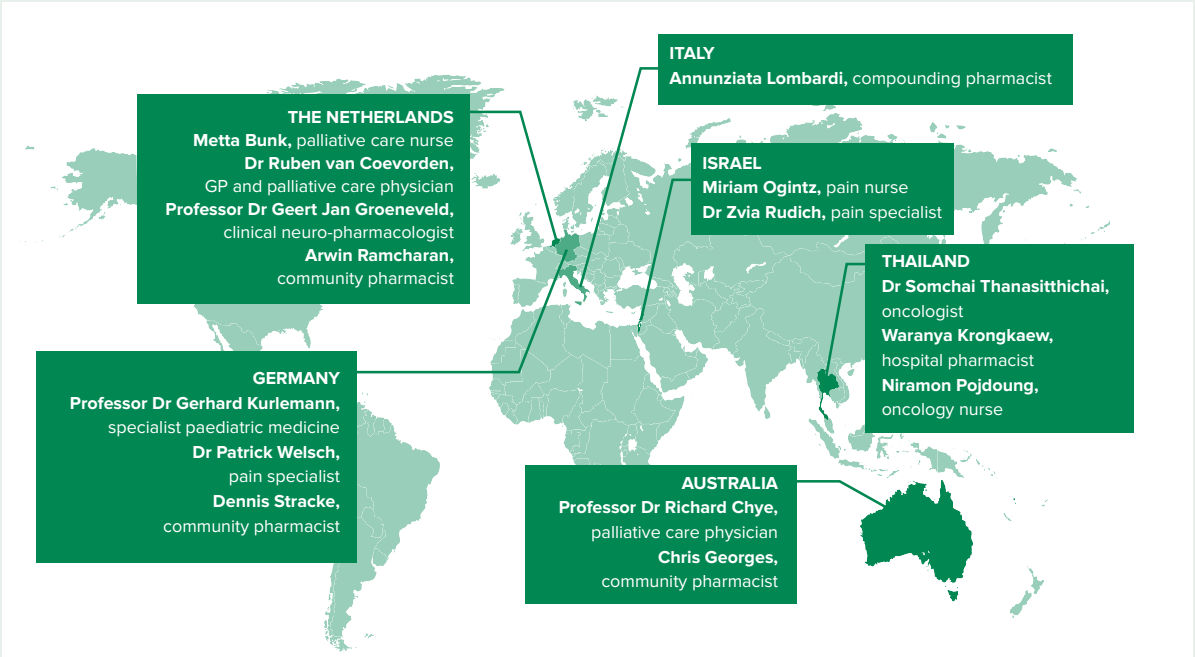
7. Insights from health professionals

There is a great deal we can learn from our experienced peers. We constructed a clinical questionnaire to provide insights for the rational use of cannabis-based medicines.

The questionnaire draws on the experience of colleagues from different parts of the world, and various fields of clinical practice, including: palliative care practitioners, an oncologist, a pain physician, neurologists, a clinical pharmacologist, pharmacists from the community and hospital setting, and hospital-based nurses and a nurse practitioner.

All have extensive experience working with cannabis-based medicines, are respected in their field of practice, and work within a typical prescriber-pharmacy model of care.

Map: location of health professionals contributing to this text



Prescribing: discourse with prescribers

In alphabetical order interviews conducted in 2023:

- Associate Professor Dr Richard Chye, a palliative care physician from Australia
- Dr Ruben van Coevorden, a GP and palliative care physician from the Netherlands
- Professor Dr Geert Jan Groeneveld, a clinical neuro-pharmacologist from the Netherlands
- Professor Dr Gerhard Kurlemann, a specialist in paediatric and adolescent medicine from Germany
- Dr Zvia Rudich, a pain specialist from Israel
- Dr Somchai Thanasitthichai, an oncologist from Thailand
- Dr Patrick Welsch, a pain specialist from Germany

Associate Professor Dr Richard Chye

Associate Professor Dr Richard Chye is head of Supportive and Palliative Care, at Sacred Heart Service, St Vincent's Hospital, Sydney, Australia. He undertook specialist qualifications in pain medicine and has significant experience in oncology and geriatric care. As a specialist general physician, he treats patients in palliative care, symptom control, and pain control. Richard runs the clinical trials unit at Sacred Heart, undertaking research on cannabis-based medicines with upcoming research into symptom control, especially in anorexia. Previously he was a member of the Australian Council for the Medicinal Use of Cannabis, advising the Commonwealth Government. He also runs a private cannabinoid assessment clinic in Sydney. While the majority of his prescribing occurs in this clinic, he has close cooperation with the Basgers Pharmacy and works inter-professionally in a hospital setting at the Sacred Heart Service.

Training/education

What training did you receive before you started prescribing cannabis-based medicines?

No formal training. I do a lot of reading and attending conferences around the world. I learn a lot from individual patient experiences. Over the last five years of prescribing, I know what cannabinoids do for those patients. For example, CBD has some psychoactivity - I've seen that CBD makes patients more relaxed.

Prescribing experience

How long have you prescribed cannabis-based medicines?

I first started prescribing in May 2017. I will occasionally prescribe in my role at St Vincent's Hospital. However, from a time-logistic point of view, I am not able to run a cannabinoid clinic in St Vincent's Hospital. Most of my prescribing occurs at my private cannabinoid assessment clinic.

Can you describe a typical patient to whom you would prescribe cannabis-based medicines?

The portion of patients with cancer in my private clinic is about 25% and for non-cancer treatment, about 70-75%.

A common group is patients with neuropathic pain from whatever cause. When I ascertain the patient has neuropathy (e.g. peripheral neuropathy, nerve damage) and that they've tried opioids, anti-epileptics (e.g. gabapentinoids), anti-depressants (e.g. amitriptyline, nortriptyline), and tried the SSRIs, and all of those treatments do not provide enough relief, then that is one reason for using cannabinoids.

It is difficult to manage neuropathic pain that affects a patient's life. For example, are they able to dress themselves, do they spend most of the time in bed, is the pain waking them at night, are they feeling refreshed in the morning? If the answer is no, then not only is neuropathic pain a problem for these patients, but it also affects their quality of life.

A lot of my private clinic patients are within the St Vincent's Hospital catchment area. Many will end up at St Vincent's Hospital, so I follow up with them there to make sure they have the right cannabinoid dose and product. At St Vincent's, I make sure that the policies and procedures are in place to ensure patients get and administer cannabinoids appropriately. I also have palliative care colleagues within St Vincent's Sacred Heart Service who prescribe cannabinoids.

Thinking about a first consultation with a patient, how do you start a conversation about the use of cannabis-based medicines?

I introduce myself to the patient explaining this is a cannabinoid clinic, and that I use it to help with their symptoms. I don't focus on all their other treatments because their referring doctor takes care of that.

My main speciality is in palliative care, and therefore many of my patients have end-stage cancer. My main goal is to make sure that their journey is as comfortable as possible. I have used cannabinoids in cancer patients, and it works for some but not for others. Alongside prescribing for pain, I also prescribe cannabinoids for muscle spasms caused by neurodegenerative diseases. Many of my other patients, for example, have Parkinson's Disease.

Most commonly, they are referred to because of muscle spasms and rigidity as very common symptoms. They would have already tried gabapentinoids, baclofen, dantrolene, and botox injections. At this stage, I build up a picture of what their condition is causing - does it result in falls or sleep disturbances. I tell them that most of the studies around spasticity come from Multiple Sclerosis and that the studies all use a combination of THC and CBD.

Then, I discuss the side effects of THC - hallucinations, psychosis, intoxication, risk of dependency, risk of addiction which is low, and that there may be a risk of stroke. I also inform them I have seen blood pressure go up, but I've seen blood pressure go down.

I give cannabinoids to patients with nausea from chemotherapy, but I see patients who get more nausea from cannabinoids. I very occasionally give cannabinoids to inflammatory bowel disease to reduce the diarrhoea. Some patients will complain of diarrhoea. I tell them that's the reason why these cannabinoids are not on the Pharmaceutical Benefit Scheme (PBS). And why they are on the Special Access Scheme - because we don't know everything about these medicines at this point.

I give them a dosing schedule, starting low, building up, and then I will review them in a couple of weeks' time to see how they're going, whether there are side effects, or whether they need to increase the dose, split the dose, reduce the dose; that's the follow-up.

I explain that it is part of the Therapeutic Good Administrations (TGA) process to get prescribing authority.

How is that different to a follow-up consult?

At follow-up, I would ask how they got on, what dose they got up to. For example, using a THC:10/CBD:10 per mL solution, with a starting dose 0.1 mL at night, with up-titration every three days by 0.1 mL until they reach 1.0 mL. I've seen patients who can't get beyond 0.1 mL or 0.2 mL.

I can't predict who will and who can't. Even the most robust patients I see can't get past 0.2 mL. I ask about side effects – whether their sleep is better or not. Their sleep may be better, say 0.6 mL (THC 6 mg). Bowels, spasm, pain gets a bit better at THC 8-9 mg per day.

Then, whether they've had any hallucinations, delusions, whether they get intoxicated, whether they're more intoxicated for the first half an hour after they wake, and whether they wake up at night. Most often, they actually go back to sleep much easier. Then I ask about nausea.

I ask them about the efficacy in the various symptoms they have and specifically about adverse events they may or may not have.

Depending on whether they've got good relief, partial relief, no relief, I may say stay on the dose or split the dose, or increase the dose to include daytime and night-time dosing.

I schedule a catch up in two months to see how they are doing.

How do you broach the issue of medicine cessation if it is found not efficacious or there are safety issues?

I talk about the risk of dependency - of almost five hundred patients I've seen only one patient felt withdrawal symptoms from THC. There is an incredibly low risk of withdrawal at low doses. Patients actually feel very relieved to hear that they're not going to get addicted. The dose is much lower (15-20 mg THC) compared to recreational doses (80 -100 mg THC). Having that explanation is important.

We also talk about driving - that it is illegal to drive in Australia, and I, therefore, cannot recommend that you drive – as the level of THC in the patient's blood, urine or saliva makes it illegal, and that cannabinoids will stay in their bodies for up to three to four weeks. I say to some patients, "you're going to have to decide, do you want to give up driving and your independence, or do you want to put up with the pain?" A lot of patients actually prefer to put up with their pain rather than give up driving, rather than giving up their independence.

Patient considerations

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

Part of my initial assessment is to go through all the medications the patients are on. The main medication I'm worried about is the antifungals – in particular fluconazole, which has had a long history of interacting with lots of other drugs – not just cannabinoids.

The other medication is ciprofloxacin; I've seen patients become toxic to THC when started on ciprofloxacin. Some of my colleagues are worried about SSRIs, but I've not seen that clinically. A lot of my patients are already on SSRIs, and I've not seen interactions or problems with it.

It is important to tell patients that cannabinoids interact with liver enzymes meaning other medicines can hang around in the body for a lot longer, causing more side effects. I explain that to them in written form.

For patients on cancer treatments - systemic therapy and chemotherapy - are metabolised and excreted by the liver and kidneys. Cannabinoids may affect blood levels and may increase side effects, or reduce the efficacy of the cancer treatments. That is another consideration for my cancer patients, especially if they want their chemotherapy to work properly.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

Usually, for neuropathic pain patients, I would prescribe a balanced product (THC:CBD), because most of the evidence, whilst limited, is still based on THC to use for neuropathic pain and not CBD alone.

How do you decide on a starting dose? How do you adjust it to achieve an optimal balance between effect and possible side effects?

The main thing is to start low and build it up slowly. Note any potential side effects reported by the patient. We have to make a judgement as to whether it is or not, but I still need to consider it and then decide whether it is a side effect, or whether it's from the disease process itself. That's where having a medical understanding of diseases becomes so important.

You need a very strong understanding of internal medicine and the disease process to be able to make that judgement. I use the Palliative Care Symptom Assessment Scale, which goes through a lot of symptoms like sleep, fatigue, appetite, bowel constipation, pain, et cetera.

It is useful to assess disease progression through time and remind patients where they were before treatment. I use that to help explain to my patients that, for example, "cannabinoids are not going to get rid of your pain, but to make pain a bit more tolerable, and yes, we've made your pain go from 8/10 to 4 or 5/10, and that may be the best we can do".

Sometimes I tell the patient; yes, your pain hasn't gotten better from cannabinoid therapy, but you are now off high-dose Pregabalin, and you are now more awake during the day, and you are actually sleeping better. So, prescribing changes from a focus on pain and toward quality of life is better. It is important we do a multi-dimensional assessment.

Sometimes I tell patients, can you stop cannabinoids for a week, and if your symptoms come back, then you know the cannabinoids actually made the difference. After three or four days. If they want to go back onto it, and yes, they have proven to themselves that the cannabinoids did make the difference. A therapeutic withdrawal, to confirm to the patients that cannabinoids were actually making a difference.

If patients have used recreational cannabis in the past, I would still probably start them at a slightly higher dose than normal; instead of 1-2 mg THC, I may start at 2.5 mg THC in someone who has used it before in the past. It's still a relatively low dose, and you build up slowly.

Administration

What are the key factors in choosing one administration form over another?

The majority of my prescribing is oil (sublingual administration). I find it to be effective and easy to administer.

I use four different types; (1) CBD only if patients want CBD only. I don't advocate for it because there's been little research that CBD will help. (2) balanced products, especially for pain and muscle spasms, (3) low THC high CBD products (i.e., THC 5 mg: CBD 20 mg) for a minority of patients not able to tolerate a balanced product, and for patients with inflammatory arthritis; and, (4) high potency THC (THC 20 mg).

The choice of which product I use also comes down to cost to the patient, given these are not funded products.

I work closely with Basgers Pharmacy, a local pharmacy which is knowledgeable of cannabis-based medicines and always have sufficient stock on hand to ensure prescriptions are able to be immediately filled for patients.

What do patients say about the administration of cannabis-based medicines by oral sublingual? What about oral ingestion?

It is not easy to get drops under the tongue all the time because a lot of my patients are frail. I will say to them, just put it on a teaspoon, and just take it into your mouth, even if it's not under the tongue.

Some patients do not like the taste, so I say they need to wash it down with a mouthful of water or orange juice.

Some patients will swallow the dose, and therefore there may be faster metabolism of the cannabinoids. That is where titration of the dose for each individual patient is required - if they are going to swallow it consistently, then maybe they need a bit more than someone who takes it consistently sublingually.

Safety

Are you aware of any patients who have experienced interactions with other medicines? If yes, please describe the major interactions.

Medicine interactions with cannabinoids are not common - I don't see a lot. The major one that I've seen is someone with respiratory disease, treated with Ciprofloxacin. They were already on cannabinoid therapy for pain and then became intoxicated by THC.

Do you encounter diversion, misuse or abuse of cannabis-based medicines? How do you identify this issue in your clinical practice?

The cost of pharmaceutical-grade cannabinoids helps reduce diversion. It is a bit more expensive than what people get on the black market.

My cannabinoid assessment clinic is a private clinic. There are advantages to this, including private consultation fees, eliminating patients who want cannabis-based medicines for recreational use and being able to self-select patients.

I also tell my patients that pharmaceutical-grade products do not have bacteria, fungi, heavy metals, which is important for patients who are immunocompromised. A lot of them will say, "wow – okay, no, I don't want that".

Prescribing and dose regimen

What are the key benefits of using cannabis-based medicines?

