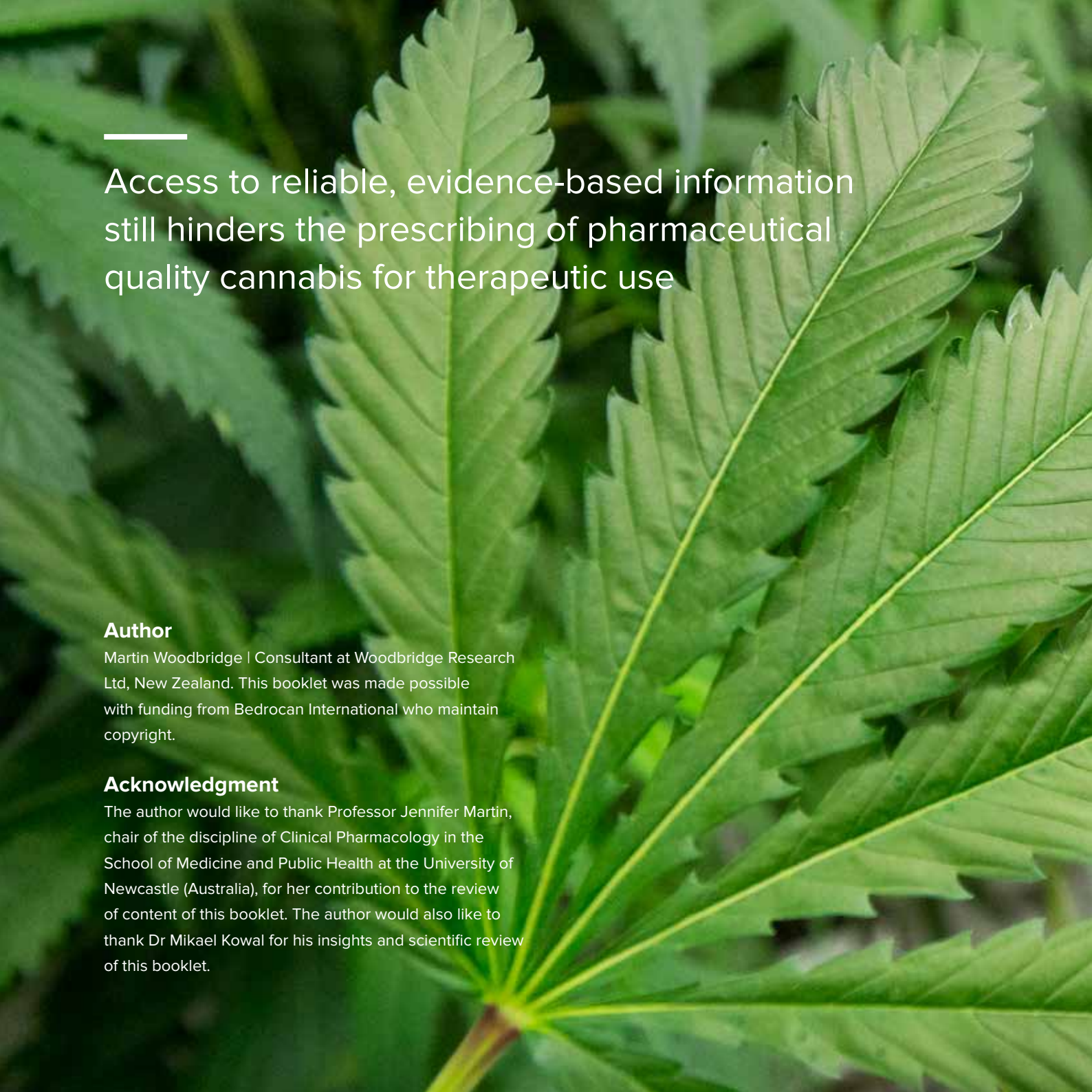


A woman with grey hair, wearing a white lab coat and a white hairnet, is working in a greenhouse. She is surrounded by numerous cannabis plants growing in black plastic pots. The plants have green, serrated leaves and are supported by black metal cages. The background is filled with more green foliage, creating a lush, indoor garden environment.

A primer to medicinal cannabis

An introductory text to the therapeutic use of cannabis



Access to reliable, evidence-based information
still hinders the prescribing of pharmaceutical
quality cannabis for therapeutic use

Author

Martin Woodbridge | Consultant at Woodbridge Research Ltd, New Zealand. This booklet was made possible with funding from Bedrocan International who maintain copyright.

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A primer to medicinal cannabis

This booklet discusses the therapeutic use of cannabis. That means we are not talking about pot, marijuana, grass, or dope for recreational use to get ‘high’. It focusses strictly on medicinal cannabis. It is meant to give health care professionals, regulators and patients insights into the medical and scientific aspects of *Cannabis sativa* L. and how this plant fits in the chain of therapeutic options.

Cannabis is a complex plant. There are over 500 chemical components identified; the chemical content of each cannabis variety is different to the next. Globally, and for generations, it has been used recreationally and associated with criminal activity - this has tainted its image as a legitimate medicine. International treaties also make its medical use complicated. However, despite illegality, vast numbers of patients across the globe use cannabis in its crude form for symptom relief, while a smaller number access pharmaceutical-quality products via their doctors and pharmacists. Access to reliable, evidence-based information still hinders the prescribing of pharmaceutical-quality cannabis for therapeutic use. Medicine regulators often do not permit cannabinoids, the active substances in cannabis, to be used as a mainstream medicine.

As early as the 1960s, the major biologically active cannabinoids THC and CBD were identified in the plant. By the late 1980s to early 1990s the cannabinoid receptors had been discovered. Both are critical time points for identifying the key therapeutic components of the cannabis plant and confirming the biological pathway for its action. Since that time clinical research demonstrates medicinal cannabis has potential therapeutic applications in certain conditions.

With the development and availability of pharmaceutical-quality products, reliable clinical data are now being generated. This knowledge will help determine the place of medicinal cannabis in the therapeutic toolbox and to separate therapeutic use from recreational.



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1 What a medicine is and where cannabis fits in

Medicines are central to modern and traditional medical practice. Medicines are tools. They are used to treat or prevent disease, and to promote health. If misused they can also cause harm.

Doctors must have access to quality, safe, and effective medicines. They must also use them rationally. Every time the doctor has to make decisions around whether it is appropriate to a patient's needs, at the correct dose, for the right length of time, and at an acceptable cost.

Doctors also need choice. For patients who do not respond well to one medicine, having an alternative therapeutic option is helpful. Medicine choice allows doctors to find the most appropriate treatment for the patient under their care.

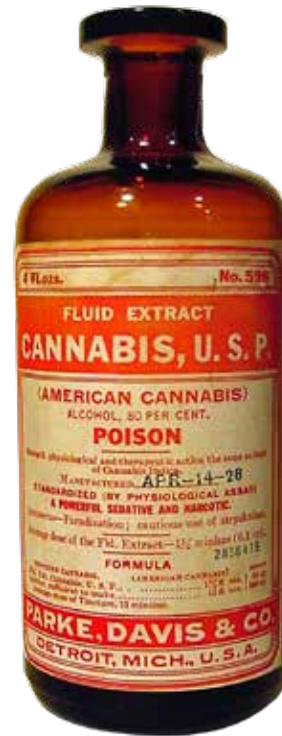
Over the last decade the number of patients exposed to medicinal cannabis (the cannabinoids THC and CBD) has increased alongside a variety of conditions where patients have reported symptomatic benefit. These include, but are not limited to, chronic pain; multiple sclerosis; nausea, vomiting and appetite stimulation; epilepsy; and anxiety. Others include sleep disorders; fibromyalgia; Gilles de la tourette syndrome; therapy-resistant glaucoma; Crohn's disease and ulcerative colitis; Parkinson's disease; rheumatoid arthritis; attention-deficit disorder (ADD); and posttraumatic stress disorder (PTSD). Each has shown varying degrees of response, and many still require being confirmed by good clinical science.

Medicinal cannabis is a novel class of medicine. It is not a panacea or a cure for disease. Currently, in most parts of the world, it is also not a first line treatment. Rather, eligible patients have not responded well to other medicines, or experience unacceptable side effects. While only few are officially registered medicines, cannabis products for medical use are still required to meet certain quality standards. As a result, government medicine regulators often are managing a patient and doctor demand for medicinal cannabis alongside the requirements of product safety, quality and efficacy. So, as much as there is a need for clinical data and prescribing guidance, robust information to support policy development and decision making by government officials is just as essential.

Medicinal cannabis is a novel class of medicine

A potted history

Cannabis is one of the oldest known medicinal plants. It is described in ancient handbooks on plant medicine. Archaeological evidence indicates the plant spread from Asia to Africa and on to the Middle-East. Eventually it arrived in Europe around 500 BC. It was later used widely for industrial purposes and was integral to early shipping as hemp fibre. History states that the therapeutic use of cannabis was introduced to Europe in around 1840 by an Irish doctor called William O'Shaughnessy. While in India he observed its widespread therapeutic use. In the following decades cannabis gained a short period of popularity in Europe and the United States. Dozens of different cannabis preparations were available. These products were recommended for conditions including menstrual cramps, asthma, cough, insomnia, labour pains during birth, migraine, throat infection and withdrawal from opium use. At the time no tools existed for quality control and standardised preparations. Patients often received a dose that was either too low having no effect, or too high resulting in unwanted side effects. These drawbacks meant the therapeutic use of cannabis was largely taken over by standardised opium-based drugs such as codeine and morphine. Cannabis gradually disappeared from all Western pharmacopoeias. In the late fifties the World Health Organisation (WHO) claimed that cannabis and its preparations no longer served any useful medical purpose.



A cannabis extract produced by the pharmaceutical company Parke Davis & Co.

The therapeutic use of cannabis was introduced to Europe in around 1840 by an Irish doctor called William O'Shaughnessy

2 The cannabis plant, its makeup and chemistry

Like other plants, cannabis is made up of hundreds of chemical compounds. It also comes in many different types. Some people refer to *indica*, *sativa*, or *ruderalis* types. But all of these belong to the same species: *Cannabis sativa* L. – a member of the *Cannabaceae* family. Many people are familiar with cannabis by the name hemp. Another of its close relatives is *Humulus lupulus* L., better known as hops, a key ingredient of beer.

Cannabis is said to originate in the arid climates of Central Asia (Eurasian steppe), most likely the Hindu-Kush region. Straddling the borders of Pakistan and Afghanistan, the 800-kilometre-long mountain range was an integral part of the ancient Silk Road. The Silk Road provided a network of trade routes connecting Eurasia. The road and maritime trading routes moved various goods, including cannabis, in its various forms (hemp fibers, oil-rich seeds, intoxicants, and medicines), to the east beyond the Korean peninsula and west beyond the Mediterranean Sea. Nowadays, cannabis can be found growing in places all around the world, except in humid, tropical rain forests.

There are male and female cannabis plants, each with a distinct way of blooming. The cannabis plant has a lifespan of one year. The plant typically reaches a height of two to three meters (seven to 10 feet), after which it blooms and the growth ceases. After fertilisation, the seeds mature and the plant dies.



A female cannabis plant

Cannabis by any other name

More than 700 cultivated varieties (cultivars) of cannabis are thought to exist. The difference between distinct cannabis varieties is not solely determined by the cannabinoid content, but also the specific terpene content. These chemical constituents act as distinct biochemical markers, and can be used to 'map the current chemical diversity of cannabis'. By analysing the concentrations of these compounds, researchers can identify specific cannabis plants with defined chemical profiles. For the purposes of medicine development, these particular plants can be used in clinical trials to determine their specific biological actions, and later introduced as new varieties to the existing product range.

