Cannabis Compendium

AURORA™ MC

Note: This document is intended for informational purposes only. This information is not intended to replace health care practitioners' process of authorizing patients' use of medical cannabis based on their specific diagnoses and proposed treatment plans.

Aurora® is a leading integrated Canadian cannabis company. With state-of-the-art production facilities and exclusive sales agreements in the European Union and beyond, Aurora® operates internationally, pursuing strategic cannabis markets to expand access to high-quality medical cannabis and grow the global industry. Aurora® has become one of the world's leading cannabis companies that continues to elevate and challenge industry standards.

The Cannabis Compendium is an informational document of scientific evidence sourced from high quality, peer-reviewed scientific papers compiled by Aurora's Medical Affairs team. It contains an overview of the cannabis plant and its cannabinoids and terpenes, as well as details on the endocannabinoid system and pharmacology of cannabinoids derived from the cannabis plant. This document also summarizes reported adverse events, contraindications and warnings of cannabis consumption from the scientific literature and the Government of Canada. This document is intended for healthcare practitioners and scientific researchers.

Table of Contents

Abbreviations:

$5HT_{1A}$: serotonin-1A
Aß: amyloid-ß
A receptor: adenosine receptor
APP: amyloid precursor protein
ASD: autism spectrum disorder
CAGE-AID: CAGE Questionnaire Adapted to Include Drugs
CES 1: carboxylesterase 1
CYP450: cytochrome P450
CB: cannabinoid
CBC: cannabichromene
CBCA: cannabichromenic acid
CBCV: cannabichromevarin
CBCVA: cannabichromevarinic acid
CBD: cannabidiol
CBDA: cannabidiolic acid
CBDAS: cannabidiolic acid synthase
CBDVA: cannabidivarinic acid
CBGA: cannabigerolic acid
CBGAS: cannabigerolic acid synthase
CBGVA: cannabigerovarinic acid
CBCAS: cannabichromenic acid synthase
COX-2: cyclooxygenase-2
DMSO: dimethylsulfoxide
GPP: geranyl pyrophosphate
IP: intraperitoneal
IV: intravenous
ECS: endocannabinoid system
EEG: electroencephalogram
FAAH: fatty acid amid hydrolase
GABA: GABAergic
GAD-7: Generalized Anxiety Disorder 7-item
GPR: g-protein coupled receptor
IBD: inflammatory bowel disease
MS: multiple sclerosis
mTBI: minor traumatic brain injury
OA: olivetolic acid
PD: pharmacodynamic
PDAC: pancreatic ductal adenocarcinoma
PHQ: Patient Health Questionnaire
PK: pharmacokinetic
$PPAR_{\gamma}$: peroxisome proliferator-activated receptors-$_{\gamma}$
PS1: presenilin 1
PS2: presenilin 2
PTSD: post-traumatic stress disorder
QOL: quality of life
QOLCE-55: Quality of Life in Childhood Epilepsy Questionnaire
REM sleep: rapid eye movement sleep
THC: Δ^9-tetrahydrocannabinol
THCA: tetrahydrocannabinolic acid
THCAS: tetrahydrocannabinolic acid synthase
THCVA: tetrahydrocannabivarinic acid
TRP: transient receptor potential
TRPV1: transient receptor potential vanilloid

Cannabis Compendium:

The Plant

1 Cannabis:

The scientific name for cannabis is *Cannabis sativa L* with the *L* denoting that the species was originally named by Carl Linnaeus in his *Species Plantarum*[1]. One of the most distinctive features of cannabis is the presence of trichomes on leaves and floral tissue. There are two categories of trichomes: glandular trichomes that produce secondary metabolites, such as Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), and non-glandular trichomes which do not produce secondary metabolites[2].

1.1

Scientific attempts to classify cannabis:

In his 1753 work *Species Plantarum*, Linnaeus determined there was one species of cannabis which he named *Cannabis sativa*[1]. In 1783, Jean-Baptiste Lamark proposed adding another species, *Cannabis indica,* based on wild samples obtained from India. Lamark noted that *Cannabis indica* plants had shorter and broader leaves and had intoxicating effects that were not present in European varieties[3]. The split of cannabis into two species was rejected by Lindley, who combined narrow and broad-leaved cannabis varieties back under the *Cannabis sativa* title in his *Flora Medica* in 1838[4].

In 1924, the Russian botanist Janischewsky proposed a three-species system of *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. The addition of *Cannabis ruderalis* was based on observations of a variety of cannabis Janischewsky had studied in southeastern Russia, which was smaller and weedier than either *Cannabis sativa* or *Cannabis indica*[3]. In 1976, Small and Cronquist proposed a monotypic classification for cannabis, recombining all species under the *Cannabis sativa* title. However, the new classification would split the *Cannabis sativa* species into subspecies' based on THC content and further into varieties based on whether the plant was cultivated or grew wild[5]. This results in the following four categories:

- *Cannabis sativa* subsp. **sativa** var. **sativa** (cultivated, non-intoxicating)
- *Cannabis sativa* subsp. **sativa** var. **spontenea** (weedy, non-intoxicating)
- *Cannabis sativa* subsp. **indica** var. **indica** (cultivated, intoxicating)
- *Cannabis sativa* subsp. **indica** var. **kafiristanica** (weedy, intoxicating)

Another classification system has been proposed by Hillig based on analysis of the terpene content of flower extract and genetic sequencing information[6,7] (Figure 1). This classification recognizes 3 species of cannabis, splitting *Cannabis sativa* and *Cannabis indica* into distinct "biotypes" and recognizing *Cannabis ruderalis* as a separate species.