Used in the right hands for the right patients, it will make their symptoms more tolerable. Cannabinoids are often seen as a panacea, which sends up red flags. From my point of view, I have to choose the patients carefully, and explain what I think that cannabinoids may or may not do.

What are the key risks of using cannabis-based medicines?

The risk is the cost for patients; when patients find that cannabinoids are helping them, but they can't afford the cost. It is very hard to know which patients will respond and which patients won't. I think that side effects can be any and everything, and also can occur even in the most robust of patients.

Driving is going to be an issue for a long time to come. That is not going to change for many years.

We need to do a lot more research – proper research if we want to see cannabinoids used as typical medicine.

What do you think are prescribing practices that improve patient outcomes?

A lot of patients come with an expectation that cannabinoids will help them. You also have to say that yes, it will help – it's not going to get rid of the problem altogether – you're only controlling the symptoms – you're not dealing with the cause of the symptoms. I think that you tell patients you can get things better, but not completely gone, symptom-wise. Pain is going to get better, but the pain is going to be there all the time. We don't understand the long-term side effects. We need to explain these side effects very carefully because we are using patients really as an experiment as to whether it's going to work or not.

Final remarks

Do you have any good advice (tips) for doctors starting out?

If you're going to start patients on cannabinoids, start low, and build up slowly. For everyone. Don't think everyone is going to be robust.

Dr Ruben van Coevorden

Dr Ruben van Coevorden is a retired General Practitioner who practised family medicine for thirty five years in the Netherlands. Ruben cofounded a hospice fifteen years ago and continues to provide medical and palliative care to the patients admitted to the hospice. He was involved in the establishment of a Palliative Care Helpdesk, providing consultancy for that service over the last twenty years. Ruben is a current member of the Palliative Team at the Amstelland Hospital in Amstelveen, and recently was recruited as a palliative physician for the Supportive Care Team of the Antoni van Leeuwenhoek Cancer Hospital. Aside from his consultancy services, he participates as a committee member to draft The Royal Dutch Medical Society Guidelines on the subjects: The use of euthanatics, Palliative sedation, and Refraining from food and fluids to hasten death. Additionally, he contributed to the Dutch General Practitioner Society's Guideline for Pain and Cancer.

Training and education

What training did you receive before you started prescribing cannabis-based medicines?

After graduation from medical school, I followed post-academic training. I did the Dutch version of the Cardiff Course on palliative medicine, where cannabis and its use was part of the program. I also followed several lectures on the use of cannabis-based medicines. Since then, I have not gone through any extra or formal training.

Prescribing experience

How long have you prescribed cannabis-based medicines?

I have prescribed cannabis-based medicines for fifteen years.

Can you describe a typical patient to whom you would prescribe cannabis-based medicines?

There are two main groups of patients to which I prescribe cannabis-based medicines. The first group is cancer patients with neuropathic pain. The second main group is MS patients with spasticity and pain.

Thinking about a first consultation with a patient, how do you start a conversation about the use of cannabis-based medicines?

In a first consultation, the focus is on how pain management has been so far. What regular medication options have not been tried. I do not mention cannabis-based medicines at this stage.

Usually, when regular medication has not fully brought pain under control, either the patient him/herself brings up cannabis-based medicines as an option, or I will initiate the subject.

How do you broach the issue of medicine cessation if it is found not efficacious or there are safety issues?

Be open and clear about it. By providing honest information, the patient can make up his/her mind. Shared decision-making is important for patient compliance.

Patient considerations

When prescribing, what are the things to keep in mind?

The most important is contraindications, these include:

- Relative contraindications:
  - Psychosis
  - Psychological problems
  - Cardiovascular problems
  - Adolescents
- Absolute contraindications:
  - Pregnancy and lactation

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

Yes, especially with CYP450 inhibitors and inducers, but there are others to consider.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

The THC and or CBD content in the cannabis-based medicine product.

How do you decide on a starting dose? How do you adjust it to achieve an optimal balance between effect and possible side effects?

I make use of a dosing schedule produced by a compounding pharmacy in the Netherlands (i.e. Cannabiszorg). It describes various indications and the corresponding type of cannabis-based medicines by their THC, CBD or THC:CBD concentration, alongside recommendations for titration for adults and children using an oro-mucosal dose form.

I follow up with patients on efficacy and the presence of side effects. I look at the balance of positive effects and side effects and the overall benefit for the patient.

Administration

What are the key factors in choosing one administration form over another?

The key factor is how easy is it to use the preparation? For instance, sublingual drops are easy to administer.

Smoking is not advised as it is not an appropriate administration method, is unpleasant for the people around the patient. Transdermal administration can be disadvantageous because of poor total absorption and tends to have a strong smell.

In your experience, what are the key benefits of using certain dose forms? What dose form and why?

I choose sublingual droplets of cannabis oil because it is easy to titrate, has no smell, is easy to administer, and are available as a standardised preparation under Government and Independent laboratory control.

What do patients say about the administration of cannabis-based medicines by vaporisation?

I only advise vaporisation when patients are smokers, as they prefer this way of administration.

What do patients say about the administration of cannabis-based medicines by oral sublingual? What about oral ingestion?

Sublingual is preferred by most of my patients. It is well-tolerated, not difficult to use and easy to administer by the patients' partner, family members, volunteers or nurses.

I do not prescribe oral dose forms.

Safety

Are you aware of any patients who have experienced interactions with other medicines? If yes, please describe the major interactions.

Yes, I use fewer opioids when in combination with cannabis-based medicines and/or have achieved better pain control.

Do you encounter diversion, misuse or abuse of cannabis-based medicines?

So far, I have not encountered misuse or abuse. Most of my experience is based on patients at the hospice, where there is 24/7 nurse control.

We identify diversion, misuse or abuse in our clinical practice if there are too early requests for refills, request for new prescriptions.

We spend a lot of time with providing information and communicating with the patient about their safe and effective use of cannabis-based medicines.

Medicine type/dose forms

How is prescribing cannabis-based medicines different to prescribing other medicines?

There are only two pharmacies in the Netherlands (Transvaal Apotheek and SMA Apotheek) that produce cannabis-based medicines. These medicines are not covered by health insurances, and a prescription is compulsory,

except for CBD. All other pharmacies can request the two mentioned pharmacies to provide them with cannabis-based medicines so that their patients can also receive a prescription. Another route is that the patient sends the prescription to one of the two pharmacies mentioned before, and then the cannabis-based medicines are sent by mail to the patient.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

I use the earlier discussed dosing schedule with indications and products by cannabinoid concentration.

Prescribing and dose regimen

What are the key benefits of using cannabis-based medicines?

The key benefits are better pain control in the presence of a neuropathic pain component, less use of opioids, and/or more efficacy of the use of opioids.

What are the key risks of using cannabis-based medicines?

The key risks are side effects and/or medicines interactions.

What do you think are prescribing practices that improve patient outcomes?

Patients who wish to use cannabis-based medicines (who are more confident in this medicine use), patient compliance, effectiveness, absence of side effects.

How do you identify adverse events, report them and learn from other events?

We screen for known side-/adverse effects and mention them in the patient file. Sometimes we include a pop-up warning in the electronic file.

Final remarks

Do you have any good advice (tips) for doctors starting out?

Talk to specialists in the field and read a lot about the use of cannabis-based medicines. Stay away from non-pharmaceutical products, since they are not standardised, not produced under independent lab control and are sold for dubious indications.

In the Netherlands, we have qualitatively excellent medicinally grown cannabis products and at least two pharmacies with a lot of experience and know-how who are ready to consult with prescribers and other pharmacists.

Professor Dr Geert Jan Groeneveld

Professor Dr Geert Jan Groeneveld is a neurologist and clinical pharmacologist with a special interest in neuropathic pain. He is CEO at the Centre for Human Drug Research (CHDR), Leiden, the Netherlands. Previously, Geert Jan has been involved in early clinical phase drug research related to new analgesics, which he undertook at the CHDR. Geert Jan also sees patients with neurological causes of chronic pain in the pain outpatient clinic of the Department of Anaesthesiology of Leiden University Medical Centre (LUMC).

Training/education

What training did you receive before you started prescribing cannabis-based medicines?

I trained as a neurologist and gained experience with prescribing cannabis-based medicines on the job. I was later also trained as a clinical pharmacologist.

Prescribing experience

How long have you prescribed cannabis-based medicines?

I've prescribed cannabis-based medicines for approximately five to ten years.

Can you describe a typical patient to whom you would prescribe cannabis-based medicines?

Most patients are experiencing neuropathic pain, have tried multiple different treatments, and are now considering third-line options.

The other patients I treat are those with chronic pain in the context of, e.g. failed back surgery syndrome or other spinal pain syndromes.

Thinking about a first consultation with a patient, how do you start a conversation about the use of cannabis-based medicines?

I simply ask them, "have you tried cannabis-based medicines before?"

How do you broach the issue of medicine cessation if it is found not efficacious or there are safety issues?

Most of my patients are being treated for neuropathic pain. There are no complications from abrupt cessation, so I just stop them, excluding them from the regimen

Patient considerations

When prescribing, what are the things to keep in mind?

The biggest issues are driving, operating machines, or otherwise. I inform patients to be careful and not to do such activities when using cannabis-based medicines.

There are known pharmacodynamic interactions with opioids, so there may be a need for lower dose levels of co-prescribed opioids.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

I warn patients about high dose levels of CBD and interactions with drugs metabolised by CYP3A4, CYP2C9 or CYP2C19.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

I look primarily at the THC content of the medicine. I don't prescribe CBD alone for pain. If available, I will prescribe a cannabis strain with THC:CBD, approximately 1:1, because of clinical evidence from Sativex®.

How do you decide on a starting dose? How do you adjust it to achieve an optimal balance between effect and possible side effects?

Up-titrate, starting with 1-2 mg, and titrating up until the patient is feeling 'high'. The dose should stay just below the point of a tolerable level of feeling high, usually around THC equivalent of 10 mg.

Do you undertake patient medicine reviews? What factors do you consider?

Yes, see my comments below about PK interactions. PD interactions: opioids.

Administration

What are the key factors in choosing one administration form over another (i.e. oral, pulmonary, transdermal)?

The key to dose form choice is determining whether patients are comfortable inhaling. If not, then droplets of an oily formulation are the next option. This option is slightly more expensive.

In your experience, what are the key benefits of using certain dose forms? What dose form and why?

Oral has advantages because of health, as opposed to inhaling through smoking. Some patients may choose to make tea from cannabis herbal material. Tea has the disadvantage that you have to make it daily, otherwise the active ingredients will stick to the container. It also is a less predictable dose compared to sublingual or pulmonary administration.

What do patients say about the administration of cannabis-based medicines by vaporisation?

Patients who use vaporisation are comfortable with it and hence tolerate it. But most of my patients will indicate not wanting to inhale.

What do patients say about the administration of cannabis-based medicines by oral sublingual? What about oral ingestion?

As above, most of my patients prefer oral dose forms as they are easy to use.

Safety

Are you aware of any patients who have experienced interactions with other medicines? If yes, please describe the major interactions.

Yes, CBD has pharmacokinetic interactions (see above – CYP450 interactions).

Do you encounter diversion, misuse or abuse of cannabis-based medicines?

Diversion, misuse or abuse is not a problem in my practice. I've had one case, but years ago. I refused to further prescribe because I felt I was maintaining the patient's 'addiction' rather than treating his pain. He got very angry and stalked me on Twitter for some time.

Medicine type/dose forms

How is prescribing cannabis-based medicines different to prescribing other medicines?

Given there is no reimbursement for cannabis-based medicines (i.e., they are paid in full by the patient), there is a need to inform the patient appropriately about the ongoing costs of treatment.

There are separate instructions required in the case of preparing and administering a cannabis-based tea. This requires a different set of information and way of prescribing compared to sublingual dose forms (i.e. oils).

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

I specifically take into account the THC content of the medicine, given the risk of overdosing.

Prescribing and dose regimen

What are the key benefits of using cannabis-based medicines?

The key benefits are in treating pain in some patients, and improving sleep in some, too.

What are the key risks of using cannabis-based medicines?

The key risks are the significant side effects of overdose, which include mild euphoria (i.e., hallucinations). There is the issue of driving while intoxicated, or feeling drowsy, which must be discussed fully with patients.

What do you think are prescribing practices that improve patient outcomes?

Starting at a low dose, and then up-titrate based on if the patient is feeling 'high'. However, it should be noted that feeling 'high' reduces with use after one to two weeks.

How do you identify adverse events, report them and learn from other events?

Cannabis-based medicines are just like other medications. I see patients back at the clinic within one to two weeks after starting treatment. I ask specifically about feeling 'high', hallucinations, or other side effects.

Final remarks

Do you have any good advice (tips) for doctors starting out?

Try it. Get the experience yourself!

Professor Dr Gerhard Kurlemann

Professor Dr Gerd Kurlemann is a paediatrician and paediatric neurologist. For more than twenty years, he was head of the Department of Pediatric Neurology at the University in Münster, Germany. Since 2018 he has retired from the University Hospital and is currently working in a specialised centre for pediatric neurology at the Bonifatius Hospital in Lingen, Germany. His areas of expertise are developmental disorders, children with epilepsy, therapy-resistant epileptogenic disorders in children (e.g. Dravet syndrome, tuberous sclerosis, intrauterine epileptic insults), skin and nervous system, pediatric movement disorders.

Training/education

What training did you receive before you started prescribing cannabis-based medicines?

No training. I read a lot. See one, do one, teach one.

Prescribing experience

How long have you prescribed cannabis-based medicines?

I started about ten years ago. Initially, I was mainly prescribing THC for children with therapy-resistant epilepsy, for children with spasticity to reduce their muscle tone. For the last five years, I have been prescribing mainly CBD oral solution because it is a registered substance for some sorts of epilepsy in children aged from two years old.

Can you describe a typical patient who you would prescribe cannabis-based medicines?

In my practice, there are three groups of children who might benefit from CBD:

1. Therapy resistant epilepsy – before starting with CBD, all first- and second line anti-epileptics were discontinued; all common anti-epileptic drugs were used beforehand
2. Children suffering from autism – not responding to neuroleptics
3. Children with spasticity
4. I am also open to other indications

Thinking about a first consultation with a patient, how do you start a conversation about the use of cannabis-based medicines?

The use of CBD has been evaluated in randomised-controlled trials, especially in paediatric patient groups. The spectrum of side effects is well known, with no serious side effects having been identified, and none are life-threatening.

The prescribing of CBD is not complicated. Therefore, I personally address the use of CBD in these situations, but often the parents raise the question if CBD is an option for their children. Indeed, for a long time now, families have come to my clinic specifically to discuss CBD for their children.

In my daily practice, I do discuss the pros and cons openly, the possible side effects, such as the possibility of diarrhoea caused by the oily suspension. If this creates a problem, then CBD suppositories can be used.

Patient considerations

When prescribing, what are the things to keep in mind?

When prescribing CBD, I have not observed any psychiatric side effects. When prescribing THC, I have observed psychotropic side effects in one child. After stopping THC, the side effects improved. When prescribing CBD, it is important to consider possible interactions with Clobazam; possibly get a blood concentration if the child becomes drowsy or sedated. Rarely there is also interaction with valproic acid from an increase of liver enzymes. Usually, this is uncomplicated. But this has to be considered in children with Lennox-Gastaut syndrome. CBD does not create any interactions with fenfluramine, which is prescribed for children with Dravet syndrome.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

Yes – see above.