Such analytical insights have led to a better understanding of cannabis taxonomy (scientific classification of plants). In the past, the distinction between *sativa* and *indica* has presented much debate. The classification was based upon differences in chemical composition, especially the differences in terpene content. However, to date there is no conclusive research displaying distinct ancestral lines for *Cannabis indica* or *sativa*. So, although cannabis plants can significantly differ from one another, the scientific emphasis has shifted to a hypothesis that all cannabis falls under *Cannabis sativa*.

The cannabinoids

Over 500 chemical compounds are produced by the cannabis plant. Of these, at least 100 are unique to the cannabis plant – the cannabinoids. The plant-derived cannabinoids are termed phytocannabinoids. The major phytocannabinoids, and those we know most about, are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC possesses psychoactive effects, while CBD

is non-psychoactive (i.e. it does not alter perception or consciousness).

The cannabinoids are biologically active chemicals. The concentration of cannabinoids varies throughout the plant (excluding seeds and roots). The highest concentration is found in the unfertilised female flower.

The biological activity is mainly linked to the major cannabinoids THC and CBD. Although THC and CBD have unique activities, it is becoming clear that a wider range of cannabinoids and other constituents of the cannabis plant may be involved in its various therapeutic effects. These include the cannabinoids tetrahydrocannabivarin (THCV), cannabichromene (CBC), and cannabigerol (CBG). These minor cannabinoids are thought to subtly modulate or enhance biological effects when taken therapeutically. This effect may be the result of them working on their own, or working together with THC and CBD.

The terpenes

The other main compounds in cannabis are the terpenes. These are aromatic compounds which give cannabis varieties distinctive smells and tastes. Terpenes may have additive therapeutic action, meaning they may work together with cannabinoids to modify or enhance medicinal effects. To date more than 120 different terpenes have been identified in cannabis. Unlike cannabinoids, all major terpenes present in cannabis (e.g. myrcene, alpha-pinene, and beta-caryophyllene) can be found abundantly in nature.

It is thought that the terpenes work together with cannabinoids to modify or enhance their effects. This is known as the 'entourage effect'.

The glandular trichomes

The cannabinoids and terpenes are produced in the plant's resin glands. These are called glandular trichomes. The trichomes are located on the surface of the entire plant. The largest concentration of the glands are found in the flowering heads of the female plant.

The cannabinoids exist mainly in an inactive acid form. The pharmacologically active cannabinoids (e.g., THC/CBD) are formed when cannabis is heated to a temperature of at least 180°C resulting in 'decarboxylation'. With the use of a vaporizer, the active cannabinoids are released from the glandular trichomes in a vapour at 230°C which can then be inhaled into the lungs.



Close up: The glandular trichomes containing cannabinoids and terpenes are found over the entire surface of the cannabis plant.



3 Our endocannabinoid system

Like in the case of the opioid system reacting to opioids (morphine, codeine), humans have a distinct receptor system for cannabinoids. The endocannabinoid system (ECS) contains cannabinoid (CB) receptors and influences the activity of many other body systems. The phytocannabinoids of the cannabis plant work in a similar way to our naturally produced endocannabinoids.

The human brain and other organs contain naturally occurring cannabinoid (CB) receptors and the chemicals that bind to them. This is called the human endocannabinoid system (ECS). The ECS role is to maintain our body's ability to function normally by influencing the functioning of other systems. It plays a critical role in our nervous system, and regulates multiple physiological processes. This includes the adjustment of our response to pain, appetite, digestion, sleep, mood, inflammation, and memory. The ECS also influences seizure thresholds (i.e. in epilepsy), coordination, and other processes such as the immune system, heart function, sensory integration (touch, balance, sense of space), fertility, bone physiology, the central stress response system (the HPA), neural development, and eye pressure.

Humans produce their own cannabinoids, the endocannabinoids. These endocannabinoids act on, or stimulate, the cannabinoid receptors. These compounds act in a similar way to phytocannabinoids which also bind to the receptors.

The plant cannabinoids are called phytocannabinoids. They are the unique constituents of the cannabis plant. Tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main constituents. There are other cannabinoids, but currently far less is known about them.

How cannabinoids work

Cannabinoids produce their effects by binding to specific CB receptors. Cannabinoid receptors are one of the superfamily of G-protein-coupled receptors (see illustration). So far, two types of cannabinoid receptors (CB1 and CB2) have been identified with certainty.

The CB1 receptor is found mainly in the brain and central nervous system. CB1 is also found in certain tissues and organs, such as the lungs, liver and kidneys.

The CB2 receptors are mainly found on certain cells of the immune system, the gastrointestinal tract, and in immune-related organs such as the spleen and tonsils.

The phytocannabinoid THC activates both CB1 and CB2 receptors, which in turn influences the activity of various physiological systems. CBD, by comparison to THC, has less affinity for the CB receptors, and works to partly block receptor activity.

Cannabinoid receptors

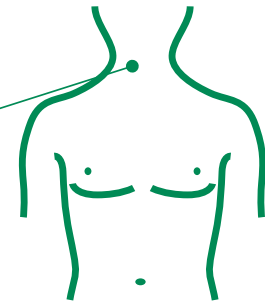
CB1 receptors

Found mainly in the brain
(hippocampus, cerebellum and cerebrum)

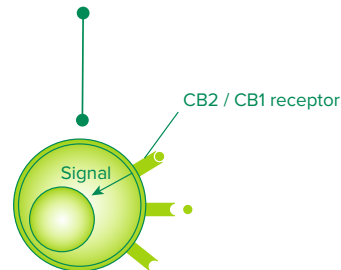


CB2 receptors

Found mainly in the organs
(spleen, tonsils, and immune cells)



CB1 & CB2 G-protein coupled receptors

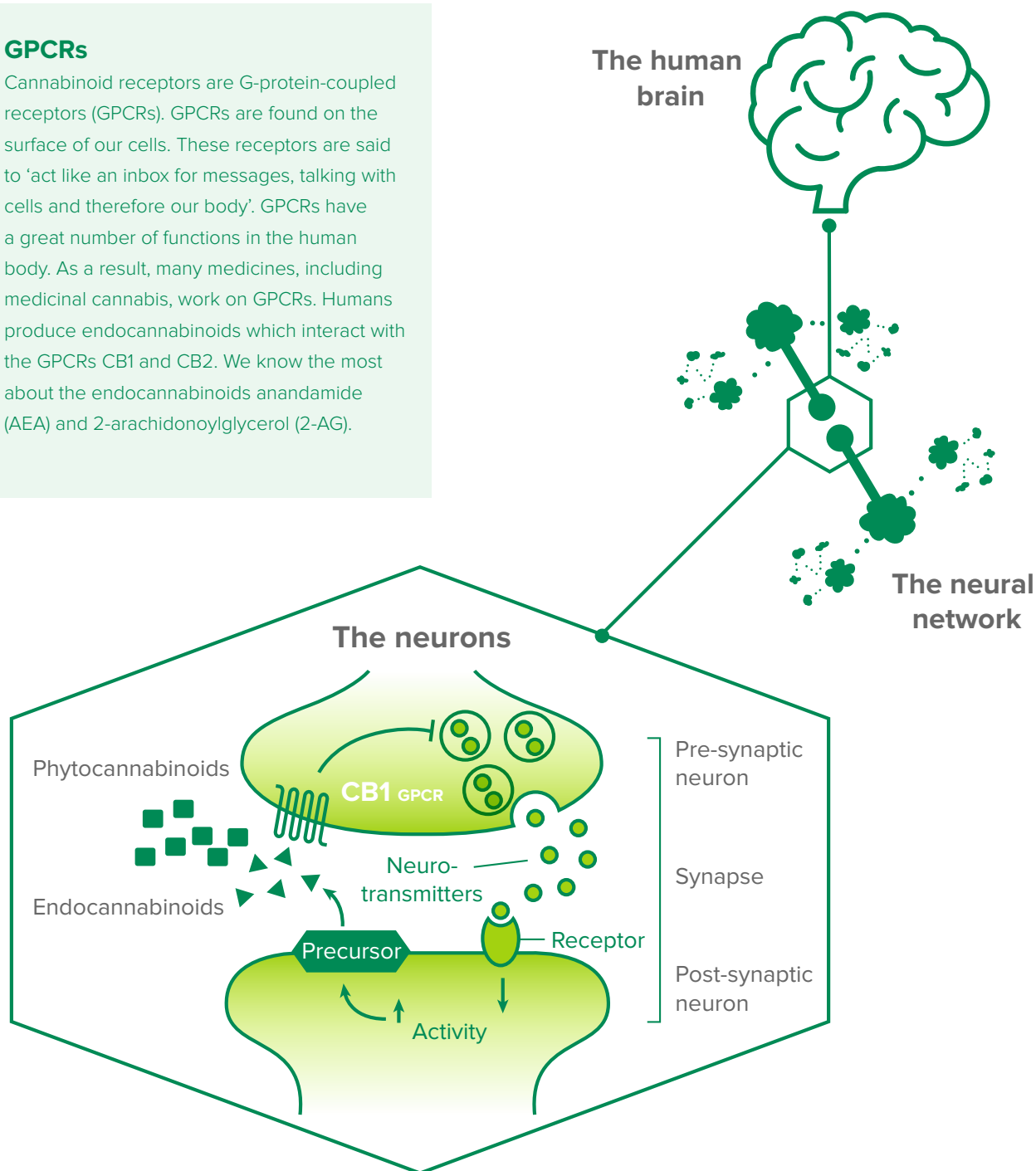


For example, the CB1 receptor is located in a number of regions of the brain which control various physical and behavioural functions. As a result, cannabinoids influence sensory and motor responsiveness (movement), heart rate, emotional reactions, appetite and nausea/vomiting, sensitivity to pain, learning and memory, and high-level decision making.

As our knowledge of the human ECS develops so will our understanding of how the phytocannabinoids, THC, CBD and other cannabinoids work. This understanding will lead to better medicines.