This results in 7 distinct classes as follows:

- ***Cannabis sativa***
  1. Hemp biotype
  2. Feral biotype
- ***Cannabis indica***
  1. Narrow leaf drug biotype
  2. Wide leaf drug biotype
  3. Feral biotype
  4. Hemp biotype
- ***Cannabis ruderalis***

Figure 1:
Schematic of the different species of cannabis

1.2

Indica/Sativa folk classification:

Perhaps the most common classification system for cannabis is an informal one. Both medical and recreational users of cannabis commonly refer to sativa, indica and hybrid "strains" of cannabis. Because this is a folk classification, no formal set of definitions exists for these classes. However, sativas are commonly described as taller plants with the narrow leaves which produce medium-to-high THC content and little CBD content. Indicas are generally defined as shorter, bushier plants with wider leaves that may have some THC content and usually have CBD content. Hybrids are plants with intermediate characteristics between sativas and indicas[8]. Some patients report that indica plants are more sedating while sativa plants are more stimulating.

There are a few points of departure between scientific classifications of cannabis and the folk classification of sativa/indica that are important to note. The first is that the term "strain" has no meaning in botany and is usually reserved in biology to refer to microorganisms[9]. However, the concept

being invoked when people refer to cannabis strains is essentially synonymous with the botanical terms "variety" (where variety is a taxonomic rank lower than species and subspecies or a genotype that has yet to be approved for production and sale to the public) and "cultivar" (where cultivar is defined as a plant variety developed by humans for a specific use such as production of grain or fruit, or flower colour or growth habitat)[10,11]. Thus, depending on where a cannabis plant is in a breeding program will determine if it should be referred to as a variety of cannabis or a cultivar of cannabis.

The second, is that the overuse of the terms sativa and indica in reference to cannabis has led to a high degree of divergence between the definitions of these terms in scientific and colloquial discourse. For example, all cannabis varieties colloquially referred to as "sativa strains" would likely be classified as *Cannabis sativa* subsp. *indica* var. *indica* under the Small/Cronquist classification system[5] and as *Cannabis indica*: Narrow Leaf Drug Biotype under the Hillig system[6,7].

Overall the terms of indica and sativa are vernacular classification systems for cannabis genotypes, which is not supported by current scientific research. Although there is debate about the evolutionary history of cannabis and how this should be reflected in taxonomic naming, it is best to stay simple and use *Cannabis sativa* for all forms of cannabis.

1.3

Hemp classification:

Different types of cannabis have been cultivated by humans for thousands of years. The hemp types of cannabis are known to contain high amounts of CBD but negligible amounts of THC and have historically been grown to utilize their seeds and fibre[12,13]. However, more recently, hemp has gained popularity as a source of CBD with little to no THC. In the USA and Canada, a cannabis plant is characterized as industrial hemp if it contains less than 0.3% THC in the flowering heads and leaves[14,15] while in some areas of Europe, the THC content must be less than 0.2%[16].

2 Biosynthesis of phytocannabinoids:

Cannabis produces several medically relevant secondary metabolites, including phytocannabinoids (such as THC and CBD, as well as over 100 others) and non-cannabinoid compounds (terpenes and flavonoids).

The two best-studied phytocannabinoids produced by the cannabis plant are THC and CBD. However, these molecules are not produced in large amounts directly by the plant. Instead, cannabis synthesizes the acid forms of THC and CBD called tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) respectively. Upon heating these compounds to ~110°C they spontaneously decarboxylate to become the active forms THC and CBD[17].

Phytocannabinoids are the product of two distinct pathways in the cannabis plant. The plastidic MEP pathway which produces geranyl diphosphate (GPP) and the polyketide pathway which produces olivetolic acid (OA). These two molecules are combined in a c-prenylation reaction to give cannabigerolic acid (CBGA) in a reaction catalyzed by the cannabigerolic acid synthase (CBGAS) enzyme. CBGA is the precursor to one set of phytocannabinoids (C5 (Pentyl) phytocannabinoids). Three enzymes have been characterized which act on CBGA to give other cannabinoids (THCA synthase, CBDA synthase and CBCA synthase) all of which oxidatively cyclize the monoterpene moiety of CBGA to THCA, CBDA and CBCA, respectively. Another set of phytocannabinoids (C3 (propyl) phytocannabinoids) are created by the C-prenylation of divarinic acid instead of OA by GPP catalyzed by CBGA synthase to give cannabigerovarinic acid (CBGVA). CBDA synthase, CBCA synthase and THCA synthase are not selective for the length of alkyl side chain, meaning they can also act on CBGVA to give CBDVA, CBCVA and THCVA respectively[18]. Decarboxylation of CBDVA, CBCVA and THCVA creates CBDV, CBCV and THCV respectively.