What are the key factors in choosing one cannabis-based medicines product over another to treat a specific symptom?

In Germany, it is fairly simple as only CBD oil is a registered medicine. THC needs to be specially prescribed in a special prescribing scheme. I use CBD oil exclusively and only medicinal CBD oil because with this preparation, I can rely on the dose which is indicated on the package. I do strongly advise against the use of CBD oil available in 'drug stores' (given there is no quality control).

How do you decide on a starting dose? How do you adjust it to achieve an optimal daily dosage?

I start with 5 mg/kg in almost all children. I increase the dose by 5 mg/kg per day.

Depending on the effect, I try to find the optimal dose for each individual.

Administration

What are the key factors in choosing one administration form over another (i.e. oral, pulmonary, transdermal)?

For pediatric patients with epilepsy, autism, spasticity, I prescribe only an oral solution. I would rarely prescribe a suppository (i.e. in patients experiencing diarrhoea caused by the oily suspension).

In your experience, what are the key benefits of using certain dose forms? What dose forms and why?

In children, only oral and suppositories are possible.

What do patients say about the administration of cannabis-based medicines by vaporisation?

In paediatrics, only oral and suppositories are available.

Safety

Are you aware of any patients who have experienced interactions with other medicines? If yes, please describe the major interactions.

CBD and Clobazam interact, resulting in increased blood concentration of clobazam. This must be discussed initially as some children may become drowsy or sedated.

CBD taken together with valproic acid may result in elevated liver enzymes.

Do you encounter diversion for misuse or the abuse of cannabis-based medicines?

This is not an issue with children and CBD.

Medicine type/dose forms

How is prescribing cannabis-based medicines different to prescribing other medicines?

There is no difference.

What are the key factors in choosing one cannabis-based medicines product over another to treat a specific symptom?

I am using CBD oral solution exclusively.

Prescribing and dose regimen

What are the key benefits of using cannabis-based medicines?

It is being used as a trial to reduce epileptic fits in children with therapy-resistant epilepsy, reduce muscle tone in children with spasticity, and improve the behaviour of children with autism.

What are the key risks of using cannabis-based medicines?

There are few risks.

What do you think are prescribing practices that improve patient outcomes?

See above.

How do you identify adverse events, report them and learn from other events?

It is important to have good informed consent from parents, and during the course of treatment, to be always open to questions.

Final remarks

Do you have any good advice (tips) for doctors starting out?

In the pediatric area, CBD is fairly easy to handle. No serious side effects or complications

Dr Zvia Rudich

Dr Zvia Rudich is an anaesthesiologist and a pain specialist at the pain clinic within the Division of Anesthesia, Soroka University Medical Center, Be'er-Sheva, the Negev, Israel. Soroka is one of the largest hospitals in Israel, treating a young and culturally diverse population. Zvia undertook a pain medicine fellowship with the Mount Sinai Hospital-Toronto Pain Programme, where she gained initial experience with the clinical use of cannabis-based medicines. She is a co-author of research articles exploring the prognosis and treatment of pain, including cannabis-based medicines. As a member of the Israeli Pain Association, she contributed to the development of Israel's cannabis-based medicine policy including the use of cannabis-based medicines.

Training/education

What training did you receive before you started prescribing cannabis-based medicines?

I undertook the Israeli Medical Cannabis Agency Programme for medical specialists prescribing cannabis-based medicines. However, I was first exposed to patients being prescribed cannabis extracts in 2001, during my pain programme fellowship at the Hospital for Sick Children in Toronto.

My colleagues and I evaluated the effectiveness of dronabinol for the treatment of neuropathic pain refractory to previous treatment and published our results – Rudich, Z., Stinson, J., Jeavons, M., Brown, S. (2003). Treatment of chronic intractable neuropathic pain with dronabinol: case report of two adolescents. Pain Research and Management; 8(4):221-4.

Since then, cannabis-based medicines have gradually gained popularity among Israeli pain physicians.

Prescribing experience

How long have you prescribed cannabis-based medicines?

Over the past 20 years, I have prescribed cannabis-based medicines to a few hundred patients. In the last 5 years, the number has increased as these medicines have become more popular and easier to prescribe.

Can you describe a typical patient to whom you would prescribe cannabis-based medicines?

In Israel, any medical specialist can recommend cannabis-based medicines in their field of specialty – after exhausting other available pharmacological or invasive procedures. In my specialty (in the pain clinic), the indications I am allowed to prescribe cannabis-based medicines are: neuropathic pain, cancer-related pain, pain related to inflammatory bowel disease, and multiple sclerosis. Within this framework, I typically prescribe cannabis-based medicines to patients with pain that is associated with a significant affective component, pain associated with sleep disturbances, and/or anxiety.

Thinking about a first consultation with a patient, how do you start a conversation about the use of cannabis-based medicines?

I start by explaining the pros and cons to the patient (just like any other medication). I emphasise the overall approach and specifically that cannabis-based medicines should be viewed as medicine (not a harmless 'natural' remedy). For example, in elderly, I would explain the risk of memory impairment and risk of dizziness and falls. In patients living with obesity, I would explain the risk of overeating (appetite stimulation) and the potential for weight gain. In young patients (< 30 years old, and even more so if < 20 years old) I would explain the risk of inducing psycho-affective disorders.

How is that different to a follow-up consult?

In the follow-up consult, I will make sure to ask about the specific side effects potentially associated with cannabis-based medicines, and whether the medicine produces the predicted beneficial effect – for example, pain reduction, sleep quality, functionality, and improved appetite.

How do you broach the issue of medicine cessation, if it is found not efficacious or there are safety issues?

Just like any other medicine, serious safety issues will require the immediate cessation of use—for example, psychiatric illness or untoward effects, or falls. If the medicine does not seem to be efficacious, I will try to consider ways to optimise the treatment before making the decision for cessation.

Patient considerations

When prescribing, what are the things to keep in mind?

There are a number of issues to consider:

- Driving is not allowed under the influence of cannabis-based medicines.
- In elderly, there is a risk for memory impairment, and risk of dizziness and falls.
- In patients living with obesity, there is a risk of overeating (appetite stimulation) and weight gain.
- In young patients (< 30 years old, and even more if < 20 years old), there is a risk of inducing psycho-affective disorders.
- There is a risk of decreased motivation (a-motivational syndrome), particularly in patients in active physical rehabilitation programmes.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

There are a number of potential interactions:

- Warfarin (official warning by the Israel Ministry of Health);
- Patients taking sleep medication (I initiate therapy with extra care, eventually replacing them with cannabis-based medicines).
- Pregabalin (may potentiate dizziness and sleepiness).

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

The THC:CBD content of the medicine is largely based on the individual response. I would start with a low-THC remedy.

For sleep disorders, I prescribe an oil-based cannabis extract, recommending to take 2-3h prior to the time they wish to go to bed.

For breakthrough pain, I recommend inhalation of a cannabis herbal product.

How do you decide on a starting dose? How do you adjust it to achieve an optimal balance between effect and possible side effects?

In determining a starting dose, I would consider a low THC medicine, and titrate upwards according to the personal response. Typically, with a THC:CBD ratio (5:5 or 10:10) oromucosal product, I would initiate with one to two drops, and setting top doses at each step. At the beginning, I would make sure to follow the patient at least bi-monthly.

Do you undertake patient medicine reviews? What factors do you consider?

I do ask patients to keep a diary of symptoms and side effects. In particular, the efficacy of the medicine on pain, sleep, and vitality.

Administration

What are the key factors in choosing one administration form over another (i.e., oral, pulmonary)?

The rapidity of the effect after administration, how long its effect is expected, and personal preference.

In your experience, what are the key benefits of using certain dose forms? What dose form and why?

In neuropathic pain, I tend to start with a THC:CBD combination because the CBD component tends to moderate the psychoactive effects of THC. After initiation of treatment, the adjustment is based on individual response.

What do patients say about the administration of cannabis-based medicines by vaporisation?

Vaporisers are expensive. So patients who smoke prefer smoking cannabis. Non-smokers usually prefer oil (oromucosal administration), but if they suffer from breakthrough pain, they prefer vaporisation over smoking. A vaporiser is better tolerated than smoking.

What do patients say about the administration of cannabis-based medicines by oral sublingual?

Non-smokers prefer an oil extract for oromucosal administration. Some prefer an olive oil-based extract, and some prefer an odour/taste-less oil-based extract. The taste is the main subject of complaints.

Safety

Are you aware of any patients who have experienced interactions with other medicines? If yes, please describe the major interactions.

See above: with sleep medications; anticonvulsants and anxiolytic medications.

Do you encounter diversion, misuse or abuse of cannabis-based medicines? How do you identify this issue in your clinical practice? How do you deal with this issue in your clinical practice?

I believe I do, but I seldom can be sure.

I suspect overdosing beyond subscription when there are obvious side effects not expected with the prescribed dose. Or when there is manipulative behaviour aimed at increasing the dose and the THC component that does not match with the clinical picture.

It is crucial to get to know the patient over time before the first prescription. We compare the percentage of cannabis-based medicines prescribed to patients to that in other pain clinics. We monitor the dose prescribed.

Medicine type/dose forms

How is prescribing cannabis-based medicines different to prescribing other medicines?

I don't think it is much different in terms of considering indications and side effects, and communicating them with the patient. A major thing is that there is variability between preparations, seasons, batches, species, which need to be taken into consideration.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

I mainly treat pain-related symptoms, as explained above.

For sleep disorders, I prescribe a sedating 'indica' oil-based cannabis extract, recommending to take it sublingually two to three hours prior to the time they wish to go to bed.

For breakthrough pain, I recommend inhalation of cannabis herbal products – an uplifting 'sativa' species for daytime and a sedating 'indica' for nighttime.

THC:CBD content is largely based on the individual response. I would start with a low-THC medicine.

Prescribing and dose regimen

What are the key benefits of using cannabis-based medicines?

For those who respond well, it may be a better option than opioids in terms of side effects and risk of addiction. Prescribing cannabis-based medicines may allow a decrease (or cessation) in the use of opioids. In addition, there is a positive effect on well-being and functionality, which extends beyond the analgesic effect.

What are the key risks of using cannabis-based medicines?

The key risks include psychiatric illness, driving (accidents), falls, and cognitive effects (memory).

What do you think are prescribing practices that improve patient outcomes?

Starting slow (low dose), and a highly personalised titration of dose.

How do you identify adverse events, report them and learn from other events?

Directly questioning patients on the possible side effects, and discussing patients' medication diary and in-person reports.

Final

Do you have any good advice (tips) for doctors starting out?

Remember, it is a medication like any other (even though it is not a synthetic pharmaceutical). Know your patient very well before initiating prescribing cannabis-based medicines, including how the individual patient copes with their pain. I feel cannabis-based medicines help more when sleep disturbances and/or affective components of pain are higher.

Dr Somchai Thanasitthichai

Dr Somchai Thanasitthichai has worked as an oncologist for more than thirty years. Currently, he is the Managing Director of the National Cancer Institute of Thailand. He has also been the Director of the Institute of Medical Research and Technology Assessment, of The Department of Medical Services, The Ministry of Public Health, Bangkok, Thailand. In that role, as one of the pioneers of cannabis-based medicine use in Thailand, he was assigned as the government official to assess the safety and efficacy of cannabis-based medicines and to implement medicine policy for their therapeutic use in Thailand. Somchai is also a lecturer in the use of cannabis-based medicines.

Training/education

What training did you receive before you started prescribing cannabis-based medicines?

Over the last ten years at the Cancer Institute, my work has been to prove which alternative medicines could be used for patient treatment, or accompanied by a current conventional treatment. I recognised the limitations of conventional treatments, which are focused on the early stages of cancer. There are a lot of patients who suffer because we cannot cure or satisfy their clinical needs with the treatment – cannabis-based medicines may meet those unmet needs.

In palliative, there are pros and cons, the evidence is limited, and it is not conclusive. Likewise, in cancer treatment, I have to evaluate the use of cannabis-based medicines.

My training in cannabis-based medicines started at this point.

Prescribing experience

How long have you prescribed cannabis-based medicines?

I've prescribed since 2019, with the implementation of the programme at the National Cancer Institute.

Can you describe a typical patient to whom you would prescribe cannabis-based medicines?

As a government officer, our prescribing policy considered which patients would present the lowest risk to public health, patients who are least likely to be harmed by these medicines.

The first group are patients in palliative care, end-of-life care, because they will not have a risk of addiction. This group of patients have fewer choices for treatment – mainly opioids – and they have no further curative treatment. They get the most benefit from cannabinoids and are at less risk from long-term use.

The second group is children who have epilepsy, given the current evidence.

We started with these two groups of patients.

Thinking about a first consultation with a patient, how do you start a conversation about the use of cannabis-based medicines?

At the first consultation, we inform patients that we are undertaking research, given this is the first time these medicines are being used in Thailand.

As part of the ethical consideration, we have informed consent in every patient, providing all relevant information on the benefits and risks, how we minimise the risks and care for them, and what monitoring and observations will occur. Patients choose to go into the project or not.

Patient considerations

When prescribing, what are the things to keep in mind?

We select patients who are quite healthy, even in the later stages of a disease. We try to minimise risk because we don't know the full adverse-effect profile, even though we know the mechanisms. We know possible medicine interactions, so we exclude all of the possible medicines among the medicines in the patient's regimen, so there are no problems arising from drug interactions.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

The Government Pharmaceutical Organisation (GPO) produced the first pharmaceutical-quality cannabis-based medicine not only in Thailand, but in Asia.

We do not know fully about the safety and efficacy. The pilot projects at the National Cancer Institute aimed to evaluate the safety first, and the possibility of the efficacy among in-patients at the end stage of cancer.

We know that everybody responds differently. We know vulnerable patients may be affected by poor hepatic metabolism. We worked with the GPO to make the preparations with mild concentrations and balanced THC and CBD options.

Our protocol, in the first instance, was to implement a balanced THC:CBD product, as CBD counteracts the adverse effects of THC. We start at a really low dose, and we try to start dosing at bedtime to avoid confusion and falls. As in patients, we were able to observe their responses.

How do you decide on a starting dose? How do you adjust it to achieve an optimal balance between effect and possible side effects?

We start prescribing at a really low dose - one drop or 1.0 mg THC plus CBD.

We try to start at dosing bedtime, so maybe they're asleep, and they have no confusion. After 48 hours, we increase another drop, and so on, like that. Every patient id different, so we observe their response across all patients. That is the protocol that we set.

One drop to ten drops is enough, but the average dose for most of our patients in palliative care is just 1-2 mg per day. Maximum is 1-4 mg per day is enough for improving the quality of life. To evaluate the quality of life, we use a multifactor symptom assessment scale - such as pain, insomnia, sleep patterns, mood, and overall feeling.

We found no drug interactions or early forms of adverse effects. However, some patients in palliative care have brain metastasis, and are prone to hallucinations. Cannabis-based medicines enhance the possibility of hallucinations. In one case, after one or two doses THC:CBD medicines, they got hallucinations in the nighttime, but it was reversible after ceasing the medicine.

Administration

What are the key factors in choosing one administration form over another (i.e. oral, pulmonary, transdermal)?

We use sublingual drops. The first time our nurses administer it for the patients, because patients take too much, or place too many drops in the wrong place in the mouth, or not. Before patients leave hospitals, we train them how to use the dropper.

