



REVIEW OF CANNABIDIOL

Report of the Science Advisory Committee on
Health Products Containing Cannabis

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. Health Canada is committed to improving the lives of all of Canada's people and to making this country's population among the healthiest in the world as measured by longevity, lifestyle and effective use of the public health care system.

Également disponible en français sous le titre :
Examen du Cannabidiol - Rapport du Comité consultatif scientifique sur les produits de santé contenant du cannabis

To obtain additional information, please contact:

Health Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: hc.publications-publications.sc@hc-sc.gc.ca

© Her Majesty the Queen in Right of Canada, as represented by the Minister of Health, 2022

Publication date: July 2022

This publication may be reproduced for personal or internal use only without permission provided the source is fully acknowledged.

Cat.: H164-334/2022E-PDF
ISBN: 978-0-660-43616-6
Pub: 220104

Table of Contents

Opening remarks.....	4
Background	6
Regulatory context.....	6
National consultation.....	7
Creating the Scientific Advisory Committee	8
Scope of work	9
Part 1—Considerations for health products containing CBD for human use	11
Committee approach to its work.....	11
Information gaps on the use of CBD in health products	13
Safety	14
What amount of CBD is safe without oversight from a doctor or nurse practitioner?	14
What do we know about the side effects of CBD?	16
Is CBD habit forming?	18
What are the considerations and risks for public health?	19
Efficacy.....	20
For which minor indications is there evidence that CBD may be effective?	20
Factors to be considered to determine dosage	21
Post-market considerations.....	22
Appropriate evidence standards	24
Are existing evidence requirements sufficient for CBD?	24
Other considerations for quality requirements.....	24
Part 2 – Considerations for animal use.....	25
Creating the subcommittee on animal health	25
Scope of work	26
Safety	26

What do we know about the safety of CBD use for animals?	26
Efficacy	27
For which indications could dogs benefit from use of CBD?	27
Suitability	28
Is CBD suitable for use in dogs without veterinarian oversight?	28
Other conditions of CBD use in animals.....	29
Part 3 - Considerations for the research and medical community.....	29
Research considerations for human use.....	29
Research considerations for use in animals.....	31
Conclusion.....	31
References	33

Opening remarks

We, the members of Health Canada’s external Science Advisory Committee on Health Products Containing Cannabis, were honoured to be asked by Health Canada to provide advice that would help shape regulations for health products containing cannabis in Canada. We recognize the importance of providing recommendations on how Canadians can safely access potential products for the short-term treatment of minor ailments through a self-care framework.

In recent years, there has been a great deal of interest within the medical and scientific community regarding the therapeutic potential of cannabis for human and veterinary health. Accordingly, the number of scientific publications has increased exponentially over the last two decades. This provided our Scientific Advisory Committee with a large body of literature to draw from in making our recommendations. However, the rapidly evolving science also provided a significant challenge in evaluating the quality and rigour of the available literature and interpretations regarding the conditions of use on which we were asked to provide recommendations.

In human and veterinary medicine, the “gold standard” of evidence comes from randomized controlled trials (i.e. studies where participants are randomly assigned to receive a treatment or a placebo, often with the participant and/or investigator being blinded to which treatment they received). Observational studies (which do not provide an intervention) follow people using cannabis products over time and can also provide important information, especially on long-term harms or benefits. While several randomized clinical controlled studies assessing the use of purified CBD exist, these studies were for indications (such as for drug-resistant epilepsy in children) that were not within the mandate of this committee. Much of the research available on cannabis-containing products comes from observational or small-scale and short-term studies that were not randomized or blinded. The study material also represented a wide variety of different cannabis preparations. Systematic reviews were helpful in providing an overview of available data, however, presented limitations as data summarized may not have been collected or analysed in a consistent manner, may not have reported details on the dose or type of cannabis exposure, or may not have accounted for different causal

factors or variables. This made it difficult to draw definite conclusions between the cannabis products and the study findings with respect to efficacy. We had to find a way to balance Health Canada's need for science-based advice with applying rigorous scientific standards to our work. What became clear during our review of the literature is that this is a rapidly evolving field of research and the knowledge base to guide recommendations on the role of health products containing cannabis will increase dramatically over time.

The committee took a cautious and conscientious approach in providing our recommendations to Health Canada. We believe our recommendations strike a balance between the desire of Canadians to access health products containing cannabis without practitioner oversight (such as oversight from a physician or nurse practitioner) while ensuring public health concerns are addressed. As this is an evolving landscape, our recommendations are based on the information available as of March 2022 and should be revisited as further scientific and clinical evidence develops. In the meantime, our objective was to help provide a foundation for future high-quality research on health products containing cannabis and support decision-making for access to these potential products.

It has been a pleasure serving on the Scientific Advisory Committee among Canadian experts in cannabis-based medicines. We feel it is important to be able to provide Canadians with the best possible advice to make well-informed decisions about their health and the health of their pets.

With sincere gratitude,

The Science Advisory Committee on Health Products Containing Cannabis

Dr. Paula Brown, Co-Chair

Dr. Richard Huntsman, Co-Chair

Patti Bryant

Dr. Nigel Caulkett

Dr. Mary-Ann Fitzcharles

Dr. Daniel Hurnik

Dr. Lauren E. Kelly

Dr. Bernard Le Foll

Dr. Karol Ann Mathews

Background

Regulatory context

Canadians have been able to access cannabis for medical purposes, in the form of dried plant material, with the authorization of a practitioner since 2001 under various regulatory regimes. In 2016 patients were allowed to purchase other types of cannabis products, such as oils, from licensed producers, with the authorization of a physician or nurse practitioner. This improved access for patients (including youth) for whom smoking dried cannabis is not a viable option¹.

Since the *Cannabis Act* came into force in October 2018, Canadians have seen cannabis products become more available across the country. When cannabis for non-medical use was legalized and regulated in Canada under the *Cannabis Act* in 2018, adult Canadians could have in their possession the equivalent of up to 30 grams of dried cannabis without any authorization or oversight from a healthcare practitioner. Importantly, patients (including children) can still access cannabis products for medical purposes with an authorization from their health care practitioner. The cannabis products sold under both streams, whether for non-medical or medical purposes, must meet the same quality-control standards of Health Canada's Good Production Practices. Unlike health products (e.g. pharmaceutical medicines) authorized under the *Food and Drugs Act* (FDA), these products do not undergo a pre-market review for safety, efficacy and quality and therefore cannot make any health claims.

Canadians also have access to prescription medicines derived from cannabis or analogues to cannabis (nabiximols and nabilone, respectively). Like all health products which make an authorized therapeutic claim, those containing cannabis are subject to the requirements of the FDA and are authorized with approved health claims supported by scientific evidence for safety, efficacy, and quality. Prescription drugs containing cannabis must also comply with Health Canada's Good Manufacturing Practices for drug products to ensure drugs meet the quality standards appropriate to their intended use before they are

sold. Compliance with Good Manufacturing Practices is a requirement under the *Food and Drug Regulations*, which is different from the Good Production Practices for cannabis that are required under the *Cannabis Act*.

Health Canada has approved the following prescription medications containing cannabis:

- Sativex (Nabiximols), which contains tetrahydrocannabinol (THC) and cannabidiol (CBD), is an approved treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis;
- Marinol, contains synthetic THC only, and was approved to treat loss of appetite in AIDS patients and nausea from chemotherapy. This product is no longer available in Canada as it was voluntarily withdrawn from the market by its manufacturer;
- Cesamet (Nabilone), contains a synthetic analogue of THC and has also been approved to treat nausea and vomiting for cancer treatment. *

A full list of drugs authorized for sale in Canada is available on Health Canada's [Drug Product Database](#).

National consultation

Health Canada's 2019 "Consultation on a potential market for health products containing cannabis" heard strong interest from Canadians and stakeholders in cannabis health products, including an interest in products containing CBD that could be bought and used without needing a physician or nurse practitioner to prescribe or oversee their use (much like widely available over-the-counter products). Although feedback received from Canadians indicated there was interest in these potential products for both human use and use in animals, respondents noted that more information was needed. The report summarizing the feedback

* Synthetic cannabinoids, which do not exist in nature, are not affected by the legalisation of cannabis as it is not captured by the definition of cannabis under the *Cannabis Act*. Therefore Nabilone remains a controlled drug under the *Controlled Drugs and Substances Act*.

received from those consultations is available [here](#).