Cannabinoid-derived therapies range from isolates of phytocannabinoids (such as a CBD isolate that solely contains CBD) to extracts, which include different ratios of phytocannabinoids and terpenes that are specific to each cannabis cultivar. While the individual compounds, such as THC and CBD, have been shown to have potential therapeutic benefits alone (i.e. when an isolate is consumed), it has been hypothesized that there are additive, therapeutic effects when the different compounds are combined together (i.e. when an extract is consumed), a hypothesis referred to as the Entourage Effect[19,20]. For example, pre-clinical studies examining the analgesic and anti-inflammatory effects of CBD have found that extracts of CBD are more effective at reducing pain and inflammation than CBD isolates[21,22]. Furthermore, in cultured brain cancer cells, THC and CBD together showed a synergistic effect in reducing cancer cell growth, while alone neither had any effect[23].

2.1

THC:

Arguably the most well-known of the phytocannabinoids, THC is the predominant intoxicating molecule in cannabis and gives rise to the euphoria associated with being "high." THC has therapeutic potential as an analgesic, anti-inflammatory and anti-emetic[20] (Figure 2).

Intoxication:

a condition that follows the administration of a psychoactive substance and results in disturbances in the level of consciousness, cognition, perception, judgement, affect, behaviour, or other psychophysiological functions and responses[24].

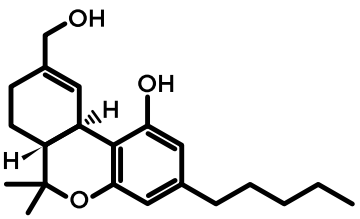


Figure 2:
THC chemical structure

2.2

CBD:

CBD is the second most familiar phytocannabinoid and has rapidly come to prominence in medical applications due to its unique therapeutic profile and effects (Figure 3). CBD is non-intoxicating at therapeutically relevant doses and may reduce pain, anxiety and inflammation[20]. It has also been found to be a potent anti-epileptic[25].

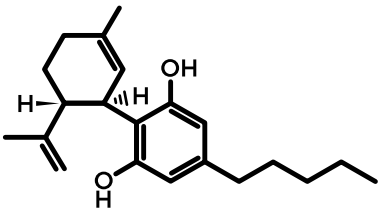
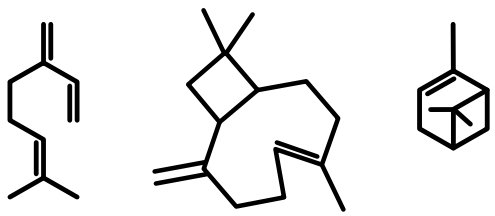


Figure 3:
CBD chemical structure

2.3

Terpenes:

Terpenes are the largest group of phytochemicals, found in many different plants[20]. The terpene profile of a cannabis plant not only determines the scent and flavour of a product but may also influence how each cannabis cultivar impacts each person. Terpenes are suspected to have medicinal properties of their own, in addition to working with CBD, THC and other cannabinoids to produce the overall therapeutic effect of a product[19,20]. Research is ongoing in this area to fully elucidate the effects of terpenes.



Myrcene ß-caryophyllene α-pinene

Figure 4:
Terpene chemical structures

Cannabis Compendium:

Biomedical

1 The endocannabinoid system:

The endocannabinoid system (ECS) regulates many crucial physiological functions in the body and contributes significantly to the maintenance of homeostasis, which is a state of steady internal conditions[26].

Some examples of functions the endocannabinoid system regulates include: learning and memory processes, sleep, stress, emotions, pain and immune responses[26]. The ECS includes signaling molecules (anandamide and 2-arachidonoylglycerol) and cannabinoid receptors (CB; CB_1 and CB_2 receptors)[26,27] (Figure 1.1–1.3). It is also now widely accepted that a number of other G-protein coupled receptors (GPR), such as GPR55, and transient receptor potential (TRP) channels, such as TRP vanilloid 1 (TRPV1) channels, are also part of the ECS[26,27].

Phytocannabinoids (derived from cannabis plants), such as THC and CBD, and synthetic cannabinoids (man-made cannabinoids chemically similar to THC, but not found in nature), such as dronabinol and nabilone, interact with the body's receptors and channels, most of which are part of the ECS, to elicit their physiological effects (Figure 1.2). While current synthetic cannabinoids have been chemically designed to have similar actions as THC, there has been little investigation to directly compare the therapeutic efficacy and safety profiles of synthetic cannabinoids to phytocannabinoids.