Additionally, every patient is admitted to an in-patient setting. In the first stage, it is fourteen days, and after that, we found that the medicine is safe. We can then reduce the in-patient times to ten days, seven days, and less time, respectively.

Safety

Are you aware of any patients who have experienced interactions with other medicines? If yes, please describe the major interactions.

We typically use a balanced THC and CBD medicine. The dose is very small in the first phase; only 1 mg at a time for a couple of days is enough for the quality of life. So, it's a very low dose, and with this dose, it is no problem with medicine interactions.

Do you encounter diversion, misuse or abuse of cannabis-based medicines? How do you identify this issue in your clinical practice?

We know the appropriate dose. That means that we can calculate the dosage for one month - the number of bottles they will use under normal conditions is not more than 1.5 bottles. Second thing, we do not prescribe or dispense too many bottles for them.

We also have nurses monitor patients by calling and checking for side effects, and efficacy, and we adjust the dose if necessary.

Medicine type/dose forms

How is prescribing cannabis-based medicines different to prescribing other medicines?

When we implemented cannabis-based medicines as a public health intervention in Thailand, we had to be 95 per cent confident of the result, good or bad. There are idiosyncrasies related to pharmacokinetics or pharmacodynamics which we still cannot predict. Monitoring patients is important.

Prescribing and dose regimen

What are the key benefits of using cannabis-based medicines?

We know sometimes that there are side effects, but these can be controlled to benefit patients. For example, THC can make patients sleepy if they have problems with insomnia. We can use this side effect to the benefit of the patient. The same thing is true for anorexia in cancer patients; this kind of medicine can stimulate the desire to eat and can improve the nutrition of the patient.

Stress is often caused by patient's symptoms, so we can alleviate the symptoms by supplementing with cannabinoids. We can calm the stress symptoms, and prevent long-term risk by using cannabinoids.

What are the key risks of using cannabis-based medicines?

Addiction is the most important risk that I think for the long-term. However, we know that if the patients use just short-term, we see no problem or addiction.

Patients do not want to die, so they look for every method, or every means that might give them hope of a cure or treatment for the disease. A lot of people then drop off from the conventional treatment, even in the early stage, in favour of a 'panacea'. We have to ensure patients do not think cannabis-based medicines will cure their disease, but rather that it is part of their overall regimen.

Final remarks

Do you have any good advice (tips) for doctors starting out?

The first thing is to have the knowledge, know the mechanisms of action, know the mechanisms of side effects and adverse events, and the mechanism of drug interactions. After you know about these things, you will be more confident about the safe and effective use of cannabinoids.

Good knowledge will mean you will not misuse, over-use or under-use cannabinoids in your patients. You will use your knowledge of the mechanisms to help the patients - the main purpose of using cannabinoids is to improve the quality of life.

The second thing is when you face the dark, do not work in the dark, and put the light on. Do your research. Figure out what is occurring. Investigate all options, and do it in a scientific way.

Dr Patrick Welsch

Dr Patrick Welsch is a senior physician and pain medicine specialist at the multi-disciplinary Health Care Centre for Pain Medicine and Mental Health, Saarbrücken-St. Johann, Germany – a regional DGS pain centre. For the past twenty-six years, he has treated patients with chronic pain in an in-patient and out-patient setting. Patrick is a Fellow of International Pain Practice and member of the German Society for Pain Medicine, and co-author of several research articles exploring the use of various drug and non-drug therapies in the treatment of pain, including cannabis-based medicines.

Training/education

What training did you receive before you started prescribing cannabis-based medicines?

I am a specialised pain therapist and Fellow of International Pain Practice (FIPP). I have attended multiple training about cannabis-based medicines, amongst others, by Professor Sven Gottschling - chief physician at the centre for palliative medicine and child pain therapy at the Saarland University Hospital.

Prescribing experience

How long have you prescribed cannabis-based medicines?

I have prescribed for about three years.

Can you describe a typical patient to whom you would prescribe cannabis-based medicines?

Patients with chronic pain who do not achieve adequate pain control and quality of life improvement, despite prescription of WHO III medications and antidepressants/ anti-epileptics.

The two main patient groups include patients suffering from neuropathic pain, and patients with high muscle tone, muscle spasms, and sleep disorders.

Thinking about a first consultation with a patient, how do you start a conversation about the use of cannabis-based medicines?

The problem in Germany is that although cannabinoids can be prescribed, reimbursement by health insurers may be difficult as government regulations can be interpreted in different ways. As a result, the full medicine cost may fall upon patients.

How do you broach the issue of medicine cessation, if it is found not efficacious or there are safety issues?

I would broach the issue in the same manner as I would do it with other medications (e.g. opioids). I consider it helpful to issue a treatment contract with the patient in which several key points in the usage of cannabinoids are stated.

Patient considerations

When prescribing, what are the things to keep in mind?

The key things to keep in mind are: patient compliance, contraindications, and the patient's history.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

Yes, but limited experience with patient medicine interactions.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

We have limited experience with patient medicine interactions, and also, due to limited published evidence (with the exception of MS), we have decided in my practice to prescribe exclusively dronabinol (THC) drops for the time being.

How do you decide on a starting dose? How do you adjust it to achieve an optimal balance between effect and possible side effects?

After getting approval by the health insurers, we titrate up according to effect and side effects. Typically we start with one drop three times a day and increase every three to four days by one drop three times daily.

Do you undertake patient medicine reviews? What factors do you consider?

The key factors in my patient populations are heart rhythm disorders (e.g. long QT) and previous experience with cannabinoids (i.e. recreational use).

Administration

What are the key factors in choosing one administration form over another (i.e. oral, pulmonary, transdermal)?

See above

We prescribe cannabis herbal material (cannabis flos or granulate) exclusively if a patient is already using it on a prescription by another prescriber. When we take over care, we continue it.

What do patients say about the administration of cannabis-based medicines by vaporisation?

See above

What do patients say about the administration of cannabis-based medicines by oral sublingual?

We see no problems at all with oral or sublingual administration.

Safety

Are you aware of any patients who have experienced interactions with other medicines? If yes, please describe the major interactions.

Patients that have experienced tachycardia and dizziness resulting from THC administration.

Do you encounter diversion, misuse or abuse of cannabis-based medicines? How do you identify this issue in your clinical practice? How do you deal with this issue in your clinical practice?

I'm not very concerned about this issue, given our current practice in prescribing opioids.

We use a patient contract in which several key points in the usage of cannabinoids are stated.

The use of a patient contract, alongside good communication.

Medicine type/dose forms

How is prescribing cannabis-based medicines different to prescribing other medicines?

I see no difference in prescribing cannabis-based medicines compared with other medicines we use in pain medicine.

What are the key factors in choosing one cannabis-based medicine product over another to treat a specific symptom?

Until now, I have no idea.

Prescribing and dose regimen

What are the key benefits of using cannabis-based medicines?

In some patients, during in-hospital testing, we see variable effects on the amelioration of:

- Mood
- Muscle tonicity
- Sleep
- Intensity of pain

What are the key risks of using cannabis-based medicines?

Ignorance of the risk of cannabis-based medicines – including an understanding of medicine interactions, contraindications etc.

What do you think are prescribing practices that improve patient outcomes?

Regular follow-ups with patients and good communication to improve patient adherence to the prescribed protocol, including the use of a contract.

How do you identify adverse events, report them and learn from other events?

Adverse events are identified during patients follow-ups and discussed during supervisory meetings.

Final remarks

Do you have any good advice (tips) for doctors starting out?

Yes. Read the text Cannabis: Verordnungshilfe für Ärzte by Franjo Grotenhermen.

Dispensing: discourse with pharmacists

In alphabetical order interviews conducted in 2023:

- Christopher Georges, a community pharmacist from Australia
- Waranya Krongkaew, a hospital pharmacist from Thailand
- Annunziata Lombardi, a compounding pharmacist from Italy
- Arwin Ramcharan, a community pharmacist from the Netherlands
- Dennis Stracke, a community pharmacist from Germany

Christopher Georges

Christopher Georges is an experienced community pharmacist from Basgers Pharmacy, Sydney, Australia. As a community pharmacist, he is focused on patient health and well-being. Christopher has a strong interest in both wound care and cannabis-based medicines. Working closely with prescribers, since 2018, he has dispensed approximately 20,000 cannabis-based medicine prescriptions.

Training/education

What training did you receive before you started dispensing cannabis-based medicines?

No formal training. Education provided by some suppliers and professional organisations - CPD accredited training.

I am unaware of any formal training for dispensing cannabis-based medicine. Most of my knowledge has been acquired during my day-to-day work.

Dispensing experience

How long have you dispensed cannabis-based medicines?

Since 2018, I have dispensed approximately 20,000 cannabis-based medicine prescriptions.

Can you describe a typical patient to whom you would dispense cannabis-based medicines?

I would not say there is a 'typical' patient. The demographics we come across vary greatly from babies being treated for treatment-resistant epilepsy to geriatric patients being treated for chronic pain.

The top two patient populations who seek treatment from my experience are patients with chronic pain and patients with anxiety/mood disorders, including insomnia.

Thinking about a first interaction with a patient, how do you start a conversation about the safe and effective use of cannabis-based medicines?

During a first interaction with a patient, a number of steps are taken, including:

- Identify previous cannabis use (i.e., recreational use)
- Confirm the correct product has been prescribed (e.g. CBD/THC or combination)
- Confirm with the patient the directions the prescriber has provided
- Explain dose titration
- Explain the risk of side effects
- Explain how the medication should be consumed (e.g. oral or vaporisation)
- Explain how the product should be stored
- Answer any questions the patient might have

How is that different to follow-up interactions at the pharmacy?

We generally do not go through all the steps again. We try to ascertain if the product has been effective and if there have been any side effects. We provide advice about further dose titration and management of side effects if they occur. If the product is not at all effective, we suggest a follow- up consult with the prescriber to consider switching formulations and/or dosage forms.

Patient considerations

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

There are a number of medicine interactions patients need to be wary of.

Some of the most important are with some epilepsy medications, HIV medications and those that can cause drowsiness.

Alcohol is another important consideration, as well as drugs metabolised by CYP450 enzymes.

Administration

Oral dose forms (oil extracts) are an increasingly popular mode of administration. What advice do you give patients on safe use?

With oral dose forms, gradual dose titration is important. The onset of effect is approx. 45 minutes – effects generally last 6-8 hours.

We recommend that the patient does not lie down for approx. 15-20 minutes to avoid aspiration. Food can affect an oral dose absorption profile. And patients should store their medicine in a cool, dark place.

Vaporisation is an increasingly popular mode of administration. What advice do you give patients on safe use?

We recommend that patients use a reliable and reputable vaporiser. We suggest the Australian Therapeutic Goods Administration approved devices to ensure the quality and safety of the device.

The patient should not smoke cannabis herbal material – it is safer to vaporise, and it is more effective. The onset of effect is approx. 2-10 minutes. Patients should take one inhalation and wait several minutes before taking another. The length of effect is usually 2-4 hours.

What do patients say about the administration of cannabis-based medicines by vaporisation?

Vaporisation is useful for patients who need a quick onset of action, such as those who suffer from acute pain or insomnia. Patients find this more useful than oils/capsules.

What special considerations should pharmacists be aware of for patients taking oral dose forms?

The main factors are driving issues (especially given a long duration of effect), drug interactions, and storage.

Safety

Are you aware of any patients who have experienced interactions of cannabis-based medicines with other medicines? If yes, please describe the major interactions.

No major side effects have been reported due to drug-drug interactions. Most experience additional drowsiness when combined with other drugs such as benzodiazepines and opioid painkillers.

From a pharmacist's point of view, what are the actual and potential complications with cannabis-based medicines?

Actual complications include drug interactions, driving restrictions, inappropriate dosage forms selected by the prescriber.

Potential complications include a lack of acceptance by the wider medical community, social stigma, and the additional regulatory burden falling on health professionals.

These medicines are expensive compared to other treatments that are government-funded.

What is the role of the pharmacy profession in ensuring patient safety with the use of these medicines?

Pharmacists must counsel and educate patients for the most effective use of the prescribed medication.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines? How do you identify this issue in your practice? How do you deal with this issue in your practice?

I have not experienced this as the price of the medication makes it relatively unattractive for diversion, misuse, or abuse.

Excessive use, patients requesting re-fills prior to their allocated repeat interval.

A discussion with the prescriber would be required.

Medicine type/dose forms

How is cannabis-based medicines different to storing and dispensing other medicines (for both herbal material and for oral dose forms)?

The storage is determined by the scheduling allocated by regulatory bodies. Those with THC need to be stored in a drug safe; CBD-only products can be stored with regular medications. Therefore storage is determined by regulation.

It is the same with dispensing – each product needs to be dispensed in accordance with government legislation, just like any other medication.

Are there any special considerations you make when dispensing cannabis-based medicines (i.e. oil extracts)?

No

Are there any special considerations you make when dispensing a 'herbal' medicine (as cannabis flos)?

Ensuring the patient knows they need to use a vaporiser rather than another administration method.

Therapeutic regimen

What are the key benefits of using cannabis-based medicines?

The key benefits of cannabis-based medicines include fewer side effects compared to other medications. They work differently from conventional medications, so they can be useful for treatment-resistant patients. Many patients have previous experience with recreational cannabis, so they are comfortable with it.

What are the key risks of using cannabis-based medicines?

The key risks include driving restrictions, cognitive impairment, tolerance/dependence on THC, diversion and abuse

What do you think are pharmacy practices that improve patient outcomes?

Pharmacists should have regular discussions with patients and their prescribers to tailor treatment to the patient.

How closely do pharmacists work with the prescribing doctor?

We deal with a number of cannabis-specific clinics and work very closely with these doctors. This is usually on a daily basis. We also help independent doctors to access the medication for their patients when they are unsure of the process.

Final remarks

Do you have any good advice (tips) for pharmacists starting out?

- Become familiar with the different dosage forms that are available
- Understand the pharmacokinetics of the different dosage forms
- Become familiar with the available brands and what formulations are available
- Recognise when vaporisation would be more useful than oral liquids
- Understand the regulations before dispensing to avoid problems later on
- Procure information from reputable sources – not online forums etc.

Waranya Krongkaew

Waranya Kronkaew has been a pharmacist at the National Cancer Institute (NCI), Bankok,Thailand, since 2011. Since 2018, she has been the Head of the Pharmacy Department at the NCI. NCI is the leading national institution for cancer control and patient care. Almost one hundred per cent of patients are cancer patients receiving surgical, radiation, and chemotherapy treatment, alongside patient end-of-life care. Her responsibilities at NCI include the control and management of all pharmacists and staff in the pharmacy department, medicine accountability, and the dispensing of: investigational products (IP) in clinical trials (including cannabis-based medicines), targeted therapy/immunotherapy/medicines, and other typical medicines prescribed by the patient's doctor. Pharmacists at the NCI manage the dispensing of IP cannabis-based medicines and provide counselling and essential information on the appropriate and safe use of cannabis-based medicines to patients. Waranya's team of pharmacists manage around twenty new patients per month.

Training/education

What training did you receive before you started dispensing cannabis-based medicines?

I've trained on the topic 'Cannabis management for healthcare professionals' by the academic department of the Department of Medical Services, The Ministry of Public Health, Thailand.

I have received some online training provided by the Department of Medical Services, Ministry of Public Health Thailand. This course is scheduled annually. Furthermore, I received training from the pharmaceutical company manufacturing this product (GPO).