Creating the Scientific Advisory Committee

During the consultations, Health Canada made a commitment to seek external scientific and clinical advice from independent experts, and subsequently created the committee, with nine members to look at the evidence that exists with respect to the potential therapeutic benefits of cannabis for human use. A subcommittee was also created to look at health products containing cannabis intended for animals. Member biographies summarizing their expertise are available on the committee [webpage](#).

Because discussions and recommendations were to reflect independent, professional opinions and expertise, committee members were all volunteers. However, the work was supported by a secretariat of Health Canada staff, who also attended meetings to provide technical support and answer administrative questions that might arise. The meetings were led by two co-Chairs and were held online through video calls on a regular basis, the first in November 2020.

The committee's [Terms of Reference](#) stated that the mandate was "to support the development of appropriate safety, efficacy, and quality standards for health products containing cannabis, including the conditions under which these products would be suitable to be used without practitioner oversight." The committee was established to provide advice to support Health Canada's decision-making and was encouraged to reach a consensus in providing advice whenever possible. When a consensus was not possible, recommendations were to reflect the diversity of opinions and/or lack of consensus. Where there was disagreement, members were asked to ensure their opinions were noted and clarified.

To ensure the integrity of the committee's advice, Health Canada and an external conflict of interest advisor assessed nominee applications for any potential risk of conflict of interest as part of the selection process. Once members were selected, the committee established a process for managing any potential risk of conflicts of interest. Throughout the committee's lifespan, members were asked to provide updated declarations of affiliations and interests and declare any factors that might potentially affect member opinions or advice.

Health Canada and an external conflict of interest advisor, assessed members' affiliations and interests, as they applied to agenda items for discussion. If a potential risk was determined by the external conflict of interest advisor, then the member's participation would need to be restricted. All declarations were assessed in consultation with an external conflict of interest advisor and there were no declarations received that restricted any member's participation. It was also important to the committee and to Health Canada to be transparent with this process, so members' declarations of affiliations and interests were made [publicly available here](#).

Scope of work

Health Canada outlined four objectives for the committee:

- Assess the evidence regarding the safety, efficacy and quality of cannabis, including specific phytocannabinoids such as cannabidiol (CBD) or Delta-9-tetrahydrocannabinol (THC), when used for therapeutic purposes for short-term minor ailments and provide advice on the harms, uncertainties and the possible benefits of using cannabis for therapeutic purposes;
- Outline information Health Canada should consider when deciding whether products can be used for self-care without practitioner oversight, and suggest ways to deal with gaps in information for making that decision;
- Explain issues with cannabis that should be considered as Health Canada determines the recommended dosage thresholds and the conditions when cannabinoids can be used without a practitioner's oversight; and,
- Suggest priority areas and considerations for the research and medical community on potential therapeutic uses of cannabinoids.

What are cannabinoids?

- The cannabis plant contains hundreds of chemical substances; more than 100 of them are known as cannabinoids which affect how cells in the brain and body behave and communicate with each other.
- Cannabinoids derived from the cannabis plant can sometimes be referred to as phytocannabinoids.
- THC, one of the commonly known cannabinoids, is responsible for causing the "high" or intoxication.
- CBD is one of the most abundant cannabinoids and is found in different varieties of the cannabis plant, including hemp. Although CBD is not intoxicating, it can have effects on the brain and the nervous system.

- When the *Cannabis Act* came into force, all phytocannabinoids were listed on Health Canada's Prescription Drug List, which means any health product containing cannabis or cannabinoids that makes a health claim requires a prescription.

Early in the committee's work, members decided to focus exclusively on products containing CBD, given the mandate for short-term self-care use. The committee made this decision as more research and evidence is available about the safety and potential therapeutic uses of CBD than for other minor cannabinoids, and because CBD was identified of interest during Health Canada's 2019 public consultation. There was also full consensus among members that any cannabinoid which causes intoxication and poses a risk of addiction, such as THC, would not be suitable for self-care in a non-prescription health product.

The committee found much variation in the types of cannabis products available that contain CBD and among those used in research studies and therefore focused the scope of their investigation by defining CBD preparations where:

- CBD is 98 per cent or more of the total cannabinoid content of the preparation.
- Any cannabinoids other than CBD must be only those naturally found in cannabis and together equal no more than two per cent of the total cannabinoid content of the preparation.
- THC content must not be more than one per cent of the total cannabinoid content.

This definition included purified CBD, CBD isolate, CBD-rich cannabis extracts and synthetic CBD ((-) enantiomer only, meaning the form of CBD produced naturally in the cannabis plant) [†] which meet these criteria.

It is important to note this definition and the recommendations are meant to inform Health Canada's decision-making to develop a potential pathway for non-prescription health products containing cannabis and that this definition does not apply to currently available CBD

[†] The positive (+) enantiomer interacts with the endocannabinoid CB1 receptor found in human brain cells and could potentially cause intoxication.

products. The goal was to establish a single definition that would provide a baseline from which measures and comparisons could be made to support committee deliberations.

Part 1—Considerations for health products containing CBD for human use

Parameters for the review of CBD for human use

- Committee review of information and advice provided is targeted for the healthy adult population, whom the committee defines as individuals over the age of majority (i.e. legal age determined within a jurisdiction) without any significant underlying medical condition and who are not taking any other medications that have potential to interact with CBD.
- The committee unanimously agreed it would not be appropriate to give any products containing CBD to individuals who are pregnant or breastfeeding, children, adolescents or youth under the age of majority without practitioner oversight. Therefore, the recommendations in this report should in no way be considered to apply to them.

Committee approach to its work

With the assistance of the secretariat, the committee began by:

- 1) Reviewing and approving the mandate of the committee, as well as the roles and responsibilities of committee members and co-Chairs.
- 2) Establishing a work plan and schedule to ensure our mandate was met in a timely manner.
- 3) Establishing conflict-of-interest guidelines.
- 4) Establishing guidelines for reaching consensus, and actions for when consensus could not be met.

Members considered a collection of approximately 1,500 sources of information related to their mandate, including relevant publications, adverse reaction information and clinical trials.

In an effort to provide committee members with a general overview of the available information, an extensive literature search of secondary publications was conducted for literature reviews, meta-analyses, scoping reviews, systematic reviews, and reports available in the last 10 years. The search was focused on information related to the safety, efficacy and quality standards for cannabis (including products containing cannabis or cannabinoids), particularly when used for health-related purposes.

In addition, other types of publications that contain information related to the committee's mandate were reviewed including consultation reports or reports published by international regulators. This included relevant information on products authorized in other jurisdictions outside of Canada, such as Epidiolex, which is a prescription CBD product used to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome or tuberous sclerosis complex. Members also considered information on adverse reaction reports of cannabis-based drugs approved for use in Canada which were retrieved through the Canada Vigilance Database. Relevant information on clinical studies listed in the U.S National Library of Medicine's ClinicalTrials.gov database were also considered.

A number of speakers provided information on relevant issues, including presentations by:

- Representatives from Health Canada, which provided background information on cannabis, prescription drug and natural health product regulations and other information relevant to the committee's work.
- International groups, including the Australian Therapeutic Goods Administration, the World Health Organization and the National Academies of Sciences, Engineering and Medicine, which provided invaluable insight into the state of evidence and how other jurisdictions approach cannabis regulations.

The committee members assessed the key information based on both their expertise and several key factors. These factors were shaped by the mandate objectives and the standard principles Health Canada considers during its drug approval process, and were therefore focused on safety, efficacy, quality and post-marketing considerations. For questions where members identified gaps in the committee's expertise, such as in public health and

epidemiology, the committee consulted external experts. The committee's recommendations are therefore based on the totality of members' expertise, members' assessment of available research and all meeting deliberations.