Endocannabinoids
are naturtally produced
cannabinoids in the body
(e.g. anandamine, 2-AG)

Phytocannabinoids
are produced
by the cannabis plant
(e.g. THC, CBD)

Synthetic Cannabinoids
are synthesized
chemical compounds
(e.g. nabilone [Cesamet®])

Figure 1.1:
Schematics of the different types of cannabinoids

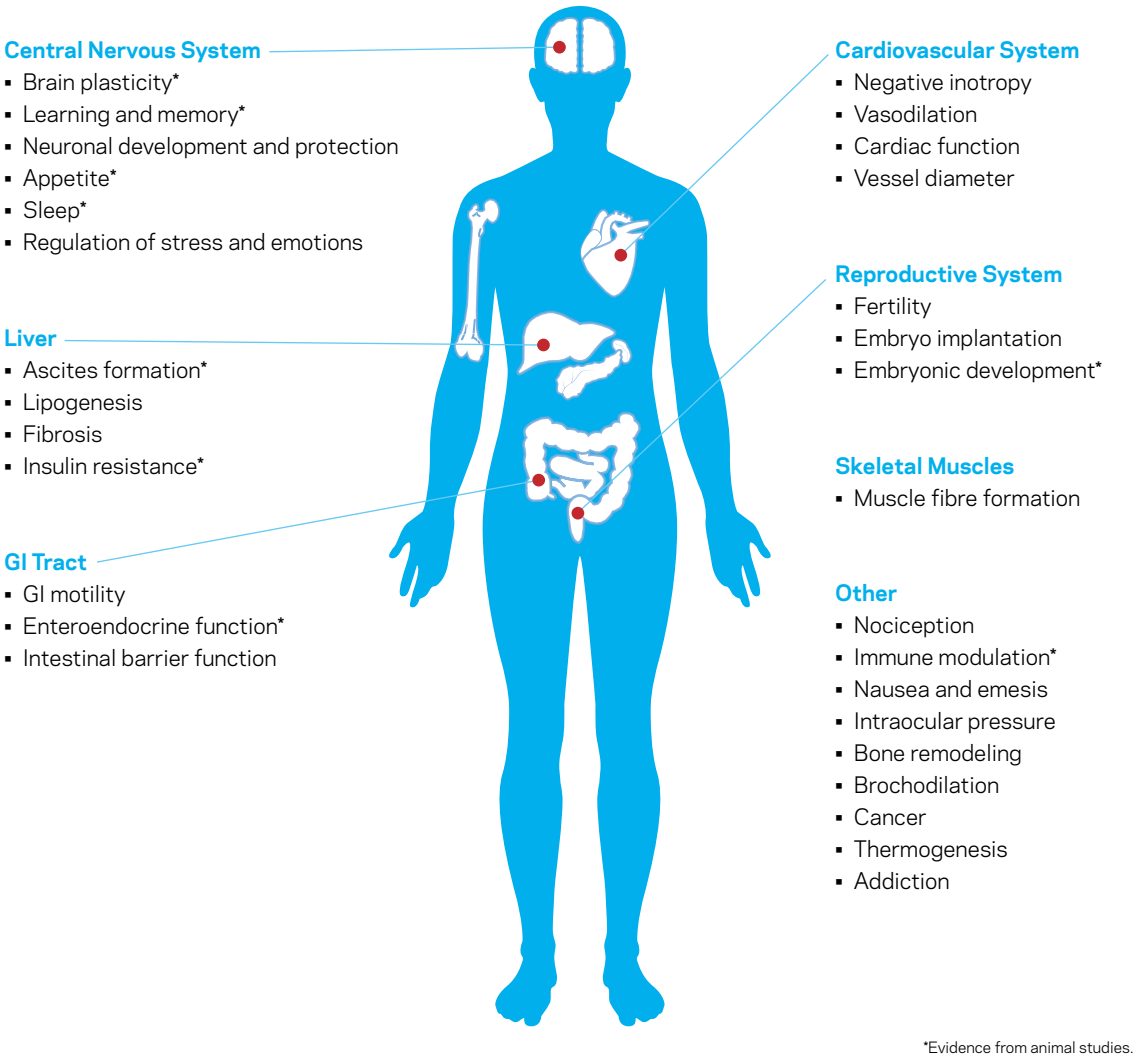
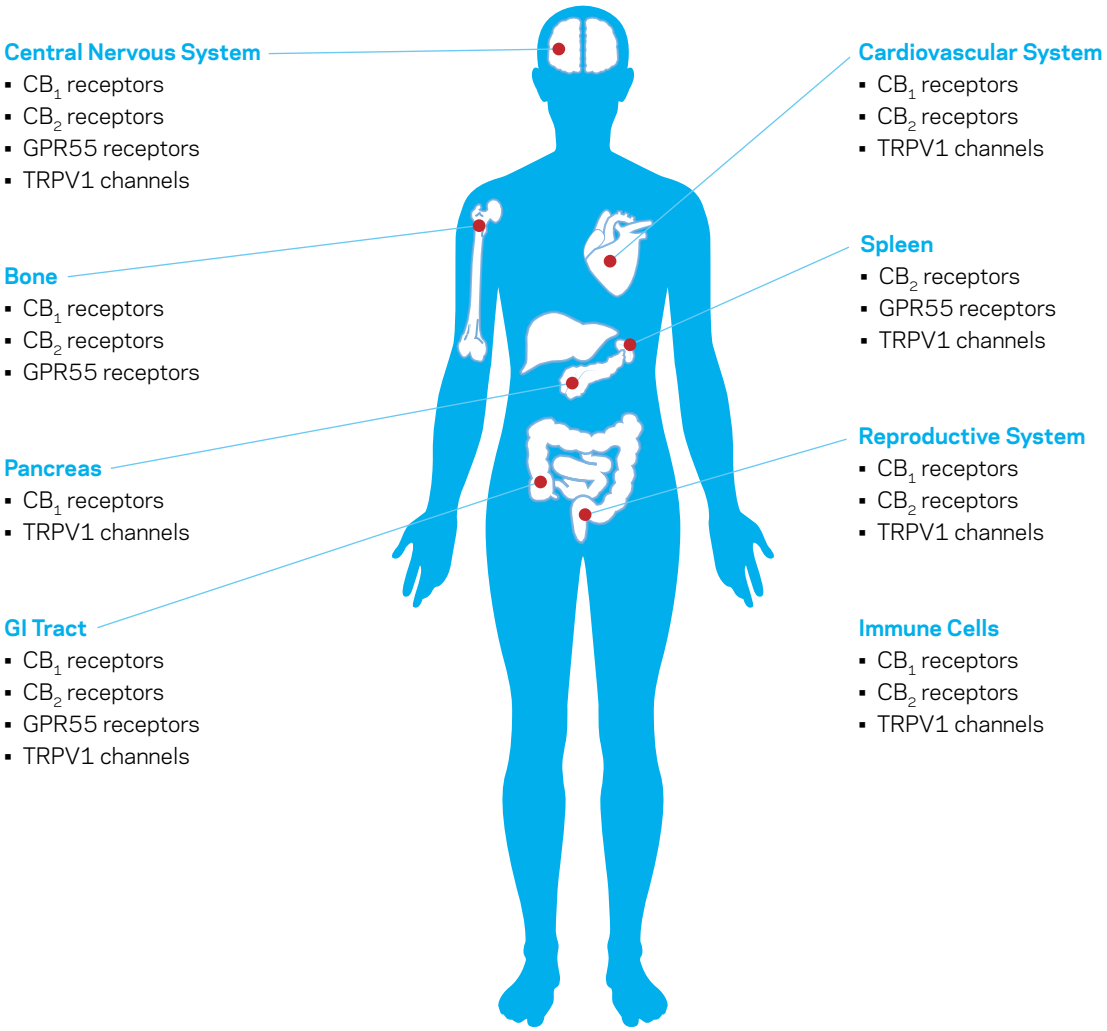