Dispensing experience

How long have you dispensed cannabis-based medicines?

I have dispensed cannabis-based medicines for over two years

Can you describe a typical patient to whom you would dispense cannabis-based medicines?

The two main patient groups are:

1. The cancer patient who is willing to use cannabis-based medicines.

2. The palliative patient who is prescribed opioid medicines for pain relief but are not completely efficacious, and the doctor considers cannabis-based medicines will help them.

Thinking about a first interaction with a patient, how do you start a conversation about the safe and effective use of cannabis-based medicines?

The dispensing pharmacist will follow up with patients after receiving the prescribed cannabis-based medicine by phone on day three, day seven, and after 1 month. After which, the patient will have been consulted with their prescribing doctor.

Patient considerations

Thinking about a first interaction with a new patient, how do you start a conversation about cannabis-based medicines?

For new patients (cancer patients), I will clearly explain the main purpose for using cannabis-based medicines, that it is not the main medicine to treat the symptoms of their disease, but it is an optional choice to help treat some of the symptoms of the disease.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

Some of the patients who received cannabis-based medicines from our pharmacy have experienced adverse reactions like headaches, 'tingling', and nausea.

Administration

Three cannabis extract products, produced by The Government Pharmaceutical Organisation (GPO), are available to NCI in Thailand:

- Delta-9-THC at 13.16 mg/1 mL, as an oromucosal drop in a 5 mL bottle
- Cannabidiol at 25 mg/1 mL and delta-9-THC at 27 mg/1 mL, as an oromucosal drop in a 5 mL bottle
- Cannabidiol at 100 mg/1 mL, as an oromucosal drop in a 10 mL bottle

Oral dose forms (oil extracts) are an increasingly popular mode of administration. What advice do you give patients on safe use?

I advise the patient to use it strictly as instructed by their doctor. Not to use more than the doctor instructed.

What issues arise for pharmacy practice because of the dose form?

It is the same issue, which is the improper use of the oral dropper. Sometimes, we have received complaints from patients who cannot control the dropper properly, making administration difficult and imprecise.

Vaporisation is an increasingly popular mode of administration. What advice do you give patients on safe use?

Thailand does not have vaporisation as an option, just the cannabis oil with a dropper to dispense to the patient.

What do patients say about the administration of cannabis-based medicines by vaporisation?

As above.

What special considerations should pharmacists be aware of for patients taking oral dose forms?

We focus attention on the other medicines patients currently use because some medicines interact with cannabis-based medicines.

Safety

Are you aware of any patients who have experienced interactions of cannabis-based medicines with other medicines? If yes, please describe the major interactions.

Since I have been dispensing cannabis-based medicines, I have not found that patients experience interaction with other medicines. This is due to our 'cannabis clinic' screening of individual patients' current medicine use before we dispense a cannabis-based medicine.

In some cases, we have found the patient will already be prescribed psychiatric medicines like lorazepam, diazepam, chlorazepam. These medicines should be used with caution due to their interactions with cannabis-based medicines containing THC. When we identify these issues, we consult with the prescribing doctor to assess if it is appropriate for the patient to use cannabis-based medicines.

The prescribing and dispensing of cannabis-based medicines at the NCI 'cannabis clinic' is considered a pilot scheme (collecting data and evaluating the success of cannabis as a medicine). The pharmacist's role includes screening the patient's regimen, and medicines currently used by the patient to assess the risk of medicine interactions or contraindications given the patient's condition. After the patient receives their cannabis-based medicine, we follow up by phone and during their next visit to the 'cannabis clinic'. We ask about side effects or other symptoms they might have. We undertake a pain score and discuss symptom improvement, such as insomnia.

From a pharmacist's point of view, what are the actual and potential complications with cannabis-based medicines?

In my opinion, the main complication of cannabis-based medicines is inconsistent dosing. To treat the symptoms of pain, for example, not every patient will use the same dose (inter-patient variability), and the same dose may vary at or between clinic visits for an individual patient (intra-patient variability). Variability is a complication.

What is the role of the pharmacy profession in ensuring patient safety with the use of these medicines?

The key role of the pharmacist is around patient safety and the cannabis-based medicine, including:

- assisting the prescribing doctor to screen for potential cannabis-based medicine interactions with other medicines currently used by the patient.
- identifying or detecting side effects and adverse drug reactions from cannabis-based medicines during patient calls and visits, and consulting with the prescribing doctor to discuss adjusting the dose appropriate to the patient.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines?

No, I've never found this.

Medicine type/dose forms

How are cannabis-based medicines different to storing and dispensing other medicines (for both herbal material and for oral dose forms)?

Cannabis-based medicines are kept in a secure cabinet, which only a pharmacist or authorised staff can access. An audit (i.e., accountability) of dispensed cannabis-based medicines is performed every month, with a report copied to the director of NCI Thailand and the Thai Food and Drug Administration (FDA).

Are there any special considerations you make when dispensing cannabis-based medicines (i.e. oil extracts)?

I advise the patient to use strictly as recommended and, at the next visit, to return the used dropper bottle to the pharmacy as part of our patient compliance check.

Therapeutic regimen

What are the key benefits of using cannabis-based medicines?

The key benefits are for the treatment of the symptoms of cancer, to make patients feel better.

What are the key risks of using cannabis-based medicines?

The key risks include using the wrong dose, misuse by another person not prescribed the medicine.

What do you think are pharmacy practices that improve patient outcomes?

The pharmacist must provide proper, easy- to-understand information, such as directions for use, describing side effects and potential adverse effects that might occur, and preparing the patient on what to do if a problem occurs when using the medicine at home.

How closely do pharmacists work with the prescribing doctor?

A pharmacist is one of the team members of the 'cannabis clinic' joint meetings. When we have a problem with our patients, we discuss it and find possible solutions.

Final remarks

Do you have any good advice (tips) for pharmacists starting out?

We must realise the proper information and the regular follow up with each patient will help the patient to use cannabis-based medicines safely and achieve the desired therapeutic target.

Annunziata Lombardi

Annunziata Lombardi is head of the compounding laboratory producing magistral preparations at Farmacia Caputo, a family-owned pharmacy in Nocera, Italy. She is a founding member of the Medical Cannabis Committee of the Campania region and was a lead contributor to the regional medicinal cannabis reimbursement law. Annunziata has post-graduate qualifications and professional interests in clinical pharmacy, pharmaceutical-medicine formulation, clinical and traditional compounding, medicine quality control, and regulatory affairs. Additionally, Annunziata directs a laboratory specialising in cannabinoid analysis, providing her insight into various analytical challenges.

Training/education

What training did you receive before you started dispensing cannabis-based medicines?

In 2013, The Italian Ministry of Health had just passed a new law, and I started considering the idea of preparing medical cannabis. Despite scepticism from my family, colleagues and physicians, I decided to challenge the status quo and give this new therapy a try. No formal training was available at that time to prepare me. I still remember my first order 10 years ago, receiving three 5-gram pharmacy containers of Bedrocan® flos. I was nervous. Now, I have dispensed over 20,000 cannabis-based medicine preparations, most as oil extracts for oromucosal administration. The number continues to grow annually.

After an initial learning-by-doing phase, I decided to improve my theoretical and practical knowledge. I travelled to the Netherlands to attend the Cannabis Master Class in Leiden. This training gave me insights which I have used in my daily laboratory practice. Since then, I have linked in with experts in this field with different backgrounds to create a very fruitful network. In 2016, I was one of the founders of the IEO (European Oncology Institute), a cannabis working group with organisations in Naples, Milan and Modena.

Dispensing experience

How long have you dispensed cannabis-based medicines?

I started preparing and dispensing in 2014 as one of the pioneers in the Italian market.

Can you describe a typical patient to whom you would dispense cannabis-based medicines?

There is no typical patient because cannabis-based medicines can be used for all age groups and for multiple pathologies. The Italian National Health Insurance reimburses cannabis-based medicines, as magistral prescription preparations, for a limited number of medical indications: anorexia/cachexia, glaucoma, Tourette syndrome, spasms and pain induced by chemotherapy, vomiting and lack of appetite in chemotherapy patients. In my experience, the most recurrent diseases are chronic pain, fibromyalgia and neurological problems. There is also a growing demand from patients suffering from autism, anxiety, and sleep disorders.

Thinking about a first interaction with a patient, how do you start a conversation about the safe and effective use of cannabis-based medicines?

My role and duty as a pharmacist is to verify that the patient has correctly understood the instructions given by his/her physician. I explain to the patient the pharmacokinetics and pharmacodynamics interactions with other medicines as well.

How is that different to a follow-up interaction at the pharmacy?

The follow-up with the patient covers questions regarding the safety and efficacy of the therapy. I normally use the Medicine Use Review process to interview the patient in a structured and organised way and keep records of their feedback. Additionally, I ask my patients about the positive effects in terms of QOL, symptom improvements such as pain relief, or seizure reduction, and the adequacy of the dosage. Patients also provide feedback on taste and intolerances, which is potentially used to develop new formulations and test new carriers and excipients.

Patient considerations

Thinking about a first interaction with a new patient, how do you start a conversation about cannabis-based medicines?

Assuming that the physician has clearly explained the basics of the therapy, I normally focus on the practical side of administering the medicine. If the administration route is inhalation, I explain how a vaporiser can be operated, cleaned, and maintained. If oral administration is chosen, I talk about the differences between oromucosal and oral administrations and train the patient on the most effective route. Dosage is a crucial point as it often determines the success or failure of a therapy and the drop-out rate. Patients are also interested in the reimbursement criteria and process of the prescriptions, and how to properly store the medicine.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

Yes. Most side effects are caused by interactions with other medicines because cannabinoids may modify our metabolism and influence their performance.

Administration

Oral dose forms (oil extracts) are an increasingly popular mode of administration, what advice do you give patients on safe use?

In Italy, cannabis extracts, for oromucosal dosing, account for 80% of prescriptions. I train my patients on the proper dosage to convert the mg of active substance (THC and CBD) prescribed by the physician into mL and/or drops of extract. This conversion is different for every extract, and it is based on the post-extraction HPLC analytical results. In Italy, pharmacists must analyse the extract for cannabinoid content after production and state this on the label before dispensing. This helps the patient know the amount of active substance taken.

Vaporisation is an increasingly popular mode of administration, what advice do you give patients on safe use?

I recommend the use of a medical device because it guarantees the quality and the reproducibility of the therapy. However, some patients cannot afford a medical device and opt for another type of vaporiser. In any case, I ask the patient to pay attention to two aspects: (1) the vaporiser temperature, because naïve patients may experience major side effects if the temperature is set too high, (2) the timing of the onset of action, which can be extremely rapid with this administration route.

What do patients say about the administration of cannabis-based medicines by vaporisation?

Patients who need an immediate effect to control tremors, intense pain, and seizures appreciate the rapid onset of action provided by inhalation. The main disadvantages of this route are: it is not discrete and often cannot be used in public spaces; the cost of the vaporiser is high; some patients do not have the pulmonary power to actively inhale.

What special considerations should pharmacists be aware of for patients taking oral dose forms?

Pharmacists must inform the patient that the onset of the oral dose form is slow and can take up to 3 hours. The patient must be aware of that and wait for the effect and not take additional medicine.

Safety

Are you aware of any patients who have experienced interactions of cannabis-based medicines with other medicines? If yes, please describe the major interactions.

Typical interactions take place with neuroleptic medicines and lead to, for example, an increase in appetite, dizziness, tachycardia, and fatigue.

From a pharmacist's point of view, what are the actual and potential complications with cannabis-based medicines?

Oil extracts as well as inhalable preparations are not tolerated by every patient. New pharmaceutical forms with improved bioavailability and usability, such as water-soluble solutions, dry inhalable powders, sublingual tablets, oral powders, and so forth, must be developed in the future to access a wider patient base. Another critical aspect of this therapy is the variability of the different Cannabis strains [cultivars]. Current studies have not identified a clear correlation between strain, type and quantity of cannabinoids, pharmaceutical form, and dosage and their effect on specific medical indications. A structured and large data collection using AI is needed to make sense of this complexity and exploit this vast pharmacological treasure.

What is the role of the pharmacy profession in ensuring patient safety with the use of these medicines?

For Italy, it might be a bit different than that of colleagues from other countries. Here, we give a lot of importance to the personalisation of this medicine. Doing an extraction in the pharmacy rather than buying standardised extracts from the industry gives us the full potential for customisation by choosing different Cannabis strains [cultivars], oil carriers, extraction methods, and concentrations. In this case, the pharmacist's role is to make a high-quality product using a safe and reproducible extraction process. In Italy, we have defined some limits and parameters to control the quality and acceptability of compounded cannabis extracts.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines?

Yes, but I consider this phenomenon limited to very few cases. The average quantity of cannabis per patient in Italy is relatively low. Indeed, most Italian patients are using oral extracts rather than inhaling or smoking, which reduces the risk of abuse to a minimum.

How do you identify this issue in your practice?

When I receive prescriptions with very high dosages for inhalation in young patients or the patient finishes the medicine earlier than expected and comes back with a new prescription, I normally become suspicious. I call the patient first, and try to understand why he/she increased the dosage and ran out of medicine. After that, I may call the physician to cross- check this information.

Medicine type/dose forms

How are cannabis-based medicines different to storing and dispensing other medicines (for both herbal material and for oral dose forms)?

I store cannabis in a separate area with restricted and recorded access. Dispensing requires a magistral prescription because it is an off-label medicine. Moreover, it is classified as doping and narcotic which makes it even more complicated.

Are there any special considerations you make when dispensing cannabis-based medicines (i.e. oil extracts)?

I make sure that the patient has clearly understood the therapeutic plan prescribed by the physician, and I check potential interactions with other medicines. With oil extracts I pay particular attention to the titration plan, and the use of pipette or graduated syringe for the correct administration under the tongue.

Are there any special considerations you make when dispensing a herbal medicine (such as cannabis flos)?

I pay attention to the vaporiser and train the patient on the use and setting of the device. I prepare single doses weighted, milled (in some cases whole flower), packed and labelled individually in aluminium bags. These are ready-to- use and the patient takes a known and precise quantity.

Therapeutic regimen

What are the key benefits of using cannabis-based medicines?

Almost no severe side effects. It improves several medical conditions where alternative medicines have low efficacy or lead to important side effects. Cannabis represents a new frontier in medicine acting on modulating the endocannabinoid system.

What are the key risks of using cannabis-based medicines?

I do not see major risks using oil extracts and only a minor risk for abuse using flos. The bigger risk is to make the wrong choice in terms of strain [cultivar] and dosage leading to poor results and a high drop-out rate.

What do you think are pharmacy practices that improve patient outcomes?

Correct and relevant information to the patient. Collect feedback from all patients and identify trends and correlations between strain, dosage, pharmaceutical form and concentration. Train physicians on cannabis magistral prescriptions because the level of clinical expertise is still relatively low.

How closely do pharmacists work with the prescribing doctor?

They have an extremely close relationship. There is an ongoing interaction between the doctor, the pharmacist and the patient to adjust the therapy. In the context of cannabis-based medicines, the pharmacist has rediscovered their dimension and vocation and is recognised by doctors and patients as in the triangle Doctor-Pharmacist-Patient.

Final remarks

Do you have any good advice (tips) for pharmacists starting out?