Information gaps on the use of CBD in health products

The lack of high-quality research on the safety and efficacy of cannabis when used to treat minor health problems led the committee to be particularly cautious in its conclusions around safe use for the healthy adult population. Much of the literature reviewed on clinical trials focused on the drug-resistant epilepsy population and other complex health care needs outside the scope of our mandate. All members agreed that safety data on CBD use are missing for key groups of patients who could be at risk, including:

- Young adults (between the ages of 18-25), due to the unknowns regarding the potential impact of CBD on the developing brain;
- Individuals with co-existing psychiatric conditions, because of CBD's influence on the brain;
- Elderly people, who are more likely to be on several medications, are more susceptible to falls, and who may metabolise CBD differently, which would require different doses;
- Individuals with underlying medical conditions or taking medication;
- People with liver disease or damage, as they may not be able to clear CBD from their body easily;
- Pregnant and lactating individuals, although much remains unknown about the potential effects of CBD on the developing child and impact on milk production/quality, there is emerging evidence that CBD may have a harmful effect on fetal development in animal modelsⁱⁱ;
- Individuals with allergies to cannabis or other non-medicinal components contained in the CBD preparation (such as the carrier oil);
- Certain ethnic groups and Indigenous Peoples, as genetics can play a role on how CBD and other cannabinoids affect the body; and
- People who identify as LGBTQ2+ — because potential gender-based impact of CBD use has not been assessed.

Overall, research on the safety and tolerability of CBD has not sufficiently evaluated sex, age, gender and diversity-based variables. Although there is long-term data (up to two years) for Epidiolex, there are other elements that remain unknown pertaining to the safety of long-term use of CBD. Further information is also required for potential drug interactions with CBD

and commonly used medications.

Safety

What amount of CBD is safe without oversight from a doctor or nurse practitioner?

There is little scientific evidence on the safety of CBD taken long term, but the committee unanimously agreed CBD is safe and tolerable for short-term use (a maximum of 30 days) at doses from 20 milligrams per day (mg/day) to a maximum dose of 200 mg/day through oral administration (i.e. by mouth via capsules or oils) for healthy adults provided they discuss the use of any other medications with their pharmacist. According to the committee's definition of CBD preparations, the committee also noted that if an individual took up to the maximum dose of 200mg/day, the maximum amount of THC that is absorbed into the blood stream and reaches the brain would potentially be too low to cause appreciable psychotropic effects for most people.^{‡iii §*}

There is not enough evidence to support that long-term use of CBD is not harmful for people, even at doses lower than 200 mg/day. The committee agreed that should a consumer need to use a health product made with CBD for more than 30 days, this would suggest a more serious condition, where a health care practitioner, such as their physician, should be consulted.

Recommendation A

The committee unanimously agrees CBD is safe and tolerable for short-term use (a maximum of 30 days) at doses from 20 milligrams per day (mg/day) to a maximum dose of 200 mg/day via

[‡] The term psychotropic refers to any effect on mental activity including mild effects such as drowsiness or dizziness.

* There are data that show many people can tolerate taking a much higher dose, potentially up to 800mg/day. However, evidence showed those high doses are used to treat conditions such as epilepsy, which require oversight by health-care professionals, so they are not appropriate for self-care, where the lower dose remains recommended.

oral administration for healthy adults provided they discuss the use of all other medications and substances used with their pharmacist.

It is important to emphasize that this recommendation would not apply to vulnerable patient populations. Committee members were particularly concerned that many people interested in using non-prescription health products with CBD may be taking other medications that might have an interaction with CBD. This is especially important as there is very little information on the safety of CBD when taken with other medications, and potential for many CBD-drug interactions which is a safety concern. For those reasons, it is recommended that clear precautionary statements on potential interactions between CBD and other drugs must be issued with products.

Due to concerns with the unknowns regarding CBD use in pregnancy and potential consequences on the development of the fetus, the committee unanimously recommended warnings state that health products containing CBD should not be used in individuals who are lactating, pregnant, or planning to become pregnant. Additional precautionary statements would also be recommended for people with allergies or hypersensitivity to cannabis or cannabinoids. The committee agreed that these are key priority areas where research is urgently needed and not available yet to support safe CBD consumption.

Recommendation B

The committee strongly recommends that all health products containing CBD should carry statements on potential interactions between CBD and other drugs or alcohol, and should not be used for individuals who are pregnant, lactating, or considering pregnancy, or people with allergies or hypersensitivity to cannabis, cannabinoids, or other components of the manufacturing process.

It is also strongly recommended that a warning be prominently placed on the product label and insert which states that due to the potential of harmful effects of CBD products on fetal development, this product should not be used by individuals who are pregnant, considering pregnancy or breastfeeding.

The committee also noted that there are still a lot of unknowns regarding how different forms of CBD are absorbed by the body. Evidence is growing, however, especially for CBD given orally. As such, members restricted their current advice to CBD products given orally.

Specifically, members were concerned about variations in the bioavailability of CBD depending on its dosage form (as the body absorbs CBD differently depending on the route of administration and the form it comes in). Accordingly, the maximum daily safe dose of CBD would be different depending on how CBD is taken. For instance, inhaled CBD goes directly into the bloodstream through the lungs and takes effect quickly, although this can vary depending on the mechanism of inhalation (e.g. deep breaths, breath-holding, etc.). Given the risks and additional harmful chemicals associated with smoking and unclear risks of vaping, the committee does not recommend these types of products for CBD delivery. When CBD is taken orally, such as a capsule or drop, it is absorbed through the digestive system, which can take more time and impact the amount absorbed. When pure CBD oil is applied to the skin, such as in a cream, very little^{iv} is able to penetrate beyond the most superficial layers of the skin. In order to penetrate deeper tissues, such as the joints or tendons, different transport mediums can be used. Therefore, CBD can be absorbed very differently depending on other ingredients present in the cream such as excipients.**

What do we know about the side effects of CBD?

Any drug or natural product can trigger an adverse reaction in some people and CBD is no exception. CBD also interacts with the body in a complex way, and its effects can differ among individuals. Its effects can also be influenced by many factors, such as underlying medical conditions, other medications and history of cannabis use. Serious side effects (requiring hospitalization) and non-serious (such as brief, mild drowsiness) have been reported at various doses of CBD administered orally, including those less than 200 mg/day. Reported side effects include:

** Excipients are substances formed alongside an active ingredient of a medication, such as diluents, preservatives, fillers, colouring or bulking agents.

- Confused thinking
- Nausea
- Decreased appetite
- Dry mouth and eyes
- Drowsiness and excess sleeping
- Lack of energy
- Liver function abnormalities
- Effects on driving
- Changes to how prescription drugs act in the body
- Physical reactions caused by two drugs mixing in the body

Because side effects can happen even at very low doses, any use of CBD needs to be approached with caution.

The committee found only limited reports of serious and enduring side effects for CBD doses below 750-800 mg/day of CBD, when CBD is taken orally (in capsules or drops) for a short time by healthy adults who are not taking any other medications. However, while it is known that the risk of side effects tends to increase with higher doses, there is very little data on the safety, tolerability or potential risks associated with CBD doses above 800 mg/day. How CBD may interact with other drugs or alcohol, especially at these higher doses, is also unknown. Therefore, the committee agreed doses above the recommended dose of 200mg/day would not be appropriate for self-selection and that the lack of information of risks associated with higher doses makes it particularly important to emphasize the risk of taking more than the recommended dose of CBD or mixing CBD with other drugs or alcohol. Committee members recommended that packages have clear dosing instructions and warnings of potential side effects that emphasize side effects can be worse at higher doses. Some members suggested limits on how many doses could be sold in one package and how many packages could be purchased at once, to lessen the risk people could take enough CBD to cause serious side effects.

Recommendation C

The committee recommends that packaging for health products containing CBD should have clear dosing instructions and warnings of potential side effects, emphasizing that side effects can be worse at higher doses.

Is CBD habit forming?

All members of the committee agreed research shows CBD alone is not habit forming, which reflects a similar finding reached in a recent CBD review done by an expert committee of the World Health Organization (WHO)^{vi}. The WHO expert committee identified CBD as non-addictive, not associated with potential human abuse and found no case reports of abuse or dependence related to pure CBD. The committee agreed unanimously that there is a very low risk CBD could be abused^{vii}, because it does not cause intoxication. Some members noted that the maximum amount of THC (2mg) in a 200 mg/day dose of CBD products meeting the committee's definition would be too little to cause intoxication. It is unlikely that people would take these products for a desired intoxicating effect, however over-consumption of CBD could lead to unpleasant but minor side effects such as diarrhea.

The committee also reviewed literature exploring the interactions between CBD and THC and found that while there are some negative reports regarding CBD interactions with inhaled or injected THC (a route of administration used in experimental studies), there is some evidence, although not substantial, which indicated that CBD may counteract the ability of THC to cause a high^{viii}. Nonetheless, it is another reason to support consideration of limits on package sizes and on the number of packages that can be purchased at one time.