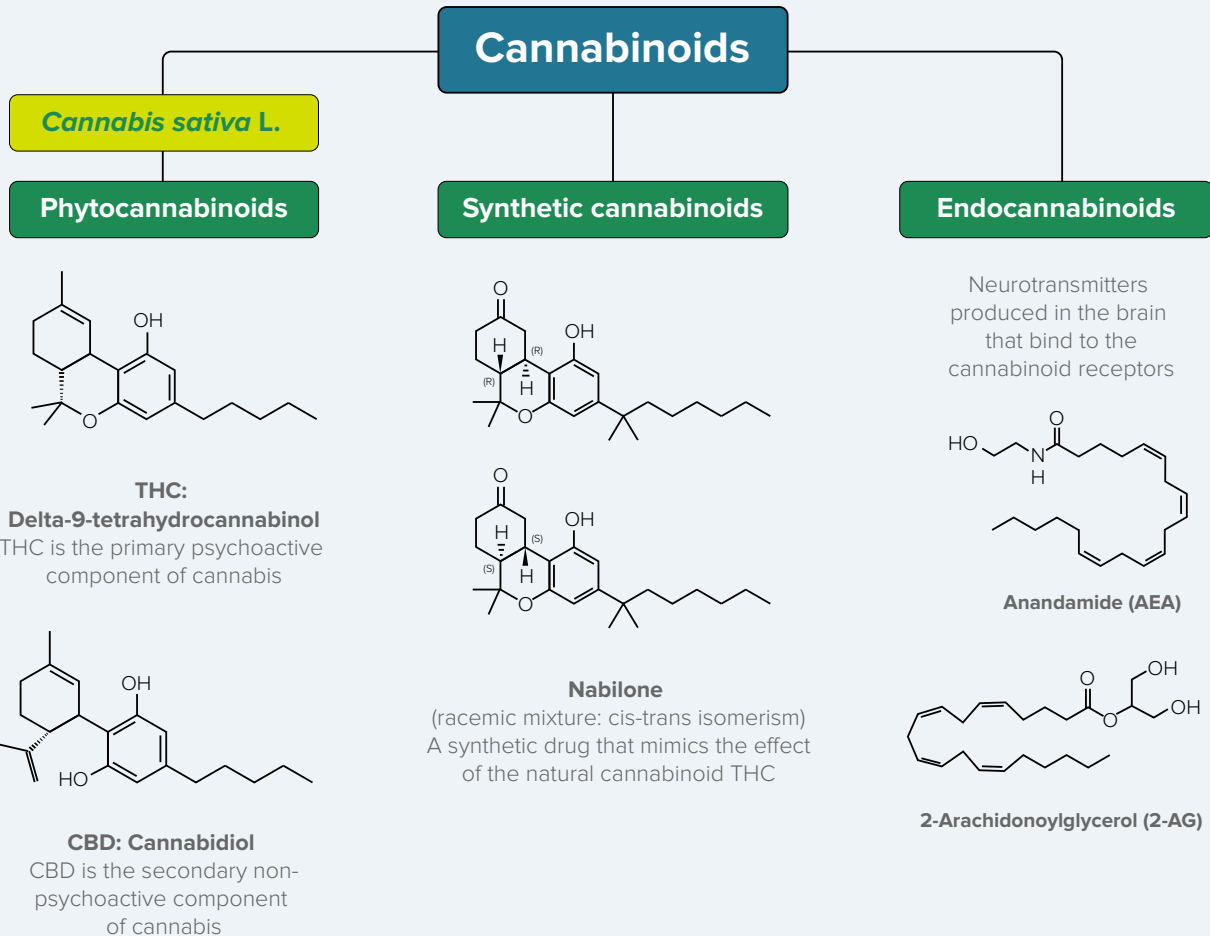
GPCRs

Cannabinoid receptors are G-protein-coupled receptors (GPCRs). GPCRs are found on the surface of our cells. These receptors are said to 'act like an inbox for messages, talking with cells and therefore our body'. GPCRs have a great number of functions in the human body. As a result, many medicines, including medicinal cannabis, work on GPCRs. Humans produce endocannabinoids which interact with the GPCRs CB1 and CB2. We know the most about the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG).



The different types of cannabinoids are briefly described in the schematic below. This includes those derived from the cannabis plant, laboratory made, and made in our bodies.

Types of cannabinoids





4 Quality and standardisation

The quality of medicinal cannabis can vary greatly. This poses risks and uncertainties to patients and their prescribers. So, why is quality so important?

Cannabis has been used in human clinical studies and found to be relatively safe for most people, compared to other medicines. However, some patients taking cannabis have had worsened symptom control and new side effects such as sleepiness, abnormal liver function and diarrhoea. Absolute safety does not exist for any medicine. All medicines can pose a risk of side effects and possibly adverse effects (resulting in harms). In particular, large doses of THC and potent synthetic cannabinoids have been shown to pose a risk of harm (e.g. postural-hypotension resulting in a fall, or a mild to severe psychotic event).

The safest and most reliable products are of pharmaceutical-quality. These products meet good manufacturing practice (GMP) standards. GMP is the highest standard of medicine manufacture. GMP is an assurance of consistently high-quality products and production processes. For medicinal cannabis, GMP practices should start from the very first step, cultivation, right through the entire production process to the finished product. It is not just about the packaging of cannabis flos, or the production of an oil extract. Under GMP, each part of the medicine production and testing process must be clearly documented. Personnel, premises and materials must meet the highest standards. These processes provide patients and prescribers with the safest and most reliable products.

A pharmaceutical-quality product could be, for example, cannabis flos for inhalation, a capsule for swallowing or a spray for the mouth. Each product type will require a slightly different set of tests for quality. These tests are often published. The pharmacopoeia monographs, for example, are the most reliable published methods for the analysis of medicines. These monographs explain the standards for potency, quality and so on. Medicinal cannabis products are required to be independently tested by specialised laboratories. The tests laboratories undertake often include:

- **The identification of cannabis** – Medicinal cannabis products typically must be derived only from the cannabis plant. An important first step is to test the plant material to confirm it is actually cannabis, and not an adulterant or substitute.
- **The identification of active ingredients** – There are numerous components of the cannabis plant. This test typically requires identifying THC and CBD, and often the terpene content.
- **The absence/presence of microorganisms** – During cultivation the cannabis plant can host harmful microorganisms like fungi and bacteria which can end up in the finished product. This may require decontamination treatment by gamma irradiation to eliminate microorganisms such as *Staphylococcus Aureus* and *Escherichia Coli*. The process must not affect the quality of the finished product.
- **The absence/presence of pesticides** – Many different types of pesticides can be used in cannabis cultivation, but none are approved for use in cannabis. This test ensures the finished product does not contain pesticides which are very harmful to patients' health.
- **The absence/presence of heavy metals** – The cannabis plant can quickly take up heavy metals from soil – termed heavy metal bio-accumulation. Every batch must be checked for the presence of harmful heavy metals such as arsenic, cadmium, lead and mercury.
- **The absence/presence of foreign matter** – It is essential that the final plant material (and the finished product dose form) is free from impurities such as soil, dust, dirt and other contaminations.
- **The total water content** – For cannabis flos which is intended to be inhaled by vaporization, the final water content is important. The right amount of moisture (water content) in dried cannabis flos assures an easy inhalation process during vaporization.



The cornerstone of reliability

Medicines must have a clearly defined composition. GMP-certified, fully standardised medicinal cannabis contains a constant composition active ingredients, batch-to-batch. This means the same dose can be taken each time. Doctors can better monitor dosage, condition progress, and reduce the risk of overdose and side effects. These products are also free of microbial contaminants (moulds, fungi, and bacteria), pesticides, and heavy metals. These are qualities which are especially important for people with weakened immune systems, and which make the products safe for vaporization and inhalation into the lungs. Finally, standardisation allows the comparison of different clinical trials and studies across time. It is a critical factor for building the evidence base of medicinal cannabis.

Batch-to-batch consistency is a challenge. The cannabis plant is chemically complex and can vary greatly from plant-to-plant. Growing standardised cannabis means consistently achieving a balance of all potential active components (specifically the cannabinoids and terpenes). This must be confirmed batch-to-batch by laboratories who issue Certificates of Analysis.

The most common approach standardisation is to select cannabis cultivars with good genetic stability and that originate from one single seed. These plants are then grown by multiplying the original plant material. Copying a fragment of the mother plant helps to prevent 'genetic drift', which can cause major changes and weakness in the plant over time.

To achieve batch-to-batch consistency in the plant is very difficult. Indeed, to date, only one company, Bedrocan in the Netherlands, has been able to achieve fully standardised cannabis flos with GMP certification.

Indoor versus outdoor cultivation

The discussion around standardisation continues with comparing indoor and outdoor cannabis cultivation. This is because the chemical composition of cannabis is determined by the plant's genetics, and the total content is most influenced by the plant's growing conditions.

Indoor, fully controlled cultivation allows for fully standardised cannabis flos (the whole dried female flowers) and whole plant extracts (containing cannabinoids and terpenes) year-round. Controlling all growing conditions and the plant's genetic composition produces a finished product, free of contaminants, and containing an exact content of active components. The production of cannabis flos, in compliance with pharmaceutical standards of GMP, is only possible within fully controlled environments and using plants with stable genetics.

Outdoor cultivation, including in fields or greenhouses, produces genetically undefined, non-standardised cannabis. Outdoor cultivation is suitable for single cannabinoid extraction (i.e. THC or CBD). Outdoor cultivation, from seed, produces plants with a dissimilar genetic composition and inexact content of active components. An uncontrolled growing environment is likely to permit cross-pollination which reduces the quantity and quality of cannabinoids. It also increases the risk of contamination with pesticides, heavy metals, and hazardous moulds, bacteria and fungi.

From cannabis cultivation to cannabis flos

Below is a pictorial illustration of an indoor cultivation growth cycle and production of standardised, GMP-certified pharmaceutical-quality cannabis flos.



A cutting is obtained



Plants are placed into Rockwool



The plants are placed in a growing room



The harvested cannabis plant is dried



The stems and leaves are removed



The cannabis flos is packaged



5 Dosage forms and their administration

Like other medicines, medicinal cannabis is available in different dose forms (e.g., inhalation, oral, transdermal) to meet different patient requirements. How medicinal cannabis is administered or taken depends on its dose form.

In this section we talk about the most common ways medicinal cannabis is taken by patients across the world. In the next section we talk about how cannabis is absorbed, distributed, metabolised and then excreted (removed) from our body.

The dose form is really important. It can influence patient behaviour in different ways, including:

- If patients actually take their medicine, and adhere to their daily regimen
- When they take it (the time of day)
- How often they take it (the frequency of use)
- How much they have to take (total daily dosage)
- The side effects and how these are tolerated



Inhalation – by the lung



Dose form

Using a vaporizer or inhalation medical device, cannabinoids are inhaled (from cannabis flos) as a vapour which then enter the bloodstream from the lungs.

Inhalation has proven to be an efficient administration route. The inhaled vapour is quickly absorbed by the lungs. The immediate onset of action means it is the preferred choice for many patients. The vapour contains cannabinoids and terpenes in consistent, measurable quantities. The speed of onset simplifies titration - the ability to achieve the correct dose without side effects - and achieve fast relief from symptoms. The amount of cannabinoids delivered depends on the depth of inhalation and breath hold. While inhalation results in higher blood levels of cannabinoids, their effects compared to oral administration is shorter in duration.

Medical vaporizer

Given the risks from smoking, patients nowadays seek reliable, affordable and portable vaporizers or inhalation devices. Research dedicated to advancing vaporizer and inhalation technology has seen major developments in device quality.

Medical vaporizers for the administration of cannabis flos - instantly we think of e-cigarettes or vape-pens - are in fact quite different. The vapour does not contain nicotine, liquid propylene glycol, glycerol nor synthetic flavours. There is also no large, socially intrusive, toxic vapour cloud. These vaporizers (or inhalation devices) offer patients an effective, safe, and easy to use delivery system.

Smoking

Ultimately, smoking medicinal cannabis is harmful to patients' health and is therefore not recommended. Toxic pyrolytic compounds are produced when the plant material is smoked (i.e. combustion). Typically cannabis flos is rolled into a 'joint' cigarette, and cannabinoids are inhaled as smoke into the lungs. The medicine enters into the bloodstream from the lungs. Smoking cannabis results a rapid onset of action. The effect is noticed within minutes. While smoking results in higher blood levels of cannabinoids, their effects compared to oral administration is shorter in duration. Furthermore, unless it is fully standardised, the amount of THC and CBD in cannabis flos can vary greatly between batches. The amount of THC delivered also depends on the depth of inhalation, puff volume and duration, and breath hold.

Pharmaceutical quality cannabis flos

For vaporization to deliver consistent therapeutic levels of cannabinoids, the product must be of pharmaceutical quality. This cannabis flos is genetically and chemically standardised according to pharmaceutical standards. From a patient safety perspective, it is free of microbial contaminants, pesticides, impurities and heavy metals. These are qualities that make the vapour safer for inhalation into the lungs.

Oral – by the mouth



Dose form

Cannabinoids (whole plant extracts or individual cannabinoids) taken by mouth and either swallowed (oral), or absorbed from under the tongue (sublingual). When swallowed, the medicine enters into the bloodstream via the stomach, intestines and the liver. When absorbed from under the tongue, the medicine bypasses the liver and enters into the bloodstream directly.