Be passionate about what you do. This is an exciting professional opportunity and it is nothing like dispensing finished drugs.

- Be convinced that you are part of the cannabis-based medicines revolution and this is just the beginning.
- Go to cannabis conferences and trainings in your country and abroad if you have the chance.
- Read scientific literature. There is a lot of academic and clinical research going on.
- Collect patient's feedback and data.
- Look for other professionals who share your interest. Do not stop at pharmacists but look for physicians, scientists, patients and anybody who can help you enrich your knowledge.
- Build up strong and solid relationships with physicians and patients.

Arwin Ramcharan

Arwin Ramcharan is a community-based pharmacist and co-owner of Transvaal Apotheek, Den Haag (The Hague), the Netherlands. Arwin is a very experienced pharmacist working closely with Dutch prescribers to advise on the correct use of cannabis-based medicines. Pharmaceutical-quality cannabis herbal material has been dispensed at Transvaal since it was legalised in 2003, and more recently, whole cannabis oil extracts for sublingual use in 2015. Arwin established the pharmacy's cannabis medicine unit to assist patients and physicians and the product unit for the manufacture of oromucosal dose forms. He now advises these units on planning and future development, and the role of Transvaal Pharmacy in the Netherlands. He also leads clinical research activities for Transvaal on cannabis-based medicines.

Training/education

What training did you receive before you started dispensing cannabis-based medicines?

Nothing. There was nothing. So, there was no schooling or training for cannabis-based medicine, so we had to do our research ourselves. That is what we did. We observed the patients, we collected the data, and with that data, we advised other patients.

Dispensing experience

How long have you dispensed cannabis-based medicines?

Since 2014.

Can you describe a typical patient to whom you would dispense cannabis-based medicines?

A typical patient is a patient with chronic pain. It can be nerve pain, but pain in general.

Thinking about a first interaction with a patient, how do you start a conversation about the safe and effective use of cannabis-based medicines?

I always begin with what other medications have been used, and if the patient already used Cannabis, like from the coffee shop. Based on that information, I can then advise what the starting dose will be and what kind of variety is most appropriate for that patient. So, that is how I always start the conversation.

How is that different to follow-up interactions at the pharmacy?

If a patient doesn't react really well to the product, then there will be a follow-up, and there will be advice for another variety, or we will advise a higher dosage. However, if a patient is reacting well to it, then normally, there is no follow-up as they are stable at that point. Only when they don't react really well to the product.

Patient considerations

Thinking about a first interaction with a new patient, how do you start a conversation about cannabis-based medicines? What are the key points of discussion?

We need to know what kind of medication they are using. Let's say if they use medication for anxiety, then we cannot supply medicines containing THC.

Cannabis-based medicines are a really safe product – it is, I think, the most investigated product I know, and in lower doses, it's really safe.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

We have only seen three patients with interactions, and that was with blood thinners like warfarin.

Administration

Oral dose forms (oil extracts) are an increasingly popular mode of administration. What advice do you give patients on safe use?

Our oromucosal product is administered under the tongue, and if someone cannot, then they have to swallow it. We always advise under the tongue – that's the most effective – and if the taste is really bad, then we advise them to take a bit of chocolate right after or before, or a banana.

Transvaal also produces a patient information leaflet which provides comprehensive advice around effective dosing, including how to administer using a syringe. We advise to go up in dosage to two times the normal dose, administered under the tongue.

Vaporisation is an increasingly popular mode of administration. What advice do you give patients on safe use?

We now have a vaporiser device available that patients can buy. Interestingly, the first patient is going to start today with thatvaporiser, so we are going to collect the data and then advise the patient. But the vaporiser, at the moment, is really expensive for most patients. The affordability of a safe and effective vaporiser medical device is a big issue actually.

Safety

From a pharmacist's point of view, what are the actual and potential complications with cannabis-based medicines?

The biggest issue is dependency. That's if the [THC] dose is really high. We only see that with cannabis herbal material, so not much with the oromucosal doses, but with the plant materials.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines? How do you identify this issue in your practice? How do you deal with this issue in your practice?

We have a few patients with whom I know that there is a dependency issue.

We see the daily use of the cannabis herbal material increasing; if it is more than 2g a day, or 3g, then we know that it's not for medicinal use.

We then have to contact the physician, and together with the physician, we have to set up a plan. It is really hard to guide the patient with only the pharmacy and the physician. Sometimes we need another organisation, a psychiatrist, to help guide the patient because it's more complicated than just the misuse of the medication.

There is a lot of mental health stuff going on. They are using the product to 'self-medicate' as they think it helps them with the 'problems' they have; they use it so they cannot feel the 'problems' they have in their life. So, someone else needs to guide them.

Medicine type/dose forms

How are cannabis-based medicines different to storing and dispensing other medicines (for both herbal material and for oral dose forms)?

Transvaal is a specialist pharmacy for cannabis-based medicines. We store these products in a separate area. It is held within the pharmacy, but it is in a separate, secure, limited-access room – not everyone can go into the room. That was based on the discussion we had with Health Inspectors; we also decided to do it that way because we have more control over the product.

Are there any special considerations you make when dispensing cannabis-based medicines?

We need a prescription from their physician. Otherwise, we treat it as a regular controlled drug.

Therapeutic regimen

What are the key benefits of using cannabis-based medicines?

The main advantage of cannabis-based medicines is that they can be used for many indications.

We see patients who have tried all available medications, and nothing helps them. With these patients, there are no other options left. If these patients can have a 10% or 20% positive effect, that's a big deal for them for their quality of life.

What are the key risks of using cannabis-based medicines?

The key risk - especially in high doses of THC - is dependency.

We have never seen severe side effects, so it is a really safe product.

What do you think are pharmacy practices that improve patient outcomes?

If the patient is reacting really well to it, then it is okay; they are fine.

I think you have to help the high-risk patients or the patients who need more guidance.

The advantage for us as pharmacists is that we can guide patients on safe and effective medicine use. Let's say, I speak with the patient and say, okay – you start with this dose and call me back in a week, and we're going to re-evaluate the dosage and effects. At that point, we can decide if the side effects are too great. If they were, then we will say – let's go down in dosage, and we will call again in a week.

At the point when the dose is stable, we say, okay – let's keep it this way and call me if you need something more or if you want to change something.

This is especially so with the parents with children with epilepsy; we guide these parents with the dosage. For example, if the patient says: "In the evening, my child is not sleeping really well." Then, I can say, okay – let's try a different ratio of cannabinoids to help the patient during the evening. We recommend specific products depending on the indication.

How closely do pharmacists work with the prescribing doctor?

In the Netherlands, the prescriber doesn't know a lot about the product, so they rely on our experience. The prescribers call us, and we advise them on what to do and how to deal with their patients. We teach them about which product is for which indication, and then they have the knowledge for the next one. If they are in trouble, they know that they can call us and that we can help them.

Final remarks

Do you have any good advice (tips) for pharmacists starting out?

My advice is to go to the Government and ask them: 'Do you see possibilities?' and 'Are you willing to help?' You need backup from your government. That is the main advantage in the Netherlands; the Government is involved in the process – the availability, diversity, quality and safety of the product. They see the advantage of cannabis-based medicines.

So, if your government doesn't see that, then you have a big problem because you are always facing hurdles. If you can show your government that it can be really beneficial for patients, I think that's the hardest part. Getting them to pass legislation permitting the product as a medication for specific indications.

Dennis Stracke

Dennis Stracke is a community-based specialist skills pharmacist with a doctorate in pharmacy. For the past eleven years, he has been the head of the Neurology and Rare Diseases Department at Medios Apotheke, Berlin, Germany. Since that time, he has been dealing with the topic of cannabis-based medicines - advising patients and physicians on therapeutic use, dosage forms, dosage, applications, drug-drug interactions and side effects. Dennis is also managing director of QMEDIS Analytics, a contract laboratory offering a range of analytical and galenic services and regulatory support for the development of medicinal products – including cannabis-based medicines.

Training/education

What training did you receive before you started dispensing cannabis-based medicines?

I had no specific training in cannabis-based medicines. I taught myself all the knowledge I have about cannabinoids through self-study. For the past five years, I have been lecturing pharmacists, doctors and patients on the subject of cannabis-based medicines.

Dispensing experience

How long have you dispensed cannabis-based medicines?

I've been working with cannabis-based medicines for the past eleven years.

Can you describe a typical patient to whom you would dispense cannabis-based medicines?

I believe there is no such thing as a 'typical patient'. Cannabis-based medicines are not a panacea but are very well suited to difficult-to-treat symptoms and disease-associated conditions. Either as a mono- or add-on therapy.

There are two patient groups. For the first, cannabis-based medicines provide an opportunity and a possible therapy option, and for the other group, cannabis is the panacea.

Thinking about a first interaction with a patient, how do you start a conversation about the safe and effective use of cannabis-based medicines?

We always educate patients about the effects of cannabis-based medicines. In particular, the pharmacological effects of THC and CBD, as well as their side effects and interactions.

In follow-up interactions, we discuss further the pharmacological effects of cannabis-based therapy and clarify therapy-related issues – e.g. problems with use, dosage titration.

Patient considerations

Thinking about a first interaction with a new patient, how do you start a conversation about cannabis-based medicines?

Pharmacies are often the first place patients go for initial information on cannabis-based medicines. We discuss possible indications with patients, provide information about the different dosage forms and the specific advantages and disadvantages, clarify possible side effects and interactions, and discuss the different dosage titrations.

The most important information is that the dosage is individually identified by a slow dosage titration.

Secondly, that cannabinoids, especially cannabidiol, can also interact with other drugs.

Are you aware of patients experiencing interactions with cannabis-based medicines and other medicines?

Yes, absolutely. As part of our medication management, we document all the medications patients take to rule out possible interactions.

Administration

Oral dose forms (oil extracts) are an increasingly popular mode of administration. What advice do you give patients on safe use?

It is important to advise patients of slow dose titration. In addition, patients should not apply oral dosage forms more than twice a day, as the pharmacological effect is longer with oral administration than with inhalation of cannabinoids.

Vaporisation is an increasingly popular mode of administration. What advice do you give patients on safe use?

For inhaled administration, it is important to start with low doses. The same applies to oral dosage forms. The onset of action is very prompt, and very high plasma concentrations are achieved. For all dosage forms, THC is the dose-limiting factor.

What do patients say about the administration of cannabis-based medicines by vaporisation?

It is usually the case that we recommend an oral route of administration to cannabis-naïve patients due to its better controllability. If patients follow the instructions - to start at the lowest dosage - the therapy is well tolerated.

What special considerations should pharmacists be aware of for patients taking oral dose forms?

With oral doses, there is a long-lasting pharmacological effect and the risk of overdose if applied more than three or four times a day.

Safety

Are you aware of any patients who have experienced interactions of cannabis-based medicines with other medicines? If yes, please describe the major interactions.

Medicine interactions are rare, as we advise patients of side effects and interactions, and we review concomitant medications.

From a pharmacist's point of view, what are the actual and potential complications with cannabis-based medicines?

The biggest issue is the media, where 'cannabis' is often touted as a miracle drug. Here it is important to point out to patients that cannabis-based medicines are not a panacea but can very well be considered a possible therapy option.

What is the role of the pharmacy profession in ensuring patient safety with the use of these medicines?

It is important to review concomitant medications to avoid interactions. In addition, misuse and abuse should be identified.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines?

Diversion, misuse, and abuse are, fortunately, rare.

Often the problem is recognised by patients' increased doses and an increase in consumption, especially of cannabis herbal material (i.e., dried flowers).

We try to get patients to switch to oral therapeutic products.

Medicine type/dose forms

How is cannabis-based medicines different to storing and dispensing other medicines (for both herbal material and for oral dose forms)?

Cannabis herbal material and cannabis extracts are narcotics that must be stored in safes. In addition, they are also compounded medicinal products, which, unlike finished medicinal products, must be tested for identity with chemical evidence.

Are there any special considerations you make when dispensing cannabis-based medicines (i.e. oil extracts)?

We provide each patient with an individual titration scheme and instructions for use or intake.

Are there any special considerations you make when dispensing a 'herbal' medicine (as cannabis flos)?

There are no special considerations in dispensing a 'herbal' medicine. It is a treatment option like any other.

Therapeutic regimen

What are the key benefits of using cannabis-based medicines?

They are medicines with a favourable benefit-risk profile - high therapeutic effect, wide therapeutic range, with comparatively low side effects and interactions.

What are the key risks of using cannabis-based medicines?

The risks are generally low and predictable. THC-dominant dosage forms should generally not be used in children and young people – a strict risk-benefit assessment must be undertaken – nor with patients with mental illness and a history of substance abuse.

What do you think are pharmacy practices that improve patient outcomes?

Often, pharmacies are more accessible than doctors' offices when it comes to queries about cannabis-based therapies. The time factor also plays a decisive role. For many patients, pharmacies are more 'barrier-free' than doctors' offices. Nevertheless, it is important that all three parties - patient, physician and pharmacist - are in close exchange to guarantee a successful cannabis-based therapy.

How closely do pharmacists work with the prescribing doctor?

For a successful and safe therapy with cannabis-based medicines, physicians and pharmacists should be in close exchange.

Final remarks

Do you have any good advice (tips) for pharmacists starting out?

Cannabis-based medicine therapy is a very exciting topic.

Nevertheless, it involves a considerable amount of work - especially the acquisition of expertise. Since the topic is not yet part of university education, you have to acquire the knowledge yourself - intrinsically motivated.

Administration: discourse with nurses

In alphabetical order interviews conducted in 2023:

- Metta Bunk, a palliative care nurse from the Netherlands
- Miriam Ogintz, a pain clinic nurse from Israel
- Niramon Pojdoung, an oncology nurse from Thailand

Metta Bunk

Metta Bunk is a nurse specialist (MSc) palliative care of Sint Jansdal Hospital in Harderwijk, the Netherlands. Before that she worked at Isala hospital, one of the largest hospitals in the Netherlands and an ESMO Designated Centre of Integrated Oncology and Palliative Care. Metta was part of a multidisciplinary consultation team comprised of oncologists, internists, radiation oncologists, anesthesiologists, a chaplain, palliative care physicians and specialised palliative care nurses. She has spent the last thirty years nursing in different capacities, including palliative care and in training in mental health care in that setting. Specialising in palliative care, she completed her postgraduate studies (MSc) as a nursing specialist.

Training/education

What training did you receive before you started administering cannabis-based medicines?

I attended a training by Dr van Coevorden. The prescription of cannabis-based medicines is always done in close cooperation with the pharmacists at our hospital. I have had no additional formal training. But I have undertaken my own evidence-based study given my interest in the topic.

Experience

How long have you been involved with patients and their administration of cannabis-based medicines?

It has been ten years now working with cannabis-based medicines.

Can you describe a typical patient who would be treated/administered cannabis-based medicines?

There are two main patient groups. The first are patients with pancreatic cancers. The second are patients with acute myeloid leukaemia (AML).

Administration

How do you discuss the starting dose and then adjusting it in order to achieve an optimal daily dosage, in accordance with the prescriber's recommendations?

Often patients have tried out cannabis on their own. This can be a starting point for a prescription.

We always coordinate prescriptions of cannabis-based medicines with our pharmacist, who is in close contact with Transvaal Apotheek, a specialist pharmacy based in The Hague. By coordinating prescriptions with our pharmacy, we try to avoid possible interactions with other medicines the patient may take, and we are also getting advice about the right dosage for that patient.