It was mentioned that some people might try to use CBD to reduce their consumption of opioids or alcohol or other substances, as there are some early and ongoing studies^{ix} looking into CBD's potential to help treat these substance use disorders and reduce opioid consumption. The committee agreed more research in this area is urgently required and recommended that non-prescription health products containing CBD should carry a warning that they are not intended for that use.^{††}

Recommendation D

^{††} Addiction, alcoholism or substance abuse are included within Schedule A of the *Food and Drugs Act* and as a result are not a suitable claim for a non-prescription or natural health product.

CBD is not habit forming, however, the committee recommends that health products containing cannabis should carry a warning to clarify they are not intended to help reduce consumption of opioids or alcohol as there are no definitive studies that have validated its use for those indications.

What are the considerations and risks for public health?

The use of CBD comes with a number of safety issues and unknowns, including a lack of research on long-term use, possible side effects, potential interaction with other drugs and the risk consumers may not use a product as intended. These are compounded by an overall lack of science communication and early education strategy on cannabis, cannabinoids and therapeutic uses. Additional concerns include the risk of children unintentionally ingesting CBD products, the use of CBD products by understudied populations and pregnant or breastfeeding individuals, and the possibility that serious diagnoses may be missed due to patients treating symptoms on their own without consulting a health professional.

As Health Canada learned from its consultation, Canadians are interested in using CBD for therapeutic purposes, but there is a wide range of misinformation about CBD, which poses a risk to public health. Committee members all agreed that to counter that, public education about non-prescription health products containing CBD would be necessary to support informed decisions by consumers. It is recommended that information in an accessible form from credible sources that is frequently updated should be readily available to the public, as well as for health care practitioners, on CBD's possible benefits, risks and the gaps in the available data. This recommendation also applies to information regarding the safety of CBD during pregnancy and lactation. Similarly, information on the safety and efficacy of potential products should be publicly available once authorized for sale by Health Canada. Instructions for dosages and use, warnings about possible side effects and other potential risks of using CBD for self-care should also be clearly indicated. It is particularly important that these products meet the extensive labelling and testing requirements appropriate for health products. This would help ensure they are not used interchangeably or mistaken by consumers with products

available in the recreational cannabis market, which are subject to different labelling and testing requirements and are not authorized to make health claims.

Recommendation E

The committee recommends that the approval of health products containing CBD should be accompanied by public education to explain possible benefits and risks, information on safety, and on gaps in research knowledge around the non-prescription use of CBD.

Efficacy

For which minor indications is there evidence that CBD may be effective?

Many of the indications for which there is stronger evidence, such as epilepsy, are serious medical conditions that require oversight from a practitioner and were outside the scope of the committee's mandate. The committee agreed to focus their efforts based on the available information and the main indications of interest identified by consumer respondents in the 2019 Health Canada consultation report. Subsequently, committee members focused their review on the following indications:

- relieving minor symptoms of stress and nervousness;
- promoting sleep; and
- relieving minor pain.

After considering the research related to the effectiveness of CBD for these three indications, the committee agreed unanimously there is some early evidence CBD may be effective for the short-term (less than 30 days) treatment of mild symptoms associated with stress and nervousness. However, the committee also agreed there is not yet enough scientific or clinical evidence to support or refute the short-term use of CBD-based products for either promoting sleep or relieving minor pain. Preliminary evidence on CBD's effect on sleep suggests it changes depending on the amount taken: while higher doses appear to promote sleep, lower doses can delay it^{xi}. More serious conditions—severe anxiety, severe pain, and diagnosed

insomnia— require practitioner supervision and are therefore not appropriate as non-prescription treatments.

Factors to be considered to determine dosage

Setting the therapeutic dose for any drug is dependent on what the drug is supposed to do, how the drug works, the way it is administered and the amount given (which in the case of cannabis products might start low and increase slowly over time). The characteristics of the individual taking the drug also needs to be taken into account (such as sex, previous exposure to cannabinoids, weight, metabolism, ethnicity and age). The limited research on CBD indication-specific considerations (for minor indications) made it particularly difficult for the committee to make dosing recommendations. Although the committee agreed to a safety limit of up to 200mg/day via oral administration, all members agreed that based on the evidence, a general dosage range of CBD could not be defined that would be effective for all types of products, all their uses and everyone who might use it. Limited and inconsistent evidence made it difficult to set a general dosage range where CBD would have a therapeutic effect for treatment of either minor pain, nervousness or promoting sleep. Members discussed potential reasons for limited evidence and agreed that one challenge in studying cannabis products is due to the current regulatory environment which does not incentivize cannabis companies to conduct rigorous clinical and pre-clinical studies. The small number of studies available cannot account for the different ways CBD is currently used, making a recommended dose range difficult to determine. The evidence on dosing for promoting sleep was more consistent than for the other two conditions, suggesting effective doses range between 150-200 mg/day, but evidence was still insufficient.

Members did, however, all agree that there is an absence of data on acute harms of a maximum daily dose of 200 mg when used in the short term. Limited epidemiological evidence also indicated that doses below that amount (even as low as approximately 20mg/day) may have therapeutic potential.

The committee urged caution when considering potential CBD dosages because most dosing limits and ranges do not account for the possible interactions between CBD and other drugs a person might take which could result in adverse effects.

Dosing recommendations must always consider what the product is being used for and allow for variation in effective doses among individuals.

Post-market considerations

Health professionals and researchers use the term “adverse reactions” to describe undesirable effects, injuries or complications, which occur as a result of a treatment or the use of a health product. Adverse reactions can result from the drug itself or as a result of interaction with other drugs. Reporting adverse reactions, and tracking their frequency and severity are essential steps that allow researchers, practitioners and governments to adjust recommended uses and doses and issue warnings of potential risks to improve the safety of drugs and health products.

Most practitioners are aware of adverse-reaction reporting, however, getting individuals to report adverse reactions with a self-care or non-prescription product can be more challenging. The committee agreed that increasing awareness about adverse reaction reporting was an important consideration for these products, and encouraging more reporting would also support data collection for the research community. The committee recommended investing in further reporting systems that balance the need for real-world safety data with the burden of completing adverse reaction reports. The committee identified product labelling as an important tool that could be leveraged to encourage patients to report adverse reactions. Having more, innovative and easy-to-use options for the public to report adverse reactions such as through a website link, Quick Response (QR) code, or a toll-free number, could encourage reporting in the non-prescription space. Additionally, the same platforms designed for reporting adverse reactions could be effective tools for giving consumers information on individual products and providing credible information on cannabinoids and cannabis more generally.

Recommendation F

The committee recommends that:

- Labels on health products containing CBD should encourage consumers to report adverse reactions that result from using the product by offering multiple, easy-to-use reporting options. All platforms and resources for reporting adverse reactions should be designed to ensure equitable access for the wider Canadian community.
- Health products with CBD should be packaged in boxes, so an insert with key details on the product can be included with every sale.
- Consultation with a pharmacist should be encouraged if taking other medications, therefore health products containing CBD should only be available in pharmacies.

Committee members unanimously recommended there should be a requirement that over-the-counter health products containing CBD are packaged in boxes, so an insert with key details on the product can be provided to the consumer. Current health product labels can be difficult to read, due to small font sizes, and do not always provide sufficient space for all the required information pertaining to the product. Inserts packaged within the boxes would be able to ensure that all the critical product information, such as information on adverse event reporting or warnings, is provided to the consumer.

The committee had a considerable discussion regarding the uncertainties and gaps in evidence around the safety and efficacy of CBD and agreed that the lack of high-quality information warranted a cautious approach for non-prescription access. Other concerns raised pertained to the risk of having products accessible to youth, potential drug-drug interactions with commonly used medications, as well as the risk of potential confusion with products available on the recreational cannabis market. Although the recommended dosage of no more than 200mg/day of CBD was considered to be safe for use by healthy adults without oversight from a physician or nurse practitioner, committee members unanimously agreed that consultation with a pharmacist should be encouraged if taking other medications to support patient safety and informed consumer decision-making. Pharmacists would be able to flag potential drug interactions and explain dosing, as well as encourage patients to read the product insert and reinforce the importance of reporting adverse reactions. Recommending pharmacists to advise on health products made with CBD would limit the sale of these products

to pharmacies, but would help ensure the product is used in a way that is aligned with the available scientific and clinical evidence.