Oral preparations are familiar dose forms. They are similar to other medicines patients already take, and are easy to administer. As a result, concentrated cannabis extracts are becoming increasingly popular.

Oils

An increasing number of patients are using extracts of cannabis flos. Whole plant cannabis extracts contain cannabinoids and terpenes in a concentrated dose form. Often they are called 'oil' because of their dark viscous appearance. The extract is dissolved in an oil (e.g., olive, sunflower, peanut) to act as a carrier and ease administration.

A single dose can be dispensed from a dropper and placed under the tongue. It is absorbed from the lining of the mouth (termed sublingual absorption) where upon it enters the bloodstream.

Sublingual delivery increases total available dose. This means smaller doses are required for the same effect, compared to swallowing capsules or drinking tea.

Sublingual dose forms can provide a reliable uniform dose.

Sprays

Sprays are also administered under the tongue just as oils. An example is Sativex™, a standardised (oromucosal) dose form of a pharmaceutical product, made from two strains of cannabis. One strain produces mainly THC and the other mainly CBD. Exacting proportions of the active compounds THC and CBD are dissolved in an alcohol solution. This is placed in a metered-dose bottle which is sprayed under the tongue.

Capsules

An alternative oral dose form are capsules. These typically contain exacting concentrations of single cannabinoids (i.e. THC and CBD) dissolved in a carrier oil. The capsule is swallowed, breaks open, the drug is released and finally absorbed in the stomach and intestines. The rate (time) of absorption can be unpredictable, and varies depending on, for example, if food is present, and if the patient is mobile (able to exercise/walk freely). Interestingly, THC itself slows the rate of gastric emptying (from the stomach to intestine). Oral administration (by swallowing) results in slower onset of action, lower total blood concentration, and a longer duration of effects compared to inhalation. Total cannabinoid content is affected by liver metabolism and stomach contents. This means oral dosing can be less unreliable and unpredictable.

Tea or infusion

A proportion of patients consume medicinal cannabis as a tea (cannabis flos infused in hot water). Teas are swallowed and the cannabinoids are absorbed in the stomach and small intestine. Similar to oral dosing, the total cannabinoid content is affected by liver metabolism and stomach contents. This means dosing by tea may be unreliable and unpredictable.

Furthermore, tea typically has a low concentration of cannabinoids, the tea composition is effected by boiling time, volume of tea prepared, and the length of time in storage. This means dosing by tea can provide a less certain therapeutic effect.

Edibles

Other whole plant dose forms include edibles such as cookies/brownies. It is difficult to obtain a consistent cannabinoid composition in edibles. Patients can easily overdose, particularly as the time to effect may be 2-3 hours and patients may ingest a second dose if they are awaiting effects.

The therapeutic effect is less certain than standardised oral products and it usually takes longer to achieve. As a result, edibles are not considered a therapeutic product.

The importance of standardisation

There are numerous oil products available on the market. Their quality and reliability relies on the quality of the starting material, cannabis flos. Because most extraction companies don't use fully standardised cannabis flos, the total cannabinoid content of the extract often is different to the medicine label. Some companies' medicine labels show a 'target' cannabinoid concentration. This is because the cannabinoid concentrations in the cannabis starting material varies from batch-to-batch. Unpredictable medicine concentrations are a concern for patient safety. This is because the quality of a medicine is partly determined by 'accuracy of dosing' and 'reproducibility' of the dose.

Transdermal – by the skin



Dose form

Transdermal literally means across the skin. The typical dose forms include creams which are applied to the skin surface or a mucous membrane; and, transdermal patches which are a medicated adhesive patch applied directly on the skin. A specific dose is then administered gradually over a set time.

Transdermal dose forms are being investigated for their clinical use and application. Currently they are being used to treat certain skin conditions and for localised muscular or joint pain.

Given that most cannabinoids dislike water (are highly hydrophobic), it can be difficult to achieve a reliable dose form that is applied to the skin and can achieve appropriate blood concentrations. However, novel nanotechnology may overcome this. Dose forms such as creams are intended for local application and action. These do not require achieving penetration through the skin into the blood stream.



The importance of form

The form in which medicinal cannabis is administered determines the onset, intensity, and duration of effects (how it moves and works in our body). The major factors which determine the selection of dose form include:

- **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 fraction of the dose that reaches the bloodstream to provide a therapeutic effect. Typically, intravenous injections have the greatest bioavailability (direct to bloodstream), then inhalation, sublingual, buccal oral mucosal, rectal and oral and transdermal dose forms.
- **Onset of action** – the amount 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, is of good quality and does not cause harm or intolerable side effects.

6 How cannabinoids move through the body

Determining how a medicine is going to work for an individual patient is very important to medicine safety and efficacy. The way the cannabinoids THC and CBD move through the body (pharmacokinetics) varies depending upon how it is taken. The duration of their action is influenced by dose size, dose form, and the route of administration - the lungs, mouth, gut or the skin.

Absorption and distribution

THC and CBD are mainly found in cannabis in their inactive acid form. To activate THC and CBD a carboxyl group must be removed by heat. In practice, this so called 'decarboxylation' occurs by heating cannabis flos in a vaporizer, or heating the cannabis flos extracts before being placed into a solution.

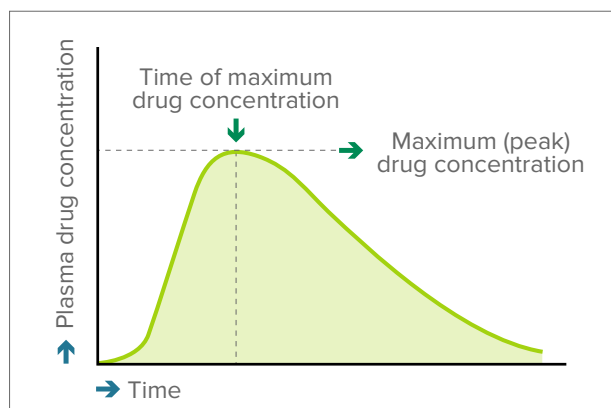
The absorption of inhaled cannabinoids results in a maximum (peak) blood concentration within minutes (see figure). Effects in the brain start within seconds to a few minutes, and reach a maximum after 15-30 minutes. They taper off within 2-3 hours.

Absorption is slower when cannabinoids are ingested. Lower, more-delayed peak concentrations occur with oral ingestion. The effects in the brain are delayed for 30-90 minutes, and reach their maximum after 2-3 hours. They last for about 4-12 hours.

Bioavailability describes the proportion of a medicine entering blood circulation after administration. The bioavailability of oral THC and CBD is low. By comparison, the inhalation of cannabinoids has been shown to be more effective and reliable compared to oral administration.

Pharmacokinetics

Pharmacokinetics is abbreviated as PK. It is the study of the movement of medicine within the body. The acronym ADME is used to describe a medicine's Absorption, its Distribution, Metabolism, and final Excretion from our body.



The pharmacokinetic profile of a medicine is described as the medicines blood plasma concentration over a period of time.

THC and CBD are fat soluble (highly lipophilic) compounds which are rapidly absorbed by the lungs. As a result, inhalation is a convenient and fast-acting method of administration, allowing easier titration to the desired dosage and biological effect. About 25% of inhaled THC enters the blood circulation.

The distribution of cannabinoids in the body are ruled by their lipophilicity (their fat solubility) and binding to blood proteins. THC is distributed widely throughout the body, particularly to fatty tissues. The body storage of THC increases with increasing frequency and duration of use.

Metabolism and elimination

The cannabinoids are mainly metabolised by a collection of liver enzymes called cytochrome P450 (CYP450). The same as many other medicines, these enzymes chemically alter the cannabinoids to remove them from our body (excretion). Besides the liver, other tissues like the heart and lungs are also able to metabolise cannabinoids, albeit to a lesser degree. THC and CBD metabolism follows a similar metabolic route.

Elimination of medicines means their complete removal from our body. Metabolism is the major route for the removal of THC. Unlike THC, a large proportion of CBD is excreted unchanged. Within 5 days of taking a single dose, a total of 80–90% of THC is excreted. The elimination of THC and its metabolites occurs via the faeces and urine. After inhalation, about 25% of the absorbed dose is excreted in the urine; about 65% is eliminated via faeces. Only very small amounts of THC are excreted unchanged. Less than 5% of an oral dose is found unchanged in the faeces. THC metabolites can be found in the urine and faeces for several weeks.

The slow elimination of cannabinoids and their metabolites is due to their slow movement out of our body fat and other tissues back into the bloodstream.



First-pass metabolism and THC

A metabolite is a substance formed during metabolism – a breakdown product. After swallowing a medicine it is then absorbed in the small intestine and carried to the liver and metabolised. This is called first-pass metabolism. First-pass metabolism greatly reduces the medicine concentration, meaning only a proportion of the original medicine reaches the blood circulation. In some cases, the metabolite can be potent and long acting. For THC, the metabolite 11-hydroxy-THC (11-OH-THC) is about twice as psychoactive as THC itself. When THC is inhaled, it avoids first-pass metabolism and its rapid conversion to 11-OH-THC.

7 Prescribing medicinal cannabis

When used rationally and correctly, medicines can be effective in treating or preventing disease. If misused, they can cause harm. This includes medicinal cannabis. In this section we discuss the prescribing of medicinal cannabis.

Medicinal cannabis is a rapidly changing field of medicine, with new products, scientific and clinical data emerging. In the last decade, clinical research has mainly focused on the therapeutic effects of cannabinoids as an analgesic in chronic neuropathic pain, as an appetite stimulant in cancer, and in the treatment of spasticity in multiple sclerosis. Other indications include for example in anxiety, psychosis, and fibromyalgia. More recently, cannabidiol (CBD) has emerged as a single cannabinoid with plausible therapeutic action in childhood epilepsy. Clinical trial reviews provide insight to relevant conditions and dosing, while newly published supporting information on plant chemistry, cultivation, quality analysis, and administration adds value to knowledge of product safety and prescribing practice.

Conditions which show promise

There is clinical research supporting the use of medicinal cannabis in certain conditions including:

- Chronic pain, particularly pain associated with the nervous system, caused for example by a damaged nerve, phantom pain and facial neuralgia
- Nausea, loss of appetite, weight loss, and vomiting associated with chemotherapy or radiotherapy used in the treatment of cancer, and anorexia and cachexia in HIV/AIDS
- Pain and muscle spasms or cramps associated with multiple sclerosis or spinal cord damage

For other conditions there is less available or negative clinical data. These include, epilepsy (particularly the drug resistant childhood epilepsies), Gilles de la Tourette syndrome, therapy-resistant glaucoma, fibromyalgia; post-traumatic stress disorder, sleep disorders, bladder dysfunction, some symptoms of Parkinson's disease, and depression. While existing scientific evidence does not fully support a specific condition, a paucity of clinical research does not necessarily reflect the potential of medicinal cannabis in a given disease for a particular patient.

The next summary covers clinical insights for areas of interest to most readers. These include chronic pain; nausea, vomiting and appetite; multiple sclerosis; and epilepsy.

Chronic pain

Severe chronic pain seems to be the major reason for which patients use medicinal cannabis. There are many types of pain, and cannabinoids do not influence each pain type identically. To date, the therapeutic benefit of medicinal cannabis has only been seen in neuropathic pain studies – the pain originating from injury or disease that affects the sensory nerves. By comparison, studies measuring the effects on acute pain (e.g. postoperative pain) often show no beneficial effects. Most likely, this difference is related to the role endocannabinoids play in both types of pain. However, the mechanism behind this difference is not yet fully understood.

Chronic neuropathic pain is common, difficult to treat, and has limited treatment options. Consequently, even the modest effects of cannabinoids may be important for patients. Patient preference studies show the side effects from cannabinoids are better tolerated than strong opioid medications. Indeed, medicinal cannabis has often been studied in combination with other medicines, including for example morphine. It has been found that cannabinoids and opioids work together with a strong combined effect.