Safety

How do you provide feedback to your clinical colleagues on the appropriateness, safety and efficacy of the prescribed dose?

When prescribing cannabis-based medicines, I always give a hand-out to the patient about the correct use of these medicines. The same instruction is placed on the digital patient chart and is communicated with the general practitioner of the patient in order to facilitate transparency.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines? How do you identify this issue? How do you deal with this issue?

I have not experienced misuse yet. Good patient instruction may reduce the chance of misuse and diversion. In general, the life expectancy of the patients I see averages only three months.

In case of misuse, I can find that in the electronic patient chart in the prescription history.

I clearly communicate this issue to the patient, explaining the risk of non-compliance and the harms of overdose and medicine interactions.

Are you aware of any patients who have experienced cannabis interactions with other medicines? If yes, please describe the major interactions.

I have not seen any medicine-medicine interactions yet.

Medicine type/dose forms

How are cannabis-based medicines different to other medicines administered?

The difference can be found in the way the medication is being used. For example, if a patient chooses to smoke it or prepare the dose as tea.

There is some detailed instruction necessary to ensure patients are taking their dose as prescribed. Also, in case we are prescribing cannabis oil, it is necessary to give good instructions to the patients on administration.

What do patients say about the administration of cannabis-based medicines by vaporisation? Aside from eliminating the harms of smoking, what are the benefits of administration by vaporisation?

I do not have any experience prescribing cannabis-based medicines for administration by using a vaporiser.

Oftentimes patients use cannabis oil drops. These forms of usage are suitable for many patients. After thorough instruction, patients are using the cannabis-based medication at their own discretion. That is why I get many positive reactions.

What do patients say about the administration of cannabis-based medicines by oral sublingual and/or oral ingestion?

Patients do not experience many problems from oral administration. Sometimes they do complain about the taste.

Dose regimen

What are the key risks of using cannabis-based medicines?

The biggest risk is if patients experiment on their own. It is important that the patient use only cannabis-based medicines on prescription because the composition is optimal for the particular condition being treated.

What do you think are administration practices that improve patient outcomes?

There is still a sort of taboo around the prescription of cannabis-based medicines. There should be more information about cannabis-based medicines for nursing and medical staff in order for them to inform patients adequately.

Final remarks

Do you have any good advice (tips) for nurses starting out?

Study yourself and follow the available training on the topic to accumulate adequate knowledge. Be able to adequately inform patients honestly so they know how to use these medicines safely at home. This facilitates the transition to a prescription cannabis-based medicine and improves a nurse's relationship with the patients.

Miriam Ogintz

Miri Ogintz has spent three decades working as an internal medicine nurse. For the past twelve years, she has worked at the Institute of Pain Medicine Rambam Health Care Campus (Rambam Hospital), Haifa, Israel. Rambam is a large tertiary referral centre for twelve district hospitals in Northern Israel. Miri provides instruction to and supervision of patients prescribed cannabis-based medicines - having now treated over 2000 patients. For years, she has acted as director of nursing at Syqe Medical, a medical device company that developed and registered a sophisticated cannabis-based medicine inhaler. In this role, she manages clinical research and oversees the patient support programme. Miri is the co-author of several related clinical research studies on inhaled cannabis-based medicines.

Training/education

What training did you receive before you started administering cannabis-based medicines?

I am a certified hospital nurse for many years, and seven years ago, I took part in a medicinal cannabis masterclass in the Netherlands. Since then, I have been teaching this course in the Netherlands and Canada. I have also been teaching doctors, nurses and pharmacists a medical cannabis treatment course in Israel for the past few years.

When we first started medical cannabis treatment at the clinic, I had no professional training. I am a specialist nurse in the field of pain, and about thirteen years ago, for the first time, I was exposed to patients whom we recommended to start treatment. At this point in time, you couldn't acquire professional and formal knowledge, so all my knowledge came from reading articles, lectures and professional literature.

How long have you been involved with patients and their administration of cannabis-based medicines?

I have been running the nurse's clinic for patients who are treated with cannabis-based medicines at the Institute of Pain Medicine at the Rambam Hospital for thirteen years. The clinic was opened since we figured that our patients didn't have proper guidance during the treatment process. The decision to open the clinic came from the need to give patients the right treatment and prevent side effects, making sure the treatment will be helpful and successful.

Can you describe a typical patient who would be treated/administered cannabis-based medicines?

At the Institute of Pain Medicine, we mostly treat patients with chronic neurological pain and patients with neurological diseases suffering from pain - like patients with Multiple Sclerosis and Parkinson's disease.

Likewise, the clinic gives guidance to patients with inflammatory bowel disease, Crohn's disease, ulcerative colitis and oncology patients.

The law in Israel allows cannabis-based medicine treatment only after trying all conventional treatments after a year in the Institute of Pain Medicine.

The patients who are treated with cannabis-based medicine are usually patients whom other treatments weren't

helpful or patients taking high doses of opiates. One of the purposes of cannabis-based medicine treatment is to reduce the dose of those other drugs.

How do you discuss the starting dose and then adjusting it in order to achieve an optimal daily dosage, in accordance with the prescriber's recommendations?

In Israel, the dosage is determined by the amount of cannabis-based medicine in a month. Before making the decision on the method of administration, we have a conversation about the purpose of the treatment and administration, the basics of the disease and other illnesses from which they suffer. Moreover, we ask about their experience using cannabis-based medicine. It is very important to examine other medicines and other background diseases, so we can give the patient-specific advice on how to prevent side effects when they start the cannabis-based medicine treatment. Likewise, patients who have other background diseases, such as diabetes and heart diseases need specific guidance according to their condition and the medicines they are using.

The safest and most efficient way to start cannabis-based medicine treatment is to start at the lowest dosage. The patient will get instructions to use before going to bed for two to three days, and then to raise the dosage until they get the desired effect at a dosage without side effects.

When a patient suffers from diabetes or high blood pressure, they will be instructed on how to monitor their blood sugar level and blood pressure to avoid said effects.

One of the most important things is to prevent falls in the elderly.

Safety

Patient medicine reviews. How do you provide feedback to your clinical colleagues on the appropriateness, safety and efficacy of the prescribed dose?

The first meeting is a guidance meeting. At this meeting, the patient will receive instructions on how to prevent the side effects and a titration plan for dose initiation during the first week. Also, in this meeting, it is very important to talk with the patient about setting expectations for the treatment as many patients think that using cannabis-based medicine will heal (cure) them. So it is very important to talk about symptom relief and not healing, and setting treatment goals such as reducing medication, sleeping better, improving day- to-day life.

At the start of the following month of the treatment, we have a follow-up call once a week, and the patient reports any changes in the symptoms, and if there were any side effects.

If there aren't side effects, but there isn't a significant relief, it is possible to raise the dosage. If there are intolerable side effects, we stop the usage and report that to the treating doctor. The doctor will decide on changing the concentration or the method of administration, which after the patient will be called again for new instructions according to the new treatment regimen.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines? How do you identify this issue? How do you deal with this issue?

The patient is under supervision for the first two months, and we track the usage and dosing. In addition, it is all written in the patient's medical files and is updated by the doctor.

In a situation where the patient reports a need to raise the dosage, they will be called for a re-evaluation with the purpose of examining the correct medicine usage and to evaluating if other medicines need to be reduced.

If the patient did not reduce their other medication or there is no improvement in pain, sleep or daily function, but there is a request to increase the monthly dose, we will consider stopping the treatment.

Are you aware of any patients who have experienced cannabis interactions with other medicines? If yes, please describe the major interactions.

Sometimes, cannabis-based medicines are combined with sedatives, opiates or psychiatric drugs, which may cause sleepiness or sedation, confusion, or hallucinations

The patient will be instructed to keep track of any side effects and report these, and as much as possible, avoid taking all those medications with cannabis-based medicines.

Since we have limited information regarding interactions between medications such as chemotherapy, biological and immunotherapy treatments, the doctor will explain this to the patient and that we will keep track of their treatment to avoid unwanted side effects.

Medicine type/dose forms

How are cannabis-based medicines different to other medicines administered?

We still don't know about the long-term effects caused by daily or regular use on a foetus or on the development of the brain in very young patients.

We don't have information regarding the interactions with other treatments and medications.

We don't have information about precise dosing or total dosage or on a specific concentration that affects a certain illness. Regarding cannabis-based medicines, we conduct treatments with a level of uncertainty, so we must supervise, guide and report the process to avoid long-term adverse effects.

Patients in Israel prefer smoking, even though the administration by using an inhalation device is the proper way to consume cannabis-based medicines (cannabis herbal material). Evaporation prevents the burning of active substances and allows to avoid smoking damages.

Patients will choose administration inhalation rather than oral use, mostly because of the faster onset and the ability to have better control of the effect. However, patients who don't smoke will prefer using oil or an inhaler.

What do patients say about the administration of cannabis-based medicines by oral sublingual and/or oral ingestion?

Patients who don't smoke prefer using the oral oily dose form. Beforehand, we make sure they don't have any allergy or sensitivity to vegetable oil since, in Israel, oral doses are formulated using vegetable oil such as coconut palm or olive oil.

Furthermore, patients with bowel diseases, diseases that cause difficulty in absorption, patients after abdomen surgeries, and patients who are having nausea will struggle using the oily dose forms. Most patients treated with oil at first will report bad taste, nausea, heartburn and sometimes even diarrhoea.

Because of the slow onset, it will not be able to help with breakthrough pain; therefore, most patients use oils for sleeping problems.

When it comes to younger patients, the oil is not prescribed because they prefer the inhalation route and long and unexpected effects can interrupt daily functioning.

What are the key risks of using cannabis-based medicines?

The main risks in cannabis-based medicines treatment are usually the side effects, such as the psychoactive effects. We also see a rise in addiction cases, and this is the reason why supervision and guidance at the outset are so important.

What do you think are administration practices that improve patient outcomes?

To give proper cannabis-based medicines treatment, we must think of it as a medication. The right treatment will be the lowest dose that causes relief in pain and other symptoms and doesn't have side effects.

Good guidance and follow up are very important, especially in the beginning to avoid side effects, gain symptom relief, and avoid misuse and abuse.

Treatment goals and setting expectations are very important. These should be clearly addressed in every meeting with the patient.

Final remarks

Do you have any good advice (tips) for nurses starting out?

Cannabis-based medicines are a small word for 500 active substances - most of which we are not familiar with, and in many cases, we don't have the information on how they will affect our bodies. Cannabis-based medicines treatment must be undertaken very carefully while guiding the patient through the entire process.

Moreover, the right supervision can be done only by staff who know the patient's specific condition, and my recommendation is that the pain nurses will take care of the chronic pain patients, oncological nurses will guide the oncological patients and gastro nurses will treat patients with Inflammatory bowel diseases who use cannabis-based medicines.

Since giving the right treatment requires learning about cannabis-based medicines treatment, it is also very important to know the patient's basic disease, their regular medications and their side effects. This will enable you to give the proper treatment and guidance to every patient and avoid misuse and abuse.

We should read and learn more about cannabis-based medicines treatment, keeping up to date with recent knowledge.

Niramon Pojdoung

Niramon Pojdoung trained as an oncology nurse and is the head nurse at the Innovative and Integrated Cancer Clinic (IICC), the Medical Cannabis Service, within the National Cancer Institute (NCI), Bangkok, Thailand. NCI is the leading national institution for cancer control and comprehensive cancer care. Almost eighty per cent of patients are cancer patients receiving surgical, radiation, and chemotherapy treatment, alongside patient end-of-life care. Nurses at the NCI are care managers for the cannabis-based medicines service, monitoring patients and providing counselling and essential information on the appropriate and safe use of cannabis-based medicines by patients and their caregivers. Niramon's team of nurses have managed around twenty new patients per month in 2021.

Training/education

What training did you receive before you started administering cannabis-based medicines?

I received a three-day training course entitled "The Role of nurses within medical cannabis services".

I have not gone through any formal training. I have updated my knowledge via the "Thai Guidance on Cannabis for Medical Use" instructions and by attending a multidisciplinary conference.

Experience

How long have you been involved with patients and their administration of cannabis-based medicines?

I have provided service to cancer patients using medical cannabis for one year and four months.

Can you describe a typical patient who would be treated/administered cannabis-based medicines?

The main group of patients are cancer patients who are suffering from disease progression and the side effects of cancer treatment.

Administration

How do you discuss the starting dose and then adjusting it in order to achieve an optimal daily dosage, in accordance with the prescriber's recommendations?

In accordance with the hospital's clinical practice guidelines, a nurse will recommend an initial dosage to the patient as per the doctors' treatment plan. After the cannabis-based medicine has been administered to a new patient, the effectiveness of the medication and the presence of side effects are monitored by phone on days 3, 7 and 21. If the patient is found to be encountering side effects, which do not show signs of improvement over time, the nurse will report this to the doctor, who will re-evaluate the treatment plan, either increasing or reducing the dosage. The nurse will then advise the patient to adjust the medication accordingly and continue to monitor the situation. Should the side effects persist following this, then the medication will be stopped.

Safety

How do you provide feedback to your clinical colleagues on the appropriateness, safety and efficacy of the prescribed dose?

I have good communication with my patient care team regarding follow-up patients after they have medications. Nurses have a channel to communicate with doctors who prescribe medications. This channel is convenient and a quick way to communicate when there is a problem with cannabis-based medicines or a required consideration for adjusting the dose of medicine. Moreover, nurses can ask pharmacists to help with checking the total amount of doses which patients are administered, as some patients are suspected that they might obtain cannabis-based medicines from other sources. Pharmacists can access the database of the use of cannabis-based medicines of every patient from every source in the country. This is in order to prevent the abuse of cannabis-based medicines.

Do you encounter diversion, misuse, or abuse of cannabis-based medicines?

No, I don't. I have not encountered this.

Are you aware of any patients who have experienced cannabis interactions with other medicines? If yes, please describe the major interactions.

I have very little experience with cannabis interactions with other medicines. In general, medicine reconciliation is performed before prescribing cannabis-based medicines. However, there was a case in which a patient with cancer received anti-tuberculosis medicine from another hospital after taking cannabis-based medicines for two weeks. In this case, the patient had to stop taking cannabis-based medicines immediately, and after that, the patient did not have any abnormal symptoms.

Medicine type/dose forms

How are cannabis-based medicines different to other medicines administered?

Cannabis-based medicines are new drugs in our service. The National Cancer Institute has a policy of providing cannabis-based medicines through The Special Access Scheme. In all cases, the safety and efficacy of these medicines must be monitored for at least one month after administration. The amount of cannabis-based medicines used and their safety in patients must be reported and presented to senior executives once a month.

What do patients say about the administration of cannabis-based medicines by vaporisation? Aside from eliminating the harms of smoking, what are the benefits of administration by vaporisation?

I have no experience with administration by vaporisation.

What do patients say about the administration of cannabis-based medicines by oral sublingual and/or oral ingestion?

Most patients are fine with sublingual drops.

Elderly patients or those who are physically weak may not be able to control the dropper. Handshaking or squeezing the dropper too hard results in an overdose. Some patients may not be able to see the amount of drops when they administer their medication.

Given this, most doctors prescribe one to two drops and request patients' relatives or caregivers to help patients with administration.

Dose regimen

What are the key risks of using cannabis-based medicines?