Figure 1.2:
Schematic of the endocannabinoid system and its physiological functions



Other Locations

- CB_1 receptors:
  - Liver
  - Fat
  - Eye
  - Skeletal muscles
  - Cancer cells
  - Lungs
- CB_2 receptors:
  - Fat
  - Liver
- TRPV1 channels:
  - Adrenal glands
  - Cancer cells
  - Skeletal muscles

Peripheral Nervous System

- CB_1 receptors
- CB_2 receptors
- TRPV1 channels

Skin

- CB_1 receptors
- CB_2 receptors
- TRPV1 channels

Figure 1.3:

Schematic of the receptors and channels in the endocannabinoid system

2 Routes of administration:

Medical cannabis can be administered in a number of different ways, such as through oral ingestion, inhalation, oromucosal absorption [either buccal (absorbed through the cheek) or sublingual (absorbed under the tongue)] and topically. Each route of administration can lead to different onset and duration of effects and thus, typically, the desired outcome will determine how a patient will administer their medical cannabis (Table 2.1).

Cannabinoids are extensively metabolized by the liver, so bypassing the liver by administering cannabis via inhalation or oromucosal absorption avoids first pass metabolism, leading to better bioavailability and a quicker onset than oral ingestion. However, oral ingestion, though subject to first pass metabolism, tends to lead to longer durations of effects. Alternatively, topical administration is useful when a localized effect is desired.

Inhaling via a vaporizer is among the most common methods to use medical cannabis. It is highly efficient, takes little time to feel the onset of effects and is discreet. There are a number of different handheld, rechargeable and desktop variations available.

2.1

Dosages:

Specific dosages for using cannabis as a pharmaceutical agent have yet to be determined. In general, in clinical trials, doses are started low (typically at the minimum allotted dose for the specific product) and titrated up to the desired maximum dose or until the dose becomes intolerable for the patients, the latter based on each individual patient's response to the cannabis-derived medicine.

Similar to other prescription medications, dosing cannabis should be done with the careful supervision of your primary health care provider. Aurora® supports the Health Canada-recommended, "start low and go slow" approach.