Nausea, vomiting and appetite

Cannabinoids can have strong effects on nausea and vomiting resulting from cancer chemotherapy or radiotherapy, hepatitis C and HIV/AIDS treatments. A synthetic THC dose form (as Marinol®) has been widely used as an antiemetic for cancer patients undergoing chemotherapy. Supporting studies suggest that the addition of THC directly before and after chemotherapy offer more benefit than using older antiemetic medications. However these have not been compared against the latest antiemetic medications which are significantly more effective in this setting than the older ones.

Cannabinoids have been shown to stimulate appetite, described as a strong desire for foods with high fat or sugar content. For example, since the 1980's, Marinol® has been used as an appetite stimulant for weight loss in patients with HIV/AIDS. For patients experiencing loss of appetite, a high caloric intake may contribute to weight gain and to the absorption of nutrients. Often this is crucial in managing medical conditions such as wasting syndrome (cachexia).

Although other drugs are available to treat nausea, vomiting, or reduced appetite, the combined effect of cannabinoids on all these symptoms at once makes it a unique option for contributing to improving a patient's quality of life.

Multiple sclerosis

Together with chronic pain, multiple sclerosis (MS) is the other medical condition in which long-term effects of cannabinoids have been extensively studied. The research show patients do not develop a tolerance for the medicinal effects, nor increase their doses over time to achieve the same therapeutic result. Although the medical evidence supporting cannabis use for MS is still limited, it is important to note the same is true for most conventional MS medications.

As a result, patients suffering from MS have historically experimented with alternative therapies, including cannabis, to improve their quality of life. Standard therapies often provide inadequate relief and can be limited by medication side effects. Existing scientific evidence supports the use of medicinal cannabis to treat disease-related pain, bladder symptoms, tremor, and spasticity. Additionally, for many patients cannabinoids improves sleep, resulting in both deeper and longer sleep.

Epilepsy

Epilepsy is typically well-controlled by existing medications. However, a significant number of people with epilepsy do not have adequate control of their seizures. As early as in 1979, laboratory studies confirmed the anticonvulsant effects of (pure) CBD. In various subsequent animal and (small-scale) human studies, CBD was able to reduce the frequency and severity of seizures. Combined with an absence of psychoactive effects, these results show the potential of CBD as a treatment for human epilepsy.

Unfortunately, the low quality of most the reported scientific data does not allow for making definite conclusions on the potential of cannabinoids as a treatment for epilepsy. In addition, the safety and tolerability of cannabinoid preparations in a paediatric population is not fully clear. Although CBD appears to be effective in reducing seizures in epilepsy patients, more controlled research is needed to understand the full clinical value of these types of products.

Dose, dosage and titration

Like with other medicines, individual patients will respond differently to medicinal cannabis. Their response depends on the cannabis product used, the condition being treated, the duration of treatment, how it is administered, and genetic predispositions. Certain ratios of cannabinoids have so far emerged to be the basis of specific effects; and appear to be better tolerated than single compounds (especially high doses of THC).

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

A treatment protocol provides patients with advice on:

- An appropriate starting dose
- How to increase their dose (minimum and maximum dose)
- How to find an optimal daily dosage based the severity of the patient's condition, and changes in their other medication
- How to maintain their daily dosage
- Medicine and food interactions
- Ways to reduce the risk of side effects or adverse reactions occurring
- A plan to stop treatment if there is a poor response

Safety

Potential medicine interactions

Medicines can interact with each other. The risk increases if a patient is taking lots of medicines at once. Indeed, patients' who are prescribed medicinal cannabis often have complex conditions and take multiple medicines.

There are a number of medicines medicinal cannabis may interact with. Care should be taken when co-prescribing medicines with sedating effects, which also includes drinking alcohol. The combination of cannabinoids and sedatives can affect response time, co-ordination, and concentration. Cannabinoids may also interact with heart and circulation medicines (e.g. adrenaline, beta-blockers, and diuretics). Also, THC appears to enhance the action of opioids (e.g. codeine, morphine).

The above list is not exhaustive. A full review should be undertaken before co-prescribing, including those medicines which interact with the CYP-450 metabolic enzymes.

Potential side effects

In general, patients seem to tolerate medicinal cannabis well. Typical side effects last a short time, are mostly benign, and resolve as tolerance builds. Side effects mainly occur after taking high doses, or when used in combination with other substances. These tend to occur quickly after use. Signs of side effects include:

- Dry mouth
- Redness of the eyes
- Heightened appetite (which may be desirable)
- Mild euphoria
- 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, all side effects will slowly decrease and then disappear within a few hours. This depends upon the dose taken and mode of administration.

Overdosing

Overdose can usually be prevented by preparing a treatment protocol. When using too large doses containing THC, a patient may experience intoxication. This is often described as a mild euphoria or results in sedation and somnolence. In some cases, this can be experienced as a distortion of reality, mild anxiety, changes in heart rate and blood pressure. In these cases, most often, it is sufficient for patients to sit or lay down in a calm and comfortable location, preferably with someone familiar to talk to. Overdosing with very high doses may result in a psychotic state or other psychiatric conditions, particularly in those with a pre-existing genetic vulnerability (see below).

Risks

Like any other medicine, medicinal cannabis is certainly not without risks. The known risk factors and precautions are briefly described in the non-exhaustive list below.

Prescribing for the elderly

Elderly patients are more sensitive to the neurological, psychoactive and postural-hypotensive (feeling dizzy or lightheaded) effects of medicinal cannabis (particularly THC). This is especially so for elderly patients who are prone to falls and those with dementia. If considered appropriate, elderly patients should start at the low end of the dosing range.

Cannabinoids can have a significant effect on heart rate and blood pressure

Psychosis or other psychiatric conditions

Medicinal cannabis should not be used in patients with a family history or previous episode of psychosis, psychiatric conditions or major depression because THC may bring on psychotic symptoms.

Heart disease cardiac/coronary conditions

Cannabinoids can have a significant effect on heart rate (hypertension, tachycardia) and blood pressure (vascular constriction) which can cause cardiac ischaemia. Patients with a history of heart disease or receiving heart medication should avoid use, or only use medicinal cannabis under careful supervision by their doctor.

Pregnancy and lactation

The use of medicinal cannabis during pregnancy is likely to affect the development of the fetus and should not be prescribed. Because certain cannabinoids – including THC – are excreted in breast milk, use is also not advised while breastfeeding.

Liver disease

After administration, the liver is the main organ involved in chemically altering the cannabinoids to remove them from our body (metabolism). Patients with liver disease should be monitored to make sure the dosage does not exceed the liver's ability to remove it (metabolic capacity).

Addiction and aberrant prescribing

The evidence suggests that the risk of developing an addiction to cannabis when taken as a medicine is not common. Nonetheless, particular care should be taken if patients have prior problematic substance use. High doses of medicinal cannabis, taken over long periods, could lead to dose escalation, misuse and harm. Abrupt ending of treatment may cause withdrawal symptoms, such as restlessness, irritability, insomnia, vivid dreams and decreased appetite.

Diversion and misuse

Cannabinoid therapeutic products containing THC are often considered desirable psychoactive substances. Like other controlled drugs, medicinal cannabis requires the same guidance and considerations by doctors and pharmacists to limit diversion and misuse.

Driving and operating machinery

At therapeutic doses, cannabis may produce undesirable effects such as dizziness and drowsiness which may impair judgement and performance. Patients should not drive, operate machinery or engage in any potentially hazardous activity under the influence of medicinal cannabis or cannabinoid therapeutic products that contain THC.

What is pharmacovigilance?

Pharmacovigilance is the collection and evaluation of information from healthcare providers and patients on the adverse effects of medicines. Monitoring the use of medicines in everyday use helps to identify previously unrecognised adverse effects or changes in the patterns of adverse effects.

Medicine quality and safety relies on patients, their carers, and healthcare professionals to report problems with medicines and administration devices (droppers, syringes, vaporizers, transdermal patches). Pharmaceutical companies and regulatory agencies can then investigate reports, identify the specific cause, and determine any necessary regulatory action to resolve the problem.

Most importantly, understanding why a medicine is causing harm can lead to improvements. This is for the benefit of patients.



8 Health professional perspectives

Who can prescribe and dispense medicinal cannabis depends on country specific policy. Most often health professionals are the gatekeepers to patient access. In particular, prescribers and pharmacists have an important role to play. In a prescriber-pharmacy model, patients are offered more objective communication of risks and benefits, and the safety of health professional guidance.

However, many health professionals do not know how medicinal cannabis should be prescribed and dispensed. This is not surprising given that medicinal cannabis is a new class of medicine. The traditional approach to drug discovery and development, including clinical trials, have not been undertaken on most products. Clinicians are now rapidly trying to understand how they work.

We have talked about the potential place of medicinal cannabis in the medical toolbox. So how should it be prescribed and dispensed? This section presents two case studies: one from the perspective of a pain specialist, and the other from a community pharmacist. They highlight prescribing and dispensing realities, and strategies to improve patient safety. The information shared in these case studies are context-specific and not intended to support decision making by prescribers and pharmacists.

This section focuses on the Netherlands. It has the longest running medicinal cannabis programme (since 2003) and provides fully standardised medicines under the guidance of prescribers and pharmacists. This is the same guidance patients receive with traditional medicines. The insights below are drawn from two professionals with extensive experience working with standardised oral and inhalation dose forms.



Many health professionals do not know how medicinal cannabis should be prescribed

Prescribing medicinal cannabis

Trained as an anaesthesiologist in Germany, **Dr Jürgen Fleisch** then undertook a fellowship in pain medicine (Portland, Oregon). He now practices anaesthesiology and pain therapy in the Netherlands at the Leiden University Medical Centre. For the last decade, his close cooperation with the Department of Oncology means he regularly treats symptoms in cancer patients using medicinal cannabis. In both settings, he typically encounters two types of patients. Those with advanced cancer experiencing loss of appetite and possibly nausea and vomiting, and often many other medications have been tried before. And, those that experience central neuropathic pain after unsuccessful trials of more common medications.

With a focus on safe prescribing practices, prescribers play a pivotal role in managing patient therapy. This is especially important when patients take multiple medicines.



Prescribing

Do you have any advice for doctors starting out prescribing?

"My advice for clinicians who are starting to prescribe medicinal cannabis is to stick to specific indications where there is a solid foundation of evidence for its use. This allows us to gain experience with the effects of this medication in a specific adult patient population."

Recreational cannabis users are, in my opinion, not a good patient category to start with. They may put considerable pressure on the clinician to prescribe for dubious indications."

How is prescribing medicinal cannabis different to prescribing other medicines?

"They are like any other medicine. However, many patients will have an opinion about cannabis. For some it has a rather negative connotation as being a substance of abuse."

What are the key benefits of cannabinoids as a therapeutic product?

"There are three main advantages of medicinal cannabis in general over other medicines used in my field of pain medicine, as follows:

- *There are analgesic effects on neuropathic pain syndromes and, depending on the medicine type, anti-emetic and appetite stimulating effects. This is especially important for cancer patients with pain.*
- *There are no known organ damaging side effects in the adult patient, aside from the potential risk to mental health. As compared to, for example, those linked with using NSAIDs when used inappropriately.*
- *Some cannabis flos variants have a soothing effect, which some patients greatly appreciate."*

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

"For patients with no experience using cannabis products, the possible psychological side effects can be distressing. In order to avoid this we advise patients to start with low dosage and use the medicine in a quiet and relaxing environment."

In our experience, it is advantageous to prescribe cannabis flos as an inhalational agent, administered by vaporization, as it creates more rapid analgesic effects and has a more reliable absorption profile."