The key risks are intentional and unintentional overdose with cannabis-based medicines outside the treatment plan.

What do you think are administration practices that improve patient outcomes?

Patients or caregivers should receive guidance on how to administer cannabis-based medicines by the oral, sublingual route, and the medical professional who provides the guidance should check the patient's understanding and ask whether they have any questions or any concerns regarding the prescribed cannabis-based medicines.

Final remarks

Do you have any good advice (tips) for nurses starting out?

Nurses need to be well prepared by undertaking further study on cannabis-based medicines in order that they can play an important role in caring for cancer patients who are interested in or receiving cannabis-based medicines. Tips for nurses are as follows:

- Information and counselling: Nurse should be able to provide information and counselling on cannabis-based medicines, especially on the topic of indications, benefits and harms. Since there are some cancer patients who still understand that cannabis can cure cancer, then if these patients do not receive enough or correct information, they might miss the standard prescribed cancer treatment.

- In addition to the formal training, nurses should seek to further their knowledge, including follow up academic progress on efficacy, side effects and post-medication care. This is in order to be able to provide accurate and up-to-date information and also keep up with social media, which might post fake information. The nurse should also be able to prevent the use of underground medical cannabis products which do not have applied quality standards and are also expensive for the patient.

- Assessment: Nurses must have the knowledge to assess patients' physical and mental readiness and should know about the risks of treatment with cannabis-based medicines before the initiation of treatment, especially drug interactions with the other medicines that patients received.

- Monitoring by follow-up care: Nurses should assess effectiveness using standardised tools such as ESAS, EQ5D, etc., as well as side effects. This will help to keep patients safe from side effects of treatment with cannabis-based medicines, and when side effects occur, patients can quickly be assisted, and the medicine dose can be adjusted appropriately. Most importantly, this means patients are confident about the safety of cannabis-based medicines.

- Team collaboration: Interdisciplinary coordination between teams of doctors, nurses and pharmacists will enable an effective medical cannabis service for cancer patients. Teams need to coordinate continuously, especially at the outset of the service, in order to adjust the guidelines for joint care in the service. This will help patients to have better access to quality services and ensure the amount of medication patients receive can be regulated appropriately, and that patients are safe when treated with cannabis-based medicines.

Appendix

Clinical evaluation tools

Clinical evaluation tools are used to support decision-making by health professionals. The following tools have been used to support prescribing of cannabis-based medicines.

Screening tools – risk of dependence

CAGE questionnaire

CAGE	
C	Have you ever felt you ought to cut down on your drinking or drug use?
A	Have people annoyed you by criticizing your drinking or drug use?
G	Have you ever felt bad or guilty about your drinking or drug use?
E	Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (eye-opener)?
Score	Score 1 for each positive response; a score of 2 or more suggests an alcohol or drug problem.

Cannabis Use Disorder Identification Test – Revised (CUDIT-R)

CUDIT-R test		
1	How often do you use cannabis?	0: Never; 1: Monthly or less; 3: 2-4 times a month; 3: 2–3 times a week, 4: 4 or more a week
2	How many hours were you “stoned” on a typical day when you had been using cannabis?	0: Less than 1; 2: 1 or 2; 3: 3 or 4; 4: 5 or 6; 4: 7 or more
3	How often during the past six months did you find that you were not able to stop using cannabis once you had started?	0: Never; 1: Less than monthly, 2: Monthly; 3: Weekly, 4: Daily, almost daily
4	How often during the past six months did you fail to do what was normally expected from you because of using cannabis?	0: Never; 1: Less than monthly, 2: Monthly; 3: Weekly, 4: Daily, almost daily
5	How often in the past six months have you devoted a great deal of your time to getting, using, or recovering from cannabis?	0: Never; 1: Less than monthly, 2: Monthly; 3: Weekly, 4: Daily, almost daily
6	How often in the past six months have you had a problem with your memory or concentration after using cannabis?	0: Never; 1: Less than monthly, 2: Monthly; 3: Weekly, 4: Daily, almost daily
7	How often do you use cannabis in situations that could be physically hazardous, such as driving, operating machinery, or caring for children?	0: Never; 1: Less than monthly, 2: Monthly; 3: Weekly, 4: Daily, almost daily
8	Have you ever thought about cutting down, or stopping, your use of cannabis?	0: Never; 2: Yes, but not in the past 6 months; 4: Yes, during the past 6 months
Score	Scores of 8 or more indicate hazardous cannabis use. Scores of 12 or more indicate a possible cannabis use disorder, for which further intervention may be required.	

Screening tools – anxiety and depression

Patient Health Questionnaire 4 (PHQ-4)

PHQ-4

Over the last two weeks, how often have you been bothered by the following problems?		Not at all	Several days	More than half the days	Nearly every day
1	Feeling nervous, anxious or on edge	0	1	2	3
2	Not being able to stop or control worrying	0	1	2	3
3	Little interest or pleasure in doing things	0	1	2	3
4	Feeling down, depressed, or hopeless	0	1	2	3
Score	PHQ-4 total score ranges from 0 to 12, with categories of psychological distress being:	None	0 - 2		
		Mild	3 - 5		
		Moderate	6 - 8		
		Severe	9 - 12		
Score	Anxiety subscale:	Sum of items 1 and 2 (score range, 0 to 6)			
	Depression subscale:	Sum of items 3 and 4 (score range, 0 to 6)			
	On each subscale, a score of 3 or greater is considered positive for screening purpose.				

Hospital Anxiety and Depression Scale (HADS)

HADS

Ask the patient to tick the box beside the reply that is closest to how they have been feeling in the past week. Request they don't take too long over your replies, as their immediate answer is best.

D: Depression A: Anxiety

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite often
3		Hardly at all		3	Very often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever

		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV programme:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not often	2		Not often
	3	Not at all	3		Very seldom

Ask the patient to check they have answered all the questions.

Score

Note: Score anxiety and depression separately.

Total score: Depression (D) _____ Anxiety (A) _____

0-7 = Normal (non-cases)

8-10 = Borderline abnormal (borderline case - mild)

11-21 = Abnormal (case – moderate to severe)

Assessment tools – quality of life

Edmonton Symptom Assessment System

ESAS		
Circle the number that best describes your average symptom over the past 24 hours:		
No pain	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst pain
No fatigue	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst fatigue
No nausea	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst nausea
No depression	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst depression
No anxiety	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst anxiety
No drowsiness	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst drowsiness
No shortness of breath	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst shortness of breath
Best appetite	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst appetite
Best felling or well-being	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst felling or well-being
Best sleep	- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 -	Worst sleep
Date:	**Completed by: O Patient O Family**	**Assessed by:**

Short Form Survey (SF-12)

SF-12	
1	Limitations in physical activities because of health problems
2	Limitations in social activities because of physical or emotional problems
3	Limitations in usual role activities because of physical health problems
4	Bodily pain
5	General mental health
6	Limitations in usual role activities because of emotional problems
7	Vitality (energy and fatigue)
8	General health perception

Note to table: alternatively measure of quality of life is the EuroQol-5D (EQ-5D) see: https://pubmed.ncbi.nlm.nih.gov/23614330/

Medicine interactions

There are few medicine interaction studies. The evidence base on medicine interactions with cannabis-based medicines is still limited. The following tables list known and potential interactions with cannabinoids. If a medicine appears in these tables, there is a likely interaction. If it does not appear, it is likely there is no interaction.

Anti-infective medicines

Inhibitors of CYP3A4, such as the antifungal agent ketoconazole, may significantly increase peak plasma concentration and AUC of THC and CBD. [126-129]

Note, this list is not exhaustive. If unsure, search up-to-date references.

Drug class	Effect	Clinical considerations
Fluconazole	CYP2C9 inhibitors	Monitor
Metronidazole Sulfamethoxazole	Increases serum concentration of cannabinoids	Consider decreasing THC levels
Ketoconazole	A CYP3A4 inhibitor	Monitor
Itraconazole Erythromycin Clarithromycin		Consider decreasing THC levels
Atazanavir	A CYP3A4 inhibitor	Monitor
Ritonavir		Consider decreasing THC levels
Ciprofloxacin	A CYP1A2, CYP2D6, and CYP3A4 inhibitor.	Monitor Consider decreasing THC levels

Cardiovascular medicines

Additive cardiac effects (e.g. hypotension, hypertension, syncope, tachycardia) may occur when THC is taken concomitantly with medicines which affect the cardiovascular system. [119, 127-130]

Drug class	Effect	Clinical considerations
Beta-blockers: metoprolol	Are CYP2D6 Substrates	Monitor
	CBD and THC may increase drug levels	Consider decreasing CBD and THC levels
Antiarrhythmics: amiodarone	A CYP2C9 and CYP3A4 inhibitor	Monitoring is suggested during initiation and up-titration
		Consider decreasing THC levels
Calcium channel blockers: diltiazem, verapamil	CYP3A4 Inhibitors	Consider decreasing CBD levels
	CBD may increase serum concentrations	Consider decreasing THA and CBD levels
Angiotensin II antagonists: valsartan, losartan	UGT2B7 substrates	Monitor
		Consider decreasing substrate levels in CBD prescribing
Statins: lovastatin, simvastatin	UGT2B7 substrates	Monitor
		Consider decreasing substrate levels
Ezetimibe	UGT2B7 substrates	Monitor
		Consider decreasing substrate levels

Anti-coagulants and anti-platelets

Medicines that compete as substrates for CYP450 enzymes or inhibit their activity may increase plasma concentrations. [127, 131-133]

Drug class	Effect	Clinical considerations
Warfarin	THC is a direct inhibitor of CYP2C9, increasing S-warfarin isomer levels, and is associated with increased (supratherapeutic) INR levels [121, 122]	Close monitoring of INR during initiation and up-titration of cannabinoids
		Check INR within three days
Direct Oral Anticoagulants (DOACs)	CBD and possibly THC can increase DOACs levels due to competitive inhibition of P-glycoproteins, and to a lesser extent, the CYP3A4.	Close monitoring
		Consider using other anticoagulants or discontinue DOACs
Clopidogrel	CBD and THC prevent the formation of the active moiety of clopidogrel by inhibition	Alternative antiplatelet

Anti-convulsants

Additive CNS effects (e.g. dizziness, confusion, sedation, somnolence) may occur when THC is taken concomitantly with CNS depressants. [24, 38, 130]

Drug class	Effect	Clinical considerations
Clobazam Topiramate Also: Rufinamide Eslicarbazepine Zonisamide	High dose CBD may increase plasma serum concentrations In children treated with CBD for epilepsy, CBD was shown to increase clobazam levels [38]	High levels of a sedating metabolite of clobazam, N-desmethyl clobazam, will require a dose reduction for that drug [24] Given the uncertainty around drug interactions, upwards dose titration is a valid precautionary practice – in particular given the narrow therapeutic range of many anti-convulsant drugs and the vulnerability of young patients.
Carbamazepine	A CYP2C9 inducer	Monitoring is suggested during initiation and up-titration Consider increasing THC level
Benzodiazepines	THC enhances the antiepileptic action of benzodiazepines	Monitor Consider decreasing THC levels
Valproic acid	A CYP2C9 inducer Abnormal liver function with CBD THC enhances the antiepileptic action	Monitoring is suggested during initiation and up-titration Consider decreasing THC levels
Phenytoin 1 Phenobarbital	CYP2C19 inducers	Monitor Consider decreasing THC and CBD levels
Pregabalin Gabapentin	Enhances activity of THC	Monitor Consider decreasing THC levels

1 Both THC and CBD may increase levels of phenytoin by inhibiting metabolism of phenytoin (CYP2C9)

Miscellaneous medications

CYP1A2 is noted to mediate theophylline metabolism, although the role of cannabinoids specifically in eliciting this effect is questionable. [113, 126]

Drug class	Effect	Clinical considerations
Theophylline	THC can decrease theophylline levels, decreasing bronchodilator effects	Monitor Consider decreasing THC levels
Proton pump inhibitors: omeprazole, pantoprazole	CYP2C19 substrates CBD and THC may increase drug levels	Monitor Decrease dose of substrate

Muscle relaxants

Drug class	Effect	Clinical considerations
Cyclobenzaprine	THC is a CYP1A2 inducer. Theoretically, THC can decrease serum concentrations.	THC enhances the action of muscle relaxants, bronchodilators and anti-glaucoma medication Skeletal muscle relaxants
Baclofen, tizanidine	THC effects may be enhanced	Monitor Consider decreasing THC levels

Anti-psychotics and anti-depressants

CYP2D6 metabolises many drug substances. Co-administration of cannabinoids (THC and CBD) may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics. [105, 126, 127, 129, 134, 135] **Additive CNS effects (e.g. dizziness, confusion, sedation, somnolence) may occur when THC is taken concomitantly with CNS depressants.** [127-129]

Drug class	Effect	Clinical considerations
Antipsychotics: clozapine, chlorpromazine, olanzapine, haloperidol	THC is a CYP1A2 inducer. THC can decrease serum concentrations by increasing clearance. CBD and THC may increase drug levels	The serum concentration of antipsychotic agents should be monitored during titration Consider decreasing THC and CBD levels
Tricyclic antidepressants	THC interacts with tricyclic antidepressants	Monitor Decrease THC and CBD levels
SSRIs: duloxetine, fluoxetine, fluvoxamine	CYP2C19 inhibitors THC interacts with SSRIs and SSNRIs	Monitor Increase CBD and THC levels

Peripheral analgesics

Cannabinoids have demonstrated anti-inflammatory effects in inflammatory and autoimmune diseases mediated through activation of cannabinoid receptor CB2. [136, 137]

Drug class	Effect	Clinical considerations
NSAIDs: naproxen	CBD and THC may increase drug levels	Monitor Consider decreasing THC and CBD levels
NSAIDs: acetylsalicylic acid, indomethacin	NSAIDs antagonise THC effects	Monitor Consider increasing THC levels, if applicable
Antipyretics: paracetamol / acetaminophen	Increased serum concentration of substrates of CYP1A2	Monitor
COX-2 inhibitors	THC effects are counteracted by cyclooxygenase inhibitors	Monitor Consider increasing THC levels

Opioids and sedatives

Additive CNS effects resulting in cognitive impairment (e.g. dizziness, confusion, sedation, somnolence) may occur when THC is taken concomitantly with CNS depressants. [71, 127-129, 138]

Drug class	Effect	Clinical considerations
Opioids (in particular opioids with a narrow therapeutic index e.g. methadone, fentanyl, morphine, oxycodone)	THC enhances the action of opioids and reinforces sedating effects Cannabinoids and opioids used in combination may augment the analgesic effects of opioids [71]	Monitor Consider decreasing THC levels Avoid alcohol
Benzodiazepines	THC reinforces sedating effects CBD may increase serum concentrations	Monitor Consider decreasing THC and CBD levels Avoid alcohol

References and reading

The References and reading chapter is your prompt to ongoing, independent learning. Delve into this module and see what articles we included the clinical primer review.

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The benefits of health professional guidance

Cannabis-based medicines are increasingly being made available on a global level. It is important that prescribers, pharmacists and nurses are equipped with practical, evidence-based guidance to support decision-making, and to improve communication of the benefits and risks of these medicines with their patients.

This Clinical Primer draws on clinical research, clinical observations, and professional experiences to provide useful, real-world insights to the rational use of cannabis-based medicines.

This text follows on from the Primer to medicinal cannabis: An introductory text to the therapeutic use of cannabis.