Appropriate evidence standards

Are existing evidence requirements sufficient for CBD?

The evidence requirements maintained under Health Canada's *Food and Drugs Act* for health products could also be applied for potential non-prescription CBD products. The committee agreed safety, efficacy and quality requirements developed for potential non-prescription CBD health products could be modelled on those used by Health Canada's Natural and Non-prescription Health Products Directorate as this provides the best mechanism for Health Canada to assess and regulate non-prescription or natural health products containing CBD. The *Food and Drug Regulations* outlines the necessary controls to authorize non-prescription products by ensuring the scientific evidence provided supports the safety, efficacy and quality of the product and maintains evidence requirements to support authorized health claims. Rules are also in place to maintain manufacturing, packaging and labelling requirements.

Different classes of natural health products also require clinical evidence on safety, efficacy and robust quality standards. The *Natural Health Products Regulations* outline requirements for how clinical trials with natural health products must be conducted, which would allow flexibility for these types of products while still requiring consistent evidence standards. The *Natural Health Products Regulations* standards for setting dosages and outlining uses could also be applied to CBD products as defined within this committee mandate.

Other considerations for quality requirements

The committee recommended the need for consistent quality standards and requirements to ensure Canadians have access to non-prescription drugs containing CBD of consistent quality. Additionally, the committee identified the following product-specific elements to consider when setting quality requirements for health products containing CBD:

- The source of the product, including the cultivar or variety and its country of origin.

- All other phytocannabinoids and terpenoids present in the product and their concentrations.
- The total carboxylated and decarboxylated forms of the CBD (these different forms may have different effects on the body).
- Which solvents were used to extract the cannabinoids from cannabis, how much of them remains in the product and the type of extraction. This is particularly important as some solvents can be toxic at certain levels.
- Allergens (e.g. some individuals with tree nuts allergies may cross-react to fractionate coconut oil).

Part 2 – Considerations for animal use

Creating the subcommittee on animal health

The veterinary subcommittee was launched in January 2021, with three members who are experts in animal health; and was led by one of the full committee’s co-Chairs. The subcommittee was given the same four objectives as the full committee, adapted for veterinary consideration. In addition to reviewing what evidence there is for whether cannabis health products might be safe and effective for animals, the subcommittee had to establish the available evidence by species. Subcommittee members also discussed potential food-safety considerations, in particular, whether treating animals with cannabis compounds might pose risks to human health given that it might be transferred into the human food chain.

The subcommittee followed the same conflict-of-interest guidelines and took the same approach to meetings as the full committee, starting by establishing a work plan to guide their efforts, discussing key factors and working by consensus. The subcommittee also received information from:

- Health Canada representatives on the requirements for veterinary drugs and drug-approval frameworks.

- Canadian Food Inspection Agency on food safety in the context of cannabis, animal-health products and animal feed.

Scope of work

In addition to the review of the scientific literature available on use of cannabis in animals, gathered and summarized by an external consultant, the subcommittee members also reviewed, and submitted scientific literature for the safety and efficacy of CBD in animals. Based on the evidence, the scope of the subcommittee's work was narrowed to focus on CBD, as the full committee had done for its work on humans. Specifically, the subcommittee considered CBD preparations in an oil dosage form for oral administration, for which there is the most evidence available.^{xii}

Similar to the broader committee, the subcommittee created its own definition of CBD to support deliberations and draw conclusions about the evidence in a consistent manner, and defined CBD where it comprises 98 per cent or more of the total cannabinoid content and THC is less than 0.3 per cent of the total cannabinoid content. Based on how products were defined within the available studies for animals, the THC limit of less than 0.3 per cent was identified to be consistent with the definition of industrial hemp used under the *Cannabis Act*. This limit differentiates cannabis plants for agricultural use versus those for human consumption.

Safety

What do we know about the safety of CBD use for animals?

The subcommittee looked at safety evidence for health products with CBD by species of animal (noting that few animals have been the subject of cannabis research). There was unanimous agreement that there was not enough evidence to consider the non-prescription use of CBD in horses. Members also discussed concerns with the use of CBD in food-producing animals, because so little is known about the extent to which residues would impact the human food chain. There are no guidelines, for instance, on acceptable maximum residue limits

(MRLs)^{††} for CBD and other phytocannabinoids in animals, which may end up within the food chain or exported internationally. Due to this factor, the use of CBD or cannabis in food-producing animals was not considered within the subcommittee's scope of work. Should there be an inadvertent administration of cannabis products to animals destined for the food chain, the subcommittee suggested the need to establish MRLs. This would also add clarity to the potential development of such products intended for food animals.

Members agreed that while there is some evidence^{xiii} regarding the safety of CBD use in cats, the available evidence is insufficient to draw any reliable conclusions or provide any specific recommendations.

Members agreed that there are significantly more studies done in dogs than other companion animals. Based on the available information, members agreed that CBD is considered safe for dogs when administered at very low doses between 0.2-2 mg/kg taken orally twice a day.

Recommendation G

Among the evidence available for CBD use in companion animals, subcommittee members agreed that there was only sufficient safety evidence for CBD use in dogs. Specifically, when administered at very low doses between 0.2-2mg/kg orally twice daily.

Efficacy

For which indications could dogs benefit from use of CBD?

Subcommittee members unanimously agreed that the only health issue for which there is sufficient evidence regarding the efficacy of CBD is for the treatment of pain associated with osteoarthritis in dogs (although there is some evidence it can work to relieve some other forms of chronic pain in dogs). There is some promising early evidence for dogs, that CBD might work to promote calmness, treat nervousness, rashes and limit aggression, but data was not strong enough to support recommendations for use.

^{††} The residue limit is the length of time required for food producing animals to clear their system of any cannabis residue to a level considered safe for human consumption.

Although uncontrolled observational consumer and veterinary reports suggest CBD administration helps control seizure frequency in dogs, there are limitations with this type of self-reported data (such as bias or inconsistent data measurement). Other than observational veterinary and owner commentary, there is no scientific evidence that CBD administration reduces anxiety in dogs (or in cats), reduces phobias or helps with sleep^{xiv}.

Most information on using CBD in cats also comes from observations by veterinarians and animal owners. There is some evidence on the effectiveness of CBD for cats, including studies of treating pain associated with osteoarthritis, chronic pain, mild anxiety, lower urinary tract inflammation, gastrointestinal inflammation and chronic gingivostomatitis (an infection of the mouth and gums). However, the subcommittee members concluded the evidence is not sufficient to provide a recommendation at this time.

Recommendation H

Subcommittee members agreed there was sufficient evidence regarding the efficacy of CBD for the treatment of pain associated with osteoarthritis in dogs, however insufficient information to recommend a specific dose.

Suitability

Is CBD suitable for use in dogs without veterinarian oversight?

The subcommittee members concluded that CBD is considered appropriate for possible use only for dogs suffering pain associated with osteoarthritis. However, they agreed any CBD product for that purpose should be accompanied by a confirmed diagnosis of osteoarthritis from a veterinarian.

That was linked to the subcommittee members' concern that some level of interaction with a veterinarian should remain a requirement for any use of CBD in dogs until more thorough safety and efficacy data is available, including information on proper dosing for specific indications and potential interactions with other drugs. The use of cannabis or cannabinoids with other medications should always require consultation with a veterinarian prior to use.

To help ensure pet-owners do consult veterinarians, the subcommittee suggested CBD products be sold only in veterinary clinics, for specific conditions diagnosed by a veterinarian.

Other conditions of CBD use in animals

The subcommittee recommended products should be sold in a box with an insert giving dosing details and other information. The label should state that the product should only be used if a veterinarian has diagnosed the animal's condition and discussed possible use of CBD (including its benefits and risks) with the owner. Members noted that labels should indicate relative contraindications and that any CBD product should not be used in dogs with liver function impairment or severe heart disease, or used in dogs who are breeding, pregnant or lactating, or immature.

Recommendation I

- The subcommittee recommends that any CBD product that it is intended only for dogs should have a confirmed diagnosis of osteoarthritis from a veterinarian.
- Until more safety and efficacy information becomes available, pet-owners should consult a veterinarian prior to administering CBD to their pets.