With cannabis flos, the prescribing clinician needs to be aware that in many countries the standards are different with respect to "regular" medicines: concerning the quality control of the active ingredient, and toxicological contamination. Using cannabis flos originating from controlled producers means patients are assured there is no biological or toxicological contamination."

Aside from eliminating the harms from smoking, what are the benefits of administration by vaporization?

"Using vaporized cannabis flos is the preferred means of use by most patients, especially when compared with an oral application. This is due to the more rapid effect by inhalation."

With vaporization cannabis flos is heated to a specific temperature without burning it. Cannabinoids and terpenes are released in a vapour which is directly inhaled."

There are three main advantages of administration by vaporization is that it:

- *Allows for exact dosing,*
- *Leads to a rapid effect, and*
- *Avoids the disadvantages of smoking (i.e., no tar, ammonia, carbon monoxide)."*

Patient considerations

Thinking about a first consultation with a patient, how do you start a conversation about medicinal cannabis?

"There are two types of discussion around the use of medicinal cannabis:

The elderly, cannabis naive patient:

An elderly cancer patient may be hesitant to use cannabis as a medication. This likely is related to prejudices about cannabis being a product for 'recreational' use. With these patients, I rarely discuss the use of these medicines during a first consult. If the patient is eligible and several other therapies did not provide sufficient pain relief, I then mention medicinal cannabis as a possible option. This allows the patient and his/her family to contemplate that treatment option until the next appointment."

The experienced patient:

There may be patients who have extensive experience using cannabis recreationally. They may be actively looking into medicinal cannabis as a potential adjunct to their pain therapy. These patients emphasise the ineffectiveness or side effects of other therapies, and may push clinicians towards prescribing a cannabis product. With these patients the topic must be discussed fully during a first consult. The main question during this consult is 'are they at all eligible to receive medicinal cannabis?'"

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

"Indeed, we do see patients who experience drug interactions using cannabinoid therapeutics alongside other CNS depressant medications (e.g. opioids).

Sedative effects can be enhanced especially in the geriatric population. Severe drowsiness and hallucinations can also be provoked.

Aside from drug interactions, the smoking of cannabis is related to an increased risk of myocardial infarction and stroke. Cannabis as a trigger of myocardial infarction is plausible, given its cardio-stimulatory effects, which may cause ischemia in susceptible hearts. Carboxy-hemoglobinemia from the smoking of cannabis may also contribute to ischemia. Smoking is never recommended."

Do you encounter diversion for misuse or the abuse of medicinal cannabis? How do you identify this issue in your practice?

"During the period when Dutch health insurers widely reimbursed medicinal cannabis, we had frequent discussions with patients, best described as 'recreational users', about their eligibility.

Patients of this group, who were already using large amounts of cannabis, were requesting access for rather dubious indications. Some patients were seeing medicinal cannabis as a cheap way to get a 'recreational drug' which they were already abusing."

How do you deal with diversion for misuse or abuse in your practice?

"This patient group can be quite challenging. They may put pressure on clinicians to prescribe medicinal cannabis as the only means to relieve their pain. Mentioning misuse and abuse can provoke abrupt reactions.

Clinicians should be coherent in prescribing medicinal cannabis only for indications with enough evidence for beneficial effects (e.g. analgesic for neuropathic pain, appetite stimulation). Misuse and abuse should be discussed openly if they become apparent."

Smoking is never recommended

Dispensing medicinal cannabis

As a pharmacist at Transvaal Apotheek, **Salma Boudhan** dispenses cannabis flos, and oil extracts for named patients throughout the Netherlands. Based in The Hague, Transvaal Apotheek has been meeting patient needs since the late 1800's. A patient recently said she had been coming there for more than 70 years. Transvaal has dispensed medicinal cannabis (flos) since it was legalised in 2003, and high quality whole cannabis oil extracts for sublingual use since 2015. A typical patient arriving at Transvaal are those suffering from cancer pain, nausea and vomiting; neuropathic pain; or epilepsy.

The role of pharmacists is just as important as prescribers. Pharmacists support prescribers with patient medicine reviews, and talk with patients about a medicine's risks and benefits. They help to minimise medicine misuse and harm, and seek feedback on safety, effectiveness and adverse reactions.



Administration

Oral dose forms (oil extracts) are an increasingly popular, what advice do you give patients on safe use?

"In accordance with their doctor's prescription, we suggest that patients start low and go slow. As a starting dose for oil, we recommend to use 2 drops (0,05ml) under the tongue, 3 times a day and increase the dose until the desired effect is achieved. The maximum dosage is 10 drops (0,25ml), 3 times a day.

The 'steady state' concentration of THC/CBD and the active metabolite is reached after 1-2 weeks. This time span should be taken into account for the assessment of the medicines effectiveness for the patient."

Vaporization is a popular mode of administration, what advice do you give patients on safe use?

"We recommend patients inhale 1-2 times a day until the desired effect is achieved or until (psychotropic) side effects occur. This means they have had too much. Per inhalation, we recommend patients wait at least 5 minutes between the inhalations.

Patients should take into account that inhaling cannabis results in a higher uptake than when using other administration routes. Patients have to dose carefully when changing to a different variety, especially if they have previously used cannabis with a lower content of THC/CBD.

The 'steady state' concentration of THC/CBD and the active metabolite is reached after one to two weeks. Like oral dosing, this time span should be taken into account for the assessment of the medicines effectiveness for the patient."

Safety

What do you tell patients about the safe and effective use of medicinal cannabis?

"First we ask the patient what they already know about medicinal cannabis. Then we inform them about the mechanism of action, how to use it, the dosage regimen, possible side-effects, how to safely store it. Finally we make sure that the patient takes notice of possible interactions with other medicines or contra-indications (certain conditions where medicinal cannabis should not be used)."

In a follow-up discussion we ask the patient about their experience with the use of medicinal cannabis, with extra attention to side-effects and effectiveness."

What are the key risks of using cannabis as a therapeutic product?

"The only known contra-indications include schizophrenia, arrhythmia and other heart conditions. We work closely with prescribing doctors and also provide adequate instructions to patients about the benefits and risk of their medicines."

Are you aware of any patients that have experienced cannabis interactions with other medicines?

"We know that cannabis is metabolised by CYP450 enzymes. When taken together with other medicines metabolised by the same enzymes, there may be the potential for drug-drug interactions. We discuss with patients about the risk of using such medicines concurrently, or recommend alternative medications."

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

"The biggest risk is getting high and triggering psychoses (especially with psychiatric patients) or worsening current depression. There are risks in prescribing in the elderly, and the potential long-term effects on children are still unknown."

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

"Pharmacovigilance is an important role of a pharmacist. We seek feedback from patients on the safety, effectiveness and adverse reactions they experience from their medicine use. We are also required to provide adequate instructions and honest information to patients about the benefits and risk of their medicines."

Do you encounter diversion for misuse, or the abuse of medicinal cannabis?

"Not often. We identify this issue by monitoring the quantities dispensed and the frequency of dispensing. We make an agreement with the patient to avoid further misuse. If this doesn't help, we consult the prescribing doctor and find solutions to the problem."

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

"Get training or read a lot into the subject, because patients are generally quite well informed but also misinformed."





9 Patient perspectives

The future of healthcare is in understanding and responding to patients' needs and wants. This is called patient centred healthcare. For medicines, this means gaining patient perspectives throughout the medicine's life cycle. In particular, patient satisfaction with their medicine is very important. This might include understanding if the dose form is acceptable, if the treatment is adhered to, and if there are real improvements in quality of life.

We have talked about all aspects of medicinal cannabis. So, what does this all mean from a patient perspective? This section talks about who uses medicinal cannabis, for what conditions, how they used it, and their relationship with health professionals.

Insights from patients

A Belgian-based social researcher, Frederique Bawin looks at medicinal cannabis from the patients' perspective. Bawin explores the legal and illegal use of medicinal cannabis among self-reported patients. While not the experience of every patient, findings from this cohort provides new insights into uses, behaviours, relationships and risks surrounding medicinal cannabis.

Reasons for use

Why do patients use medicinal cannabis? Patients use medicinal cannabis for multiple reasons, including the following:

- It is perceived to be more effective than other medicines or it was the only effective drug for certain symptoms (e.g. cramps, pain, inflammations, chemotherapy induced nausea and vomiting).

- It is considered healthier than other medication as it is 'natural', and as a 'herbal' medicine is perceived to be less harmful than other 'chemical' medications.
- Patients are often searching for alternatives for their usual medicines due to unbearable side effects (e.g. gastrointestinal problems, drowsiness, numbness, allergic reactions).
- Conventional medicine side effects are considered problematic – patients become emotionless, depressed or apathetic. Patients had experienced significant adverse events caused by conventional medicines.

Most patients found that medicinal cannabis was an effective treatment for their conditions, often mentioning that other people noticed improvements.

Patients used it for symptom management, to relieve symptom complaints. Patient state it suppresses symptoms but it did not cause them to disappear. It is not seen as providing a solution to everything, and generally is not regarded as a cure. Indeed, some patients reported medicating with medicinal cannabis to cope with certain symptoms for which it turned out to be unsuccessful or only partially successful (e.g. bladder problems due to MS, acute headache).

Medicinal cannabis was mainly used as a treatment for pain. While their pain had not completely disappeared, it had lessened and became bearable as a result of their medicinal cannabis use. While higher doses were seen to be more effective in relieving pain, patients balanced this against possible side effects including mild intoxication. Similarly, while typical medicines were more effective in alleviating pain, patients preferred medicinal cannabis because of the adverse effects associated with conventional pain medications.

Treatment response

How did they respond to treatment?

Overall, patients report very few or no side effects from medicinal cannabis. Most adverse effects were perceived to be less severe than their conventional medicines. The side effects that were not considered highly problematic or negative include: dry mouth, laughing, feeling happy, increased appetite, increased heart rate, dizziness and being easily distracted. Some patients, however, did report experiencing negative side effects such as dry mouth, feeling high, increased appetite, memory problems, bad taste, blackouts, multitasking problems and increased heart rate.

Side effects from medicine use are subjective. A side effect reported by one person is not necessarily considered a side effect by another. For example, several patients dealing with insomnia did not regard drowsiness as an adverse effect. While a craving for 'sweets' was a complication for patients who are attentive to maintaining their weight, it was viewed by others as important given their condition meant they were dealing with weight loss.

Health professional relationships

Are their doctor and pharmacist actively involved in their treatment?

Sativex® is the only registered product in Belgium, however, doctors are allowed to prescribe unlicensed medicines* which are available in Dutch pharmacies. This puts doctors in a difficult position. Most doctors' response to patient requests were that they did not want themselves or their patient to face legal problems because of illegal cannabis, they were not allowed to prescribe by the National Medical Association and so on. Patients therefore searched for doctors who were willing to prescribe medicinal cannabis.

Medical support for medicinal cannabis use was very diverse among patients. Some patients reported that their doctors accepted their use and were supportive, whereas others had negative experiences. Numerous patients indicated their doctors were sceptical, disapproved, not interested, or silent about this subject.

For patients who were provided medical guidance, it differed significantly from instructions and advice they received for their other medicines. Most of the time their doctor wrote a prescription and provided very general advice. Patients had to experiment with their patterns of use. Typically those doctors were not willing to supervise use because of a lack of expertise, and the possible harms and legal consequences arising from using medicinal cannabis.

** In Belgium, physicians are allowed to prescribe unlicensed medicines because of the so-called 'therapy freedom'. As written in law, practitioners cannot be subject to regulatory limitations in the choice of the medicines being used, either for making a diagnosis, for setting up a treatment and its execution, or for the execution of magisterial preparations.*

Most patients sourced their own medicinal cannabis and did not discuss this with their general practitioner (family doctor) because of a lack of interest or a lack of knowledge. As a result, these patients are not supervised by a doctor. Patients therefore self-selected the cannabis product, the dosage, the method of administration, and when they took it.