When beginning medical cannabis use, many patients will use a vaporizer with dried cannabis flower. When doing so, it is recommended to start with a single, moderate inhalation and then turn the vaporizer off to preserve the cannabis loaded inside. It is advised to wait a minimum of 10 minutes to determine the effects prior to inhaling more. If the desired effect is not achieved, turn the vaporizer back on, allow it to reach the selected temperature and then take two more inhalations before turning it off again and waiting another few minutes to see if the desired effect is achieved.

For cannabis oils or capsules, it is recommended a patient starts with the lowest possible starting dose. For instance, for Aurora® oils, this would be approximately 0.2 ml of oil and for a softgel cannabis oil capsule, it would be one capsule. Dose amounts should be increased in small increments and more than one dose should not be consumed within a 6–8 hour period.

Journaling the results from different dosages and products is suggested to help patients determine how much cannabis to use to achieve the desired therapeutic effect.

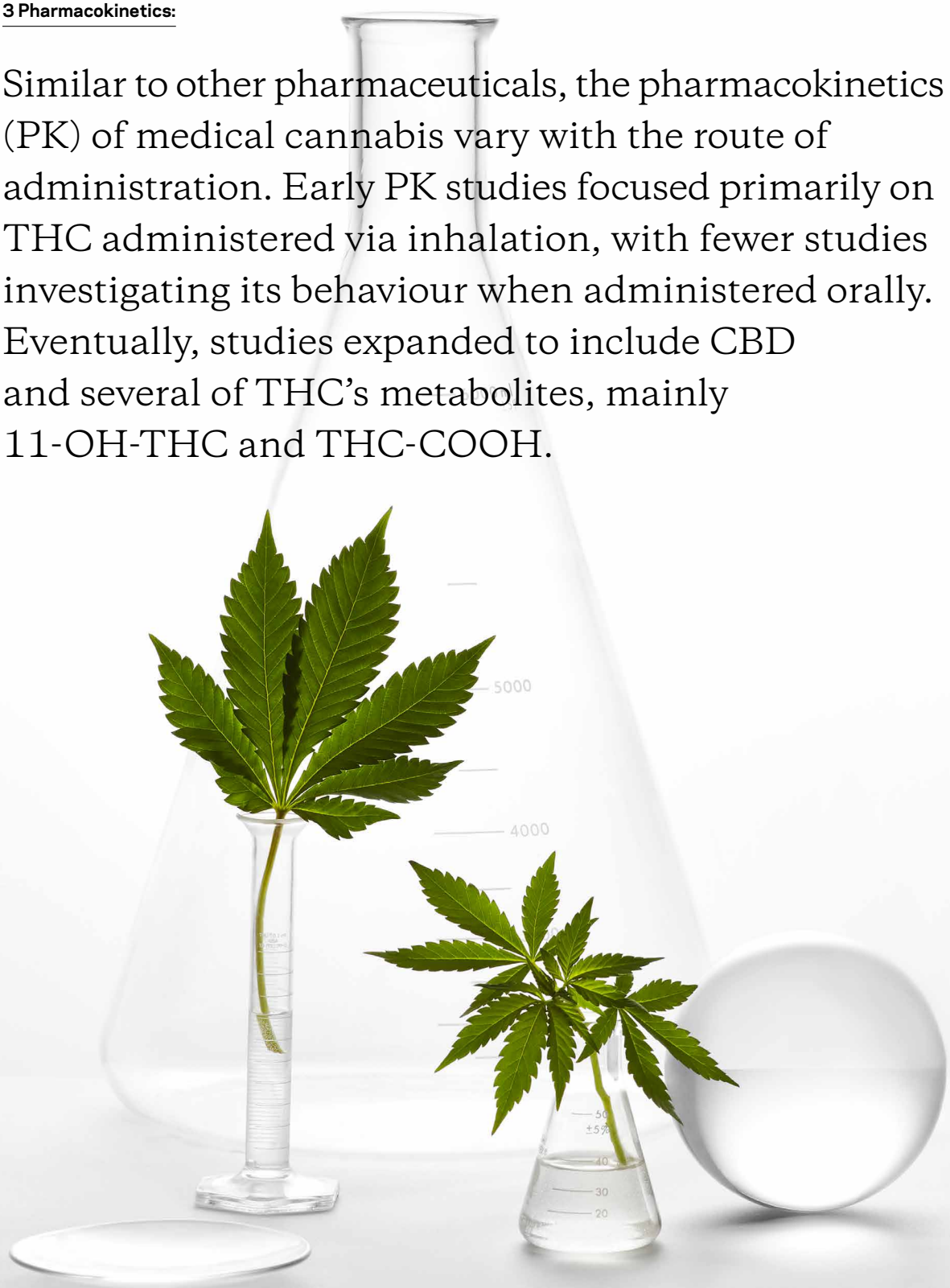
Table 2.1:

Onset and duration of effects for inhalation and oral administration[28]

	Inhalation	Oral
Onset of Effect	Within seconds to minutes	Within 30 minutes to 2 hours
Peak Effect	Full effects peak within 30 minutes	Full effects peak within 4 hours
Duration of Effect	Up to 6 hours or longer	Up to 12 hours or longer

3 Pharmacokinetics:

Similar to other pharmaceuticals, the pharmacokinetics (PK) of medical cannabis vary with the route of administration. Early PK studies focused primarily on THC administered via inhalation, with fewer studies investigating its behaviour when administered orally. Eventually, studies expanded to include CBD and several of THC's metabolites, mainly 11-OH-THC and THC-COOH.