Part 3 - Considerations for the research and medical community

Research considerations for human use

Most of what is known about CBD safety and efficacy is drawn from studies focused on serious conditions that would require practitioner oversight, such as for epilepsy or severe psychiatric illnesses. The data available on how CBD may promote sleep, or help with symptoms associated with nervousness or mild pain, tends to be secondary in nature and were not what the studies were designed to investigate. Therefore, these outcomes are identified as observations from studies where a severe condition is the primary focus. That makes it difficult to draw conclusions from them on how the results would apply to a healthy adult population.

Most of the pain studies combined CBD and THC or added CBD to opioid treatment for severe chronic pain, which made it difficult to distinguish the effects of CBD.

Recommendation J

The committee recommends that high-quality clinical research into the safety and efficacy of cannabis, CBD and other phytocannabinoids, should be further supported by governments and funding agencies.

Studies also used CBD products of different quality and product type, and the doses tested varied. Further information is needed on different routes of administration such as for CBD creams and ointments, which are administered topically, for example. In many instances, the cannabis product being investigated in a study was not defined which made it difficult to draw conclusions regarding the committee's definition of CBD and made comparisons between studies challenging. There were limited randomized placebo-controlled trials, and among the information available, many of the studies were comprised of a small number of participants. This lack of consistent quality data limits the ability to draw clear conclusions.

Furthermore, committee members also discussed the barriers currently in place in Canada to conduct this type of research and agreed that implementing a less complex regulatory framework and providing easier access to quality products to conduct studies would support the research community.

As mentioned throughout this report, the committee's review and discussions revealed numerous gaps in research evidence on CBD and cannabis in general. These gaps, which should be made priorities for research, include:

- Long-term safety data, including from studies of people using cannabis products over time;
- Potential interactions between cannabis health products and other medications (including for use in animals);
- Bioavailability and safety data for delivery formats other than by mouth;
- Safety and efficacy data for people with unique risks and understudied populations, including the elderly, individuals with liver damage, ethnic populations, Indigenous

peoples, pregnant and lactating individuals, children and young adults (particularly between 18-25 years of age), people who identify as LGBTQ2+ or two-spirited, and individuals with certain mental and psychiatric conditions;

- Appropriate dosing; and
- Studies focused on effective treatment of minor health problems.

Research considerations for use in animals

The subcommittee on animal health noted that more scientific evidence is needed on specific indications for CBD use in companion animals, such as for dogs, horses and cats. The overall absence of research meant there was little information on possible side effects of CBD or cannabis use in these species. Most of the available safety and efficacy information came from scientific studies and surveys of owners and veterinarians where the most commonly reported side-effect was sedation. No serious side effects were reported, however further scientific information is needed.

With regards to food-producing animals, more information is needed to support the establishment of maximum residue limits for cannabis in food-producing animals. This information would inform potential risks for humans that consume animals who have ingested CBD.

Conclusion

These recommendations made by the Scientific Advisory Committee were made using a rigorous methodology based on the most up to date scientific and medical literature. All possible effort was made to prevent any potential conflict of interest and we are satisfied that our recommendations have been made without any undue external influence.

In forming our recommendations, we also had to consider several factors unique to Canada including provincial and territorial jurisdiction over the sale of health products, the long standing history of medical cannabis use in Canada and the recent legalization of cannabis for non-medical purposes available to all adults over the age of majority. This last factor played an especially important role in our deliberations as we wanted to provide recommendations which

would support consumer access to potential non-prescription CBD products, while also preventing consumers from self-medicating or treating their pets with products currently available on the commercial market that have not been reviewed for safety, efficacy and quality.

We recognize that while these recommendations may not meet the perceived needs of all stakeholders, we feel that our recommendations strike a balance between safety and accessibility (which are not mutually exclusive of each other). While our goal is to support consumer access to safe products, we also need to consider knowledge gaps and public health risks. The recommendations provided are based on the scientific evidence available at the time of the committee's review and will evolve as the information on CBD continues to develop. We strongly encourage Health Canada to review these recommendations on a regular basis as further high-quality research is conducted on cannabis for health indications and as experience is gained on the use of health products containing cannabis in Canada and internationally.

References

- ⁱ Huntsman RJ, Tang-Wai R, Acton B et al . Cannabis for the treatment of paediatric epilepsy? An update for Canadian paediatricians. *Paediatrics & Child Health*. 2018; 23(6):368-73.
- ⁱⁱ Greenwich Biosciences, I. Epidiolex-Highlights of Prescribing Information. 2018; Epidiolex Drug Monograph.
- ⁱⁱⁱ Boggs DL, Nguyen JD, Morgenson D, Taffe MA, Ranganathan M. Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ^9 -Tetrahydrocannabinol. *Neuropsychopharmacology*. 2018 Jan; 43(1):142-154. doi: 10.1038/npp.2017.209. Epub 2017 Sep 6.
- ^{iv} Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur J Pharm Sci*. 2001 Sep; 14(2):101-14.
- ^v Lodzki M, Godin B, Rakou L, Mechoulam R, Gallily R, Touitou E. Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model. *J Control Release*. 2003 Dec 12; 93(3):377-87.
- ^{vi} World Health Organization. (2019). *WHO Expert Committee on Drug Dependence: Fortieth Report*. World Health Organization.
- ^{vii} Babalonis et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Elsevier*. 2017; 172:9-13.
- ^{viii} Niesink, R., van Laar, Margriet. Does Cannabidiol Protect Against Adverse Psychological Effects of THC? *Front Psychiatry*. 2013; 4: 130.
- ^{ix} Karimi-Haghighi S, Razavi Y, Iezzi D, Scheyer AF, Manzoni O, Haghparast A. Cannabidiol and substance use disorder: Dream or reality. *Neuropharmacology*. 2022; 207:108948.
- ^x Noori A, Miroshnychenko A, Shergill Y, et al. Opioid-sparing effects of medical cannabis or cannabinoids for chronic pain: a systematic review and meta-analysis of randomised and observational studies. *BMJ Open* 2021;11:e047717.
- ^{xi} Babson et al. Cannabis, Cannabinoids, and Sleep: a Review of the Literature. *Curr Psychiatry Rep*. 2017; (4):23.
- ^{xii} Morris et al. Feeding Cannabidiol (CBD)-Containing Treats Did Not Affect Canine Daily Voluntary Activity *Front Vet Sci*. 2021; 8:645667.
- ^{xiii} Kulpa JE, Paulionis LJ, Eglit GM, Vaughn DM. Safety and tolerability of escalating cannabinoid doses in healthy cats. *J Feline Med Surg*. 2021; (12):1162-1175.
- ^{xiv} McDonell, DVM, PhD, Dipl ACVAA, unpublished. Report on the Available Scientific Literature Related to the Use of Cannabis in Animals. Submitted to Health Canada December 30, 2020

Additional key references

As indicated in Part 1 of this report, the committee reviewed a compilation of a variety of resources. The following is a list of some of the key references and resources that the committee members discussed and considered while developing their advice and recommendations. This is a non-exhaustive list of all information that supported the committee's work.