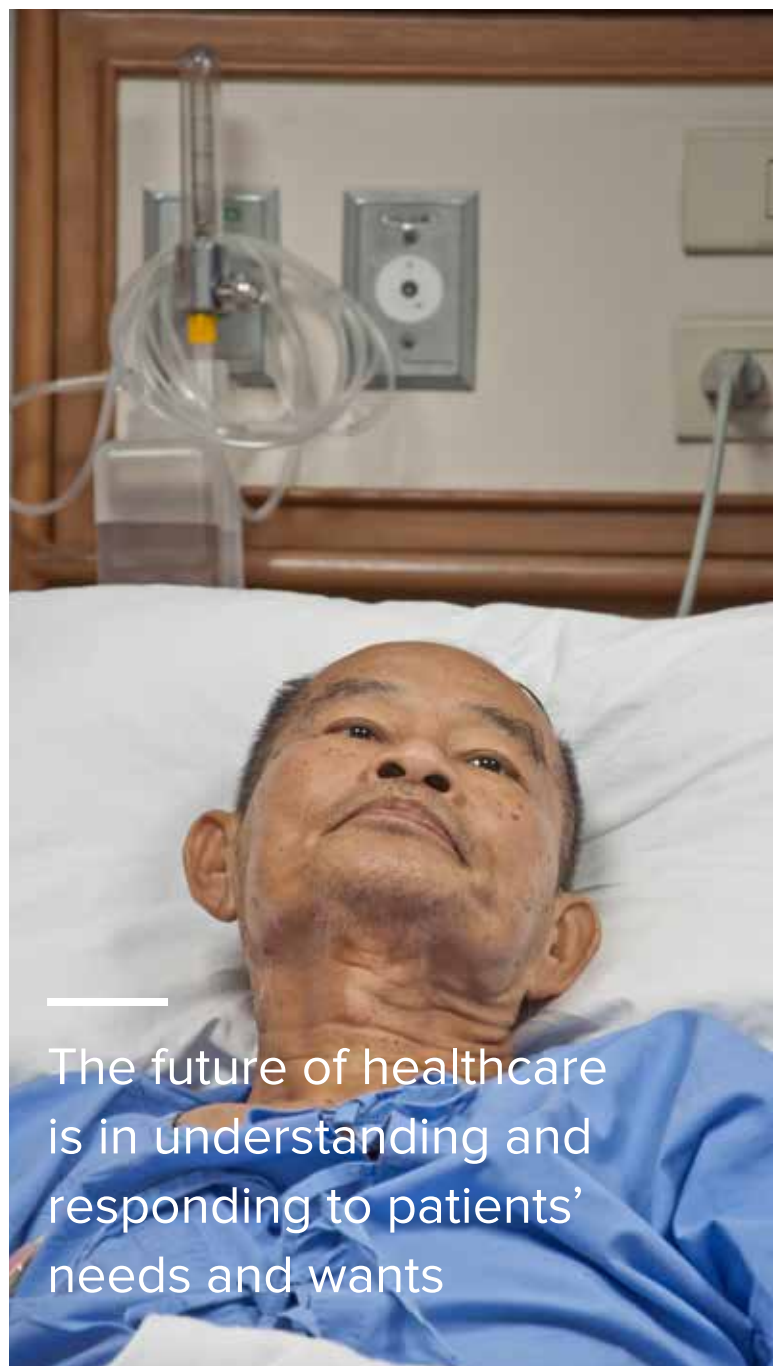
Patients prefer to be supervised by a doctor however, and regretted that few doctors had experience or knowledge in medicinal cannabis. Often, it was the patient providing insights and advice, turning the doctor-patient relationship upside down.

Social cultural issues

What did their family or caregivers think?

For most patients, their use of medicinal cannabis was accepted and supported by family and caregivers. They noticed the difference medicinal cannabis made and were glad the cannabis product appeared to relieve their symptoms. Patients often explained the purpose of using medicinal cannabis in order to gain acceptance.

Although most experience social support, some had to deal with teasing comments, or stereotypical or negative reactions because others were not pleased about a patient's 'cannabis use'. Some patients deal with serious consequences including conflicts in the home and at work. Most patients believe disapproval of medicinal cannabis is because people are ill-informed and have a wrong image of medicinal cannabis.



The future of healthcare
is in understanding and
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needs and wants

Insights from surveys

The table below compares findings from patient use surveys drawing on a global and Dutch perspective. The purposes of both surveys were slightly different, but still provide useful insights.

A global perspective	A Dutch perspective
General	
In 2010, The International Association for Cannabinoid Medicines (IACM) surveyed patients from 31 countries. It is a large study of 953 participants. These findings likely reflect the diversity of the current global patient population.	In 2016, a Dutch patient survey provided a snap shot of a group of patients. It is a large study of 582 participants (17% on prescription). These findings likely reflect the total Dutch patient population receiving a prescription for cannabis.
Patients and the conditions being treated	
Few patients had sourced their medication from a pharmacy (10%) or received a pharmaceutical product. This is not surprising, considering in most countries the medical use of cannabis is illegal. The results therefore tend to reflect the use of herbal cannabis.	Patients were prescribed medicinal cannabis for the treatment of conditions from pain through to severe mental illness. The top ten indications are spread across physical and psychological disease states. These included pain, insomnia/ sleeping disorder, nerve pain, spasms, stress, MS, depression, anxiety, appetite, nausea and cancer.
Patients used medicinal cannabis to treat various conditions. The most common conditions were back pain, sleeping disorders, depression, pain resulting from injury or accident, and multiple sclerosis.	The average daily dose was reported to be 0.67 grams/day for cannabis flos and 0.3 mL/day for oil.
An average daily dose of 3.0 grams was reported for vaporizing and smoking (median dose was 2.0 g/day and 1.5, respectively).	At these doses, the majority (80+ %) patients reported some to substantial improvements in their quality of life and a reduction in complaints resulting from their illness.

A global perspective

A Dutch perspective

The mode of administration

The advantages and disadvantages of different administration forms were identified. Patients described their experience using different modes of delivery by the: dose needed, onset of effect, duration of effect, ease of dose finding, ease of exact dosing, ease of preparation and intake, irritation of lungs, side-effects and cost.

There are various routes of administration for medicinal cannabis. Cannabis oil was the most commonly prescribed, followed by vaporization and tea as popular modes of administration.

Patients reported high satisfaction (approval) scores with the inhalation route. In general, whole plant cannabis based medicines received higher appreciation scores than products containing isolated or single cannabinoids.

While smoking was also popular, it is evident that, like in other countries, patients look for alternatives to smoking. Patient use of oil, or a move to administration by vaporization is evident. The duration of effects and ease of dosing reported by study respondents by the mode of administration were approximately equivalent.

Study limitations

Most survey participants had experience with herbal cannabis and the results may be biased towards the use of herbal cannabis.

The quasi-legal status of cannabis in the Netherlands means some cannabis may have been sourced outside of the pharmacy by patients also receiving prescriptions.



10 Legal perspectives

We have talked about the place of medicinal cannabis in the medical toolbox. This section discusses why cannabis is treated differently from other medicines.

Marijuana or medicinal cannabis

The idea of what medicinal cannabis is varies across the globe. The number of patients with access to or having used pharmaceutical products is low, compared with illegal cannabis.

Cannabis is the most commonly used illegal or quasi-legal recreational drug worldwide. The recreational cannabis economy is enormous. It supplies a large group of patients who otherwise do not have access to pharmaceutical-quality cannabis products. However the quality of recreational cannabis is often unreliable and unpredictable. Cannabis from this market has varying potency and is at risk of adulteration (for example, the addition of synthetic cannabinoids, or other illegal drug substances). It likely also contains fungi, bacteria and other microbial content, heavy metals and foreign particles. The risk to patients is high, especially patients with weakened immune systems as we see with cancer.

Today, across the globe, there are various ways in which cannabis is supplied to patients. Put simply, two distinct sources exist: the informal illegal/quasi-legal market, and the formal medical market under the control of medicine regulators. Under a formal model, medicinal cannabis is often a last-resort medication, prescribed when other options have failed.

From medicinal cannabis to cannabinoid therapeutics

Medicinal cannabis is an old term used to describe the use of cannabis to treat or manage illness. In recent years there have been major developments in cultivation techniques, product quality and controls. Today, government regulators seek the use of standardised products (e.g., Sativex®, Marinol®, Bedrocan®) and safer modes of administration (sublingual, oral and inhalation by vaporization).

This change in focus from ‘medicinal cannabis’ to ‘cannabinoid therapeutics’ reflects our knowledge and understanding of the endocannabinoid system, the cannabinoid receptors, endogenous (human) cannabinoids, and exogenous (plant) phytocannabinoids. The future appears to be about the therapeutic use of cannabinoids. The class of medicines containing cannabinoids (e.g., THC and CBD) and other chemical compounds secreted by cannabis plant (e.g., terpenes) intended to be used for a therapeutic purpose.

A prescriber-pharmacy model

Government regulators have to make tough calls on managing patient and health professional demand for products, alongside the need to ensure safety and efficacy of products on the market. This is ruled by country specific regulations on controlled drugs and medicines.

Two approaches exist. One is often described as an office of medicinal cannabis, controlling access to cannabis products separate to other medicines. The other is a medicine regulatory pathway, which treats medicinal cannabis the same as any other medicine. Both approaches expect high levels of product quality, safety and efficacy.

Who can prescribe and dispense medicinal cannabis depends on country specific policies and regulations. Most often, health professionals are the gatekeepers to patient access. In particular, doctors are allowed to prescribe medicinal cannabis to treat a defined set of conditions and pharmacists can store and dispense reliable and safe products for patients.

Typically, a prescriber-pharmacy model offers patients better communication of risks and benefits, and the safety of health professional guidance. In some countries the therapeutic use of cannabis is well advanced. However, in other countries medicinal cannabis is a new class of medicines. In both situations health professionals will have variable knowledge, skills, abilities and attitudes. This is because, it is a topic which is not often talked about in their medical training. And often practical, evidence-based guidance and evaluation tools are not available to support decision making by health professionals.

The objectives of the UN Conventions

The United Nations International Drug Control Conventions are the pinnacle international agreement on the control of narcotic drugs, such as cannabis. The Conventions require a global shared responsibility to control manufacture, trade and use of controlled drugs.