Summary tables are found below; see Tables 3.1 and 3.2.

From PK studies, parameters such as bioavailability (the percentage of drug consumed that reaches systemic circulation and is thus, able to have an effect on the body), time to peak plasma concentration (how long it takes for the drug to reach its highest concentration in systemic circulation after consumption), area under the curve (AUC; total exposure of a drug over a period of time), plasma and elimination half-lives (how long it takes for half of the dose to leave the plasma into tissue and how long it takes for half of the dose to leave the body, respectively) and clearance rates (volume of plasma the drug is removed from per unit of time) can be determined for different routes of administration for each cannabinoid. These values help inform healthcare practitioners in their prescribing practices by aiding in dose decisions, time between doses and duration of effect from a dose. However, the available PK data for cannabinoids is limited, so while values from the scientific literature are reported below, more studies are required to generate PK parameters for specific cannabinoid-derived therapeutic products. Furthermore, there is no clear relationship between cannabinoid concentrations in the blood and the physiological effects, based on the evidence in the scientific literature.

3.1

Oral:

CBD oral bioavailability has not been determined in humans[29], though it was reported as 13–19% in dogs[30]. Mean time to peak plasma CBD concentration ranges from approximately 1–5 hours[31–34] with plasma half-life approximately 1 hour[32]. Elimination half-lives have been reported as approximately 60 hours after chronic dosing[31] or approximately 8 hours for an acute dose[34] of Epidiolex® (GW Pharmaceuticals; 11 mg/ml CBD oral solution) in healthy participants and 20–30 hours after an acute dose of a synthetic CBD in patients with severe epilepsy[33]. Rate of clearance from the body has been shown to be 1111–1909 l/h[31] or 422 l/h[34] after chronic dosing or an acute dose of Epidiolex®, respectively, in healthy participants. Furthermore, Wheless et al. showed time to peak plasma concentration and clearance to be independent of dose, while peak plasma concentration and mean absorption was dose dependent when a synthetic CBD in patients with severe epilepsy was consumed[33].

THC's oral bioavailability has been reported as 6 ± 3% (ranging from 4–24%)[35,36] when consumed in a cookie and 10–20% when administered in sesame oil[37]. Oral THC PK parameters are similar to CBD's with time to peak THC plasma concentration ranging from 1 to greater than 3 hours[32,35,37–40]. THC's plasma half-life has been reported to range from approximately 1 to 4 hours[32,37] while its elimination half-life is approximately 20 hours[37,41]. Rate of clearance from the body has been reported as approximately 10–15 l/h[37] and as high as 58.62 ± 18.24 l/h[41].

The effect of food consumption on the absorption of cannabinoids after oral administration is still currently under investigation. For instance, THC, CBD and 11-OH-THC absorption (time to peak plasma concentration or peak plasma concentration) was found to be unaltered when a meal was consumed one hour after oral ingestion of a cannabis extract (10 mg THC: 5.4 mg CBD) in healthy participants[39]. Alternatively, a fed versus fasted state was shown to increase the time it took to reach peak THC plasma concentration after Bedrocan® (20% THC and 0.5% CBD cannabis oil extract) was administered to dogs[42]. Interestingly, in the dogs administered Bedrocan®, peak THC plasma concentration was lower under fed conditions than under fasted ones[42]. Additionally, in healthy humans, there was a 4.85-fold increase in CBD's peak plasma concentration when Epidiolex® was ingested following a high-fat breakfast in comparison to being administered under fasting conditions[31] and Birnbaum et al. reported the consumption of a high fat meal enhanced CBD's C_{max} and AUC by 14-fold and 4-fold, respectively, after consumption of a 99% CBD extract as a 100 mg CBD softgel by adults with refractory epilepsy[43].

Due to conflicting findings currently available in the scientific literature, MedReleaf® recently investigated the PK parameters of an orally consumed THC extract capsule under different fed states[44]. Lunn et al. found that the consumption of a high fat meal prior to THC administration significantly increased the time to peak plasma concentration and mean levels for both THC and 11-OH-THC while also significantly reducing THC's apparent volume of distribution and apparent clearance rate in comparison to administration of THC under a fasting state[44]. Thus, MedReleaf®'s study findings supports the wider literature that a fed state versus a fasted one is likely to alter the PK of orally ingested phytocannabinoids[44].

3.2

Inhalation:

CBD bioavailability after inhalation has been found to range from 11–45%[45]. CBD reaches peak plasma concentration 5 minutes after inhalation and has an elimination half-life that ranges from 27–35 hours[45]. Its rate of clearance has been reported as 74 ± 14.4 l/h[45].