List of key references for human use

- Arkell et al. 2020. Effects of Cannabidiol and 9-Tetrahydrocannabinol on Driving Performance: A Randomized Clinical Trial. *JAMA Research*. 324(21):2177-2186.
- Babalonis et al. 2017. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. *Elsevier*. 172:9-13.
- Babson et al. 2017. Cannabis, Cannabinoids, and Sleep: a Review of the Literature. *Curr Psychiatry Rep*. (4):23.
- Batalla et al. 2021. The Impact of Cannabidiol on Human Brain Function: A Systematic Review. *Front Pharmacol*. Issue 11.
- Bebee et al. 2021. The CANBACK trial: a randomised, controlled clinical trial of oral cannabidiol for people presenting to the emergency department with acute low back pain. *Med. J. Aust*. 214(8):370-375.
- Bergamaschi et al. 2011. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naive social phobia patients. *Neuropsychopharmacology*. 36(6):1219-1226.
- Berger et al. 2020 Treatment of social anxiety disorder and attenuated psychotic symptoms with cannabidiol. *BMJ Case Rep*. 13(10).
- Bhattacharyya et al. 2018. Effects of Cannabidiol on Medial Temporal, Midbrain and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. *JAMA Research*. 75(11):1107-1117.
- Boehnke et al. 2021. Cannabidiol Use for Fibromyalgia: Prevalence of Use and Perceptions of Effectiveness in a Large Online Survey. *J Pain*. 22(5):556-566.
- Boehnke et al. 2021. Cannabidiol Product Dosing and Decision-Making in a National Survey of Individuals with Fibromyalgia. *J Pain*. S1526-5900(21)00252-2.
- Boehnke et al. 2021. Substituting Cannabidiol for Opioids and Pain Medications Among Individuals With Fibromyalgia: A Large Online Survey. *J Pain*. S1526-5900(21)00220-0.
- Boggs et al. 2018. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. *Psychopharmacology (Berl)*. 235(7):1923-1932.
- Capano et al. 2020. Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. *Postgrad Med*. 132(1):56-61.
- Chagas et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *J Psychopharm*. 28(11):1088-1092.
- Chesney et al. 2020. Adverse effects of cannabidiol: a systemic review and meta-analysis of randomized clinical trials. *Neuropsychopharmacology*. 45:1799-1806.
- Consroe et al. 1986. Open label evaluation of cannabidiol in dystonic movement disorders. *Int Journ. Neurosci*. 30(4):277-282.
- Consroe et al. 1991. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav*. 40(3):701-708.
- Crippa et al. 2011. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol*. 25(1): 121-130.

-
- Crippa et al. 2021. Efficacy and Safety of Cannabidiol Plus Standard Care vs Standard Care Alone for the Treatment of Emotional Exhaustion and Burnout Among Frontline Health Care Workers During the COVID-19 Pandemic. *JAMA Netw Open*. 4(8):e2120603.
 - De Almeida et al. 2021. Cannabidiol for Rapid Eye Movement Sleep Behavior Disorder. *MovDisord*. 36(7): 1711-1715.
 - de Faria et al. 2020. Effects of acute cannabidiol administration on anxiety and tremors induced by a Simulated Public Speaking Test in patients with Parkinson's disease. *J.Psychopharmacol*.
 - Dos Santos et al. 2020. Serious adverse effects of cannabidoil (CBD): a review of randomized controlled trials. *ISSN Journal*. 16(6):517-526.
 - Efron et al. 2020. A pilot randomised placebo-controlled trial of cannabidiol to reduce severe behavioural problems in children and adolescents with intellectual disability. *BJCP*. 87:436-446.
 - Farkas et al. 2021. Cannabis-Related Health Effects: An Updated Overview. Health Technology Assessment Unit, University of Calgary.
 - Freeman et al. 2021. Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systemic review and meta-analysis. *SSA Addiction*. 116:1000-1010.
 - Geffrey et al. 2015. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 56(8):1246-51.
 - Good et al. 2019. Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo controlled, randomised clinical trial of efficacy and safety of cannabidiol (CBD). *BMC Palliat Care*. 18(1):110.
 - Gusho et al. 2020. A Brief Review of Its Therapeutic and Pharmacologic Efficacy in the Management of Joint Disease. *Cureus*. 2020:12(3):73-75.
 - Hegazy et al. 2019. Cannabidiol (CBD) for Treatment of Neurofibromatosis-related Pain and Concomitant Mood Disorder: A Case Report. *Cureus*. 11(12):e6312.
 - Hundal et al. 2017. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. *J Psychopharmacol*. 32(3):276-282.
 - Hunter et al. n.d. Knee Pain due to Osteoarthritis. Royal North Shore Hosp. and Inst. of Bone and Joint Res., Pendlebury Res. and Zynerva Pharmaceuticals.
 - Hurd et al. 2019. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *AmJ.Psychiatry*. 176(11):911-922.
 - Kopelli et al. 2020. The role of cannabidiol oil in schizophrenia treatment: a systemic review and meta-analysis. *Elsevier*. 291: 1-6.
 - Laczkovics et al. 2021. Cannabidiol treatment in an adolescent with multiple substance abuse, social anxiety and depression. *Neuropsychiatrie*. 35(1):31-34.
 - Larsen et al. 2020. Dosage, Efficacy and Safety of Cannabidiol Administration in Adults: A Systematic Review of Human Trials. *Journal of Clinical Medicine Research*. 12(3): 129–141.
 - Laux et al. 2019. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: expanded access program results. *Elsevier*. 154:13-20.
 - Leweke et al. 2021. Cannabidiol and Amisulpride Improve Cognition in Acute Schizophrenia in an Explorative, Double-Blind, Active-Controlled, Randomized Clinical Trial. *Front Pharmacol*. 12.
 - McGuire et al. 2018. Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. *J Psychiatry*. 175:3(225-231).
 - Millar et al. 2019. A systematic review of cannabidiol dosing in clinical populations. *Br J Clin Pharmacol*. 85(9):1888-1900.
 - Mongeau-Perusse et al. 2021. Cannabidiol as a treatment for craving and relapse in individuals with cocaine use disorder: a randomized placebo-controlled trial. *SSA Addiction*. 116:2431-2442.

-
- Naftali et al. 2017. Low-Dose Cannabidiol is Safe but Not Effective in the Treatment for Crohn’s Disease, a Randomized Controlled Trial. 62:1615-1620.
 - Ponton et al. 2020. A pediatric patient with autism spectrum disorder and epilepsy using cannabinoid extracts as complementary therapy: a case report. J Med Case Reports. 14(1):162.
 - Qian et al. 2019. Cannabinoid Inhibition of Carboxylesterase Drug Metabolism and Disposition. 47 (5) 465-472.
 - Rapin et al. 2021. Cannabidiol use and effectiveness: real-world evidence from a Canadian medical cannabis clinic. J.cannabis res. 3(1):19.
 - Shannon et al. 2019. Cannabidiol in Anxiety and Sleep: A Large Case Series. Perm.j. 23:18-41.
 - Skelley et al. 2019. Use of cannabidiol in anxiety and anxiety-related disorders. J Am Pharm Assoc. 60(1):253-261.
 - Suraev et al. 2020. Cannabinoid therapies in the management of sleep disorders: A systematic review of preclinical and clinical studies. Sleep Med Rev. 53.
 - Taylor et al. 2018. A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects. CNS Drugs. 32:1053-1067.
 - Taylor et al. 2020. Abrupt withdrawal of cannabidiol: A randomized trial. Elsevier. 104:1-8.
 - Thomsen et al. 2014. In vitro drug metabolism by human carboxylesterase 1: focus on angiotensin-converting enzyme inhibitors. Drug Metabolism Disposition 42:126–133.
 - Urits et al. 2020. Use of cannabidiol (CBD) for the treatment of chronic pain. Best Pract Res Clin Anaesthesiol. 34(3):463-477.
 - van Orten-Luiten et al. 2021. Effects of Cannabidiol Chewing Gum on Perceived Pain and Well-Being of Irritable Bowel Syndrome Patients: A Placebo-Controlled Crossover Exploratory Intervention Study with Symptom-Driven Dosing. Cannabis Cannabinoid Research X:X, 1–9.
 - Wade et al. 2003. A preliminary controlled study to determine whether whole plant cannabis extracts can improve intractable neurogenic symptoms. Clinical rehabilitation. 17:21-29.
 - Xu et al. 2020. The Effectiveness of Topical Cannabidiol Oil in Symptomatic Relief of Peripheral Neuropathy of the Lower Extremities. Curr.Pharm.Biotechnol. 21(5):390-402.