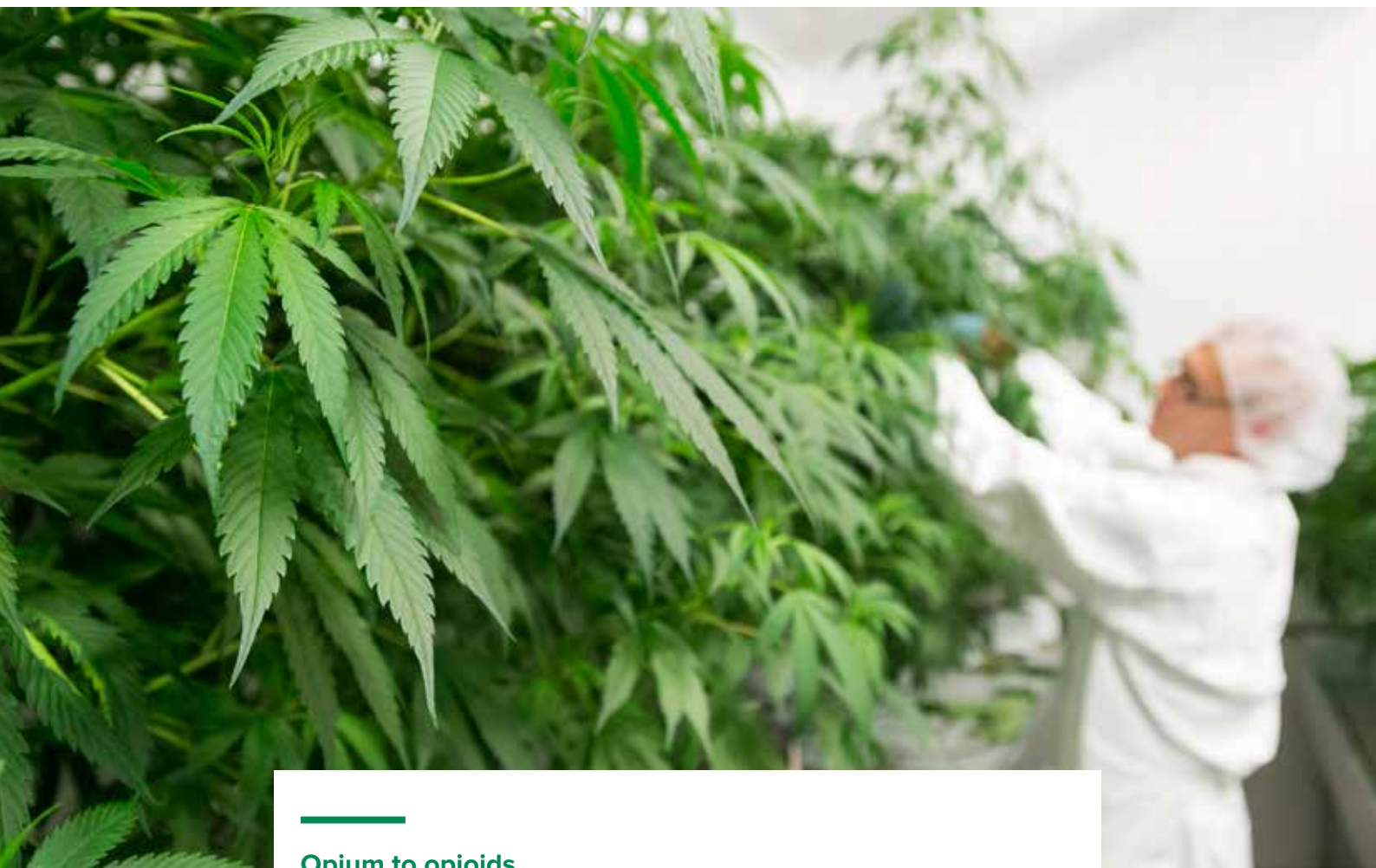
Typically, individual countries develop drug laws which interact with medicines legislation and regulations. For medicinal cannabis, a country's regulatory and other control measures aim to:

- Control legal access and use of medicinal cannabis
- Allow access to adequate supplies of pharmaceutically derived cannabis for medical purposes, in certain cases
- Permit the cultivation and manufacture of cannabis for that purpose

Signatory nations are obliged to carefully control the import, export, and wholesale of cannabis and its preparations. This is most often the responsibility of a country's Ministry of Health who work closely with the International Narcotics Control Board (INCB) in Vienna.

All nations are required to facilitate a working relationship with the INCB. The INCB controls the global flow of cannabis and other controlled drugs intended for medical use. Individual countries provide an annual estimate of the national requirements for medicinal cannabis. These estimates limit the amount of cannabis able to be accessed each year. This is to ensure that the legal manufacture of, trade in and use of cannabis is adequate for national medical and scientific requirements, with negligible diversion to the 'black market'.

These are binding requirements. The idea is that limiting access to controlled drugs makes them difficult to obtain and then be misused. It is the responsibility of the government regulators, health profession and patients to ensure there is no risk of diversion for misuse.



Opium to opioids

The UN Conventions and country specific legislation permits the cultivation of opium in Tasmania Australia, its shipment to global pharmaceutical manufacturing sites, its distribution on the global medicine market, and the ability for a hospital or community pharmacy to fill a patients codeine, morphine, or oxycodone prescription.

The cultivation, manufacture, distribution, and dispensing of opioids is carefully controlled. These are the same requirements for cannabis, when used for therapeutic purposes.



11 Glossary of terms

Cannabis terms

Cannabinoids: naturally occurring or synthetic chemicals that act on the cannabinoid receptors.

Cannabis: *Cannabis sativa* L. – a member of the Cannabaceae family – contains a number of active elements. The main active constituents include THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol).

Cannabis flos: the whole dried flower of the cannabis plant.

Cannabinoid receptors: cell membrane receptors found in the brain, the peripheral nervous system, and many organs and tissues. These receptors recognise our own endocannabinoids and phytocannabinoids (i.e., THC, CBD) from the cannabis plant. They are typically inclusive of the CB1 and CB2 receptors, but also include other receptors that cannabinoids bind to.

Decarboxylation: the cannabinoids exist mainly in an inactive acid form. The pharmacologically active cannabinoids (e.g., THC/CBD) are formed when cannabis is heated to a temperature of at least 180°C resulting in 'decarboxylation'. Specifically, decarboxylation is a chemical reaction that removes a carboxyl group and releases carbon dioxide (CO₂).

Endocannabinoids: the cannabinoids (endogenous neurotransmitters) produced naturally in the bodies of humans and animals that bind to cannabinoid receptors.

Endocannabinoid system: the endocannabinoid system is critical to the bodies overall homeostasis, and influences all of our main organ and tissues systems. This is a unique biological system; its mechanisms are responsive and capable of adaptation and thus allows for a biological response aligned to system demand or environmental conditions.

Endogenous: produced by the body, not delivered from external sources. The endogenous cannabinoids are called endocannabinoids.

Entourage effect: suspected synergistic interactions between cannabinoids and terpenes that lead to modifying or enhancing the therapeutic effects of cannabinoids in different ways. Terpenes are a major component of *Cannabis sativa* L., responsible for the plant's aroma and taste. The therapeutic synergy between cannabinoids and terpenes has not yet been confirmed in clinical research.

Medicinal cannabis: cannabis that is intended for therapeutic use. Is prescribed by a trained medical professional, for a known medical condition or a set of conditions where it has proven to be an effective treatment.

Phytocannabinoids: cannabinoids that occur naturally in cannabis and are derived from the cannabis plant. There are a number of known cannabinoids. The most studied phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD):

- THC is the most well-known cannabinoid. THC is responsible for many of the medicinal effects of cannabis. These may include, among others, reduction of nausea, vomiting, pain and muscle spasms, and improvement of sleep and appetite.

- CBD is another major cannabinoid. It has medicinal effects, but does not induce a psychotropic state (i.e. its use does not result in feelings of intoxication). CBD may be effective in conditions such as epilepsy, post-traumatic stress disorder (PTSD), and anxiety disorder.

Standardisation: pharmaceutical-quality cannabis flos is the whole, dried flowers of the cannabis plant which is genetically and chemically standardised according to pharmaceutical standards, with a defined cannabinoid composition. Also, it is free of contaminants such as microbial contaminants (moulds, fungi, and bacteria) pesticides (residues), aflatoxins, impurities and heavy metals.

Synthetic cannabinoids: a class of man-made chemicals that bind to cannabinoid receptors, (typically) mimicking the effects of THC.

Terpenes: the aromatic compounds which give cannabis its smell and taste. Each distinct cannabis variety has a unique composition of terpenes. The terpenes are suspected to be involved in different interactions with cannabinoids.

Medical terms

Dose: the specified amount of a medicine taken at one time.

Dosage regimen (therapeutic regimen): the number of doses in a given time period, and the time between doses, that is chosen to reach the therapeutic objective (i.e., to treat the symptoms of a disease). This depends on the drug used, the condition being treated, and the patient's characteristics.

Harm: anything that impairs or negatively affects the safety of patients. Medicine harms include adverse drug reactions, treatment side-effects, and other undesirable consequences from a health intervention. Medicine quality, frequency of use and mode of administration modify the type and severity of drug-related harms.

Illegal: not according to or authorised by law (unlawful and illicit); not permitted.

Ligand: a ligand binds to a specific receptor. The ligands of the cannabinoid receptor are called cannabinoids. The endogenous ligands of the cannabinoid receptor are called endocannabinoids, while exogenous ligands are the phytocannabinoids.

Medicine: the branch of medicine concerned with the nonsurgical treatment of disease, and/or the alternative name for pharmaceuticals.

Misuse (of pharmaceuticals): to use a pharmaceutical incorrectly; taking medication where the dose is increased or used with the intention of achieving an intoxicating effect.

Oral: a medicine is taken by mouth; to be taken orally.

Risk (factor): an aspect of personal behaviour or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased risk of a person developing a disease.

Route (administration of a drug): how a medicine is taken into the body, including the location it is applied. Common examples include oral, inhalation, sublingual, and topical administration.

Sublingual: 'under the tongue'; referring to the route of administration by which a medicine diffuses into the blood through tissues under the tongue.

Therapeutic terms

Active ingredient: the therapeutically active component in a medicine's final formulation that is responsible for its physiological action.

Administration (mode of drug use): describes the way in which a drug is taken or used, includes for example inhalation (vaporisation), ingestion or taking orally, and the injecting of a drug substance.

Batch: a quantity of a product that is (i) uniform in composition, method of manufacture and probability of chemical or microbial contamination; and (ii) made in one cycle of manufacture and, if required, sterilised or freeze dried in one cycle.

Certificate of Analysis (CoA): a document of quality assurance that confirms that a product meets its specifications, and results of quality control test on the individual batch of a product.

Formulation (of a therapeutic product): the different chemical substances, including the active drug substance, which are combined to produce a specific dose form.

Good manufacturing practice (GMP): the acronym GMP is used internationally to describe a set of principles and procedures for the manufacturer of medicines; it helps ensure that the products manufactured are of a certain quality.

Manufacture: the production of medicines or any part of the process of producing medicines or bringing the goods to their final state, including the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

Pharmacokinetics: the branch of pharmacology concerned with the movement of drugs within the body; describing how a medicine is absorbed, distributed, metabolised and excreted from the body.

Pharmacovigilance: the collection and evaluation of information from healthcare providers and patients on the adverse effects of medicines.

Therapeutics: the branch of medicine concerned with the treatment of disease and the action of medicines. A treatment, therapy or drug.

Therapeutic option: the idea that expanding medicine options for a disease provides the prescribing doctor with options to search for a more appropriate treatment for their patient. This may be to reduce the number, frequency or severity of side-effects, and also the total number of medicines taken by the patient in their daily regimen.



12 Suggested reading

Administration and dose forms

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Disclaimer

This booklet reflects published data, information and clinical insights as at June 2018. It mainly considers the use of medicinal cannabis as a therapeutic product within a prescriber-pharmacy model which is governed by traditional medicine frameworks.

This booklet is intended for information purposes only. It is not intended to support decision making by prescribers and pharmacists on the safe and effective use of medicinal cannabis or cannabinoids. It should not be relied upon as a definitive text.

While all efforts have been made to ensure the accuracy and scientific nature of information at the time of its production, the author make no representations, implied or otherwise, as to the safety and efficacy of medicinal cannabis or cannabinoids 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 rapid scientific and clinical developments in this field.

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A primer to medicinal cannabis discusses the therapeutic use of cannabis. That means we are not talking about pot, marijuana, grass, or dope for recreational use to get ‘high’. It focusses strictly on medicinal cannabis. It is meant to give health care professionals, regulators and patients insights into the medical and scientific aspects of *Cannabis sativa* L. and how this plant fits in the chain of therapeutic options.