List of key references for use in animals

- Bartner *et al.* (2018) Pharmacokinetics of cannabidiol administered by 3 delivery methods at 2 different dosages to healthy dogs. *Canadian Journal of Veterinary Research*. 82:178–183
- Brioschi *et al.* (2020) Oral Transmucosal Cannabidiol Oil Formulation as Part of a Multimodal Analgesic Regimen: Effects on Pain Relief and Quality of Life Improvement in Dogs Affected by Spontaneous Osteoarthritis. *Animals*.
- Brown (2018) Center for drug and evaluation research. Application number: 210365Orig1s000 Department of Health & Human Services. Public Health Service, Food and Drug Administration. (Retrieved: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000PharmR.pdf)
- Brutlag *et al.* (2018) Toxicology of Marijuana, Synthetic Cannabinoids, and Cannabidiol in Dogs and Cats. *Vet Clin Small Anim*. 48; 1087–1102.
- Buranakarn (2020) Sarcoma Cancer Treatment using Extracted Cannabis Oil in Cats. *International Journal of Science and Innovative Technology*. 3(1):35-40
- Campora *et al.* (2012) Cannabinoid receptor type 1 and 2 expression in the skin of healthy dogs and dogs with atopic dermatitis. *Am J Vet Res*. 73:988–995
- Chicoine *et al.* (2020) Composition of unapproved cannabinoid products directly marketed to Canadian pet owners. *Can Vet J*. 61(5):477-480. PMID: 32355346; PMCID: PMC7155876

-
- Chicoine *et al.* (2020) Pharmacokinetic and Safety Evaluation of Various Oral Doses of a Novel 1:20 THC:CBD Cannabis Herbal Extract in Dogs. *Frontiers in Veterinary Science*. Vol 7 | Article 583404
 - Cital *et al.* 2021. Cannabis Therapy in Veterinary Medicine. *A Complete Guide Springer*
 - Corsetti *et al.* (2021). *Cannabis sativa* L. may reduce aggressive behaviour towards humans in shelter dogs. *Scientific Reports*. 11:2773
 - Deabold *et al.* (2019) Single-Dose Pharmacokinetics and Preliminary Safety Assessment with Use of CBD-Rich Hemp Nutraceutical in Healthy Dogs and Cats *Animals*. 9:832
 - ElleVet Sciences Announces Results of Atopic Dermatitis Study Using Its CBD+CBDA Oil On Dogs. (2020) *ElleVet Sciences*.
 - Fernández-Trapero *et al.* (2020) Pharmacokinetics of Sativex® in Dogs: Towards a Potential Cannabinoid-Based Therapy for Canine Disorders. *Biomolecules*. 10:279
 - Fischer *et al.* (2013) Effects of a topically applied 2% delta-9-tetrahydrocannabinol ophthalmic solution on intraocular pressure and aqueous humor flow rate in clinically normal dogs. *American Journal of Veterinary Research*. 74(2): 275-280.
 - Freundt-Revilla *et al.* (2017) Spatial distribution of cannabinoid receptor type 1 (CB1) in normal canine central and peripheral nervous system. *PLOS ONE*. 12(7):e0181064.
 - Gamble *et al.* (2018) Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs. *Frontiers in Veterinary Science*. 5:165
 - Galiazzo *et al.* (2018) Localization of cannabinoid receptors CB1, CB2, GPR55, and PPARα in the canine gastrointestinal tract. *Histochemistry and Cell Biology*. 150: 187-205
 - Gesell *et al.* (2013) Alterations of endocannabinoids in cerebrospinal fluid of dogs with epileptic seizure disorder. *BMC Veterinary Research*. 9:262
 - Graham and Li (1973). Cardiovascular and respiratory effects of cannabis in cat and rat. *Br. J. Pharmac.* 49:1-10
 - Hartsel *et al.* (2019) Cannabis in Veterinary Medicine: Cannabinoid Therapies for Animals. *Nutraceuticals in Veterinary Medicine*. 121-155
 - Jalimnson (2020). Cannabis Showing Promise For Treating Dermatitis in Dogs. *HEMP GAZETTE*
 - Janczyk *et al.* (2004) Two hundred and thirteen cases of marijuana toxicoses in dogs. *Vet Hum Toxicol*. 46(1):19-21.
 - Kleinhenz *et al.* 2022. Short term feeding of industrial hemp with a high cannabidiolic acid (CBDA) content increases lying behavior and reduces biomarkers of stress and inflammation in Holstein steers. *Scientific Reports*. 12:3683.
 - Kogan *et al.* (2016) Consumer's Perceptions of Hemp Products for Animals. *AHVMA Journal*. Volume 42 Spring: 40-48
 - Kogan *et al.* (2019) US Veterinarian's Knowledge, Experience, and Perception Regarding the Use of Cannabidiol for Canine Medical Conditions. *Frontiers in Veterinary Science*. 5:338
 - Kogan *et al.* (2019) Canadian dog owners' use and perceptions of cannabis products. *Can Vet J*. 60:749-755
 - Kogan *et al.* (2020) The Use of Cananbidiol-Rich Hemp Oil Extract to Treat Canine Osteoarthritis-Related Pain: A Pilot Study. *AHVMA Journal*. Volume 58 Spring: 35-45
 - Kulpa *et al.* (2021) Safety and tolerability of escalating cannabinoid doses in healthy cats *Journal of Feline Medicine and Surgery*.
 - Landa *et al.* (2016) The use of cannabinoids in animals and therapeutic implications for veterinary medicine: a review. *Veterinarni Medicina*. 61, (3): 111–122.
 - McGrath *et al.* (2018) A report of adverse effects associated with the administration of cannabidiol in healthy dogs. *J Am Holistic Vet Med Assoc*. 52:34–8
 - McGrath *et al.* (2019) Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy *JAVMA*. 254 (11)

-
- Mejia *et al.* (2021) Evaluation of the Effect of Cannabidiol on Naturally Occurring Osteoarthritis-Associated Pain: A Pilot Study in Dogs. *JAAHA*. 57:2
 - Meola *et al.* (2012) Evaluation of trends in marijuana toxicosis in dogs living in a state with legalized medical marijuana: 125 dogs (2005-2010). *J Vet Emerg Crit Care*. 22(6):690-6.
 - Mercati *et al.* (2011) Identification of cannabinoid type 1 receptor in dog hair follicles. *Acta Histochem*. 114(1):68-71
 - Morris *et al.* (2020) The Impact of Feeding Cannabidiol (CBD) Containing Treats on Canine Response to a Noise-Induced Fear Response Test. *Frontiers in Veterinary Science*. 7:569565.
 - Morris *et al.* (2021) Feeding Cannabidiol (CBD)-Containing Treats Did Not Affect Canine Daily Voluntary Activity *Front Vet Sci*. 8:645667.
 - Pertwee (2001) Cannabinoid receptors and pain. *Progress in Neurobiology*. 63: 569–611
 - Polidoro *et al.* (2020) Expression of cannabinoid and cannabinoid-related receptors in the oral mucosa of healthy cats and cats with chronic gingivostomatitis. *Journal Feline Medicine and Surgery*. <https://doi.org/10.1177/1098612X20970510>
 - Richardson (2000) Cannabinoids Modulate Pain by Multiple Mechanisms of Action. *The Journal of Pain*. 1(1): 2-14
 - Stanzani *et al.* (2020) Localization of cannabinoid and cannabinoid related receptors in the cat gastrointestinal tract. *Histochemistry and Cell Biology*. 153(5):339-356.
 - Stephens (2019) Species-specific susceptibility to cannabis induced convulsions. *British Journal of Pharmacology*. 176:1506–1523
 - Thompson *et al.* (1973) Comparison of acute oral toxicity of cannabinoids in rats, dogs and monkeys. *Toxicology and Applied Pharmacology*. 25(3):363-372.
 - Valastro *et al.* (2017) Characterization of endocannabinoids and related acylethanolamides in the synovial fluid of dogs with osteoarthritis: a pilot study. *BMC Veterinary Research*. 13(309):1- 5
 - Verricoa *et al.* (2020) A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *International Association for the Study of Pain*. 161(9):2191-2202
 - Vaughn *et al.* (2020) Preliminary Investigation of the Safety of Escalating Cannabinoid Doses in Healthy Dogs *Frontiers in Veterinary Science*. Volume 7 | Article 51
 - Vaughn *et al.* (2021) Randomized, placebo-controlled, 28-day safety and pharmacokinetics evaluation of repeated oral cannabidiol administration in healthy dogs *Am J Vet Res*. 82(5):405-416.
 - Verrico *et al.* (2020) A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain*. 161(9):2191-2202
 - Wakshlag *et al.* (2020) Pharmacokinetics of Cannabidiol, Cananbidiolic Acid, delta-9-Tetrahydrocannabinol, Tetrahydrocannabinolic Acid and Related Metabolites in Canine Serum After Dosing With Three Oral Forms of Hemp Extract. *Frontiers in Veterinary Science*. 7:505
 - Zadik-Weiss *et al.* (2020) Feline cognitive dysfunction as a model for Alzheimer’s disease in the research of CBD as a potential treatment—a narrative review. *Journal of Cannabis Research*. 2:43.