THC's bioavailability has been reported to range from 10–37% after inhalation[35,36,46]. Interestingly, significant differences were found between heavy and light consumers in two separate studies; bioavailability for heavy consumers was reported as 23 ± 16%[36] and 27 ± 10%[46] versus bioavailability for light consumers at 10 ± 7%[36] and 14 ± 1%[46]. Thus, prescribed dosages may need to be tailored to an individual based on if they have experience with cannabis or not, if the route of administration is to be inhalation.

THC has been reported to reach peak plasma concentration within 3–11 minutes after inhalation[35,47-49]. Its plasma half-life was found to be approximately 6.7 minutes[49] with variability in the elimination half-life, as one study reported 150 minutes[49] and another found it to be 4.3 days[50]. THC's clearance rate after inhalation has been found to be dependent on whether or not a consumer has experience in consuming cannabis. For infrequent consumers, THC's clearance rate was found to range from 5.25–89.99 l/h[46,51] while for frequent users, it ranged from 29.09–69 l/h[46,51].

3.3

Oromucosal:

Oromucosal administration offers rapid drug absorption due to high vascularity of the oromucosal region[52]. In addition, oromucosal administration bypasses first pass hepatic metabolism and therefore, is an appealing drug delivery method for compounds that are extensively metabolized in the liver, such as THC or CBD[52].

In Canada, Sativex® (GW Pharmaceuticals) is an approved cannabis extract used as an adjunct therapy to treat pain in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerated dose of strong opioids[53,54]. It is also used as an adjunct therapy to treat spasticity and neuropathic pain in adult patients suffering from multiple sclerosis (MS)[53,54]. This product contains equal concentrations of tetranabinex® (27 mg/ml THC extract) and nabidiolex® (25 mg/ml CBD extract), as well as residual cannabinoids (5%) and other extracted compounds, such as terpenes and flavonoids[53].

CBD reached peak plasma concentration in 0.5–4 hours while THC did so in 0.5–6.02 hours after the administration of Sativex®[55,56]. Furthermore, absorption of CBD and THC after Sativex® administration, was significantly improved when taken on a full stomach[56], suggesting that cannabinoid absorption after oromucosal delivery can be influenced by the presence of food similarly to how absorption of orally administered cannabinoids was altered by a fed or fasted condition.

3.4

Topical/transdermal:

Topical delivery (via a cream or gel product) is preferred when a localized effect of phytocannabinoids is desired. When a topical product is used, the phytocannabinoids have their effect in the area it is applied, and they do not get absorbed into systemic

circulation. Alternatively, transdermal delivery (also through a cream or gel product) is when phytocannabinoids are absorbed into systemic circulation where they have effects on the entire body. Transdermal delivery is a promising method of cannabis administration as it avoids first-pass hepatic metabolism, may provide targeted or localized drug delivery and therapeutic action, and could lead to a more constant dose level, avoiding the peak plasma concentrations that can lead to adverse events[57,58]. As phytocannabinoids are extremely lipophilic in nature, the rate limiting step of the absorption process is cannabinoid diffusion across the aqueous layer of skin[57-59]. THC has been shown to accumulate in the lipophilic pathways of the skin such as stratum corneum, upper epidermis and around hair follicles[58].

To date, there have been minimal human clinical trials involving the transdermal or topical application of cannabinoids. The limited research that has been published on this topic primarily involves *in vitro* skin models or animal studies, with the PK parameters varying widely[58,60,61]. Differences between the duration and time to steady state in the currently published studies is likely due to different formulations and potentially, the animal skin used. THC's permeability coefficient when applied to animal models was different depending on if propylene glycol-ethanol, oleic acid, dimethylsulfoxide (DMSO) and/or water was used as the solvent[61]. Interestingly, it has been reported that there are significant differences in the permeability of Δ^8-THC between different animal models and human skin[58,60], suggesting animal models should be chosen with care for future studies in order for findings to be more applicable in the clinic.

More work is required for topical and transdermal products in clinical trials in order to fully elucidate the PK parameters for cannabinoids when applied to the skin using different formulations.

Table 3.1:
Pharmacokinetic parameters for CBD and THC after oral administration or inhalation

Cannabinoid	Pharmacokinetic Parameter	Route of Administration	
		Oral	Inhalation
CBD	Time to peak plasma concentration	1-5 hours[31,32]	5 minutes[62]
	Plasma half-life	~1 hour[32]	
	Elimination half-life	~60 hours[31]	27-35 hours[45]
	Rate of clearance	1111-1909 l/h[31]	74 ± 14.4 l/h[45]
THC	Time to peak plasma concentration	1- greater than 3 hours[32,35,37-40]	3-11 minutes[35,47-49]
	Plasma half-life	0.97-3.9 hours[32,37]	6.7 minutes[49]
	Elimination half-life	~20 hours[37,41]	150 minutes[49] 4.3 days[50]
	Rate of clearance	58.62 ± 18.24 l/h[41] ~10-15 l/h[37]	Infrequent consumers: 5.25-89.99 l/h[46,51] Frequent consumers: 29.09-69 l/h[46,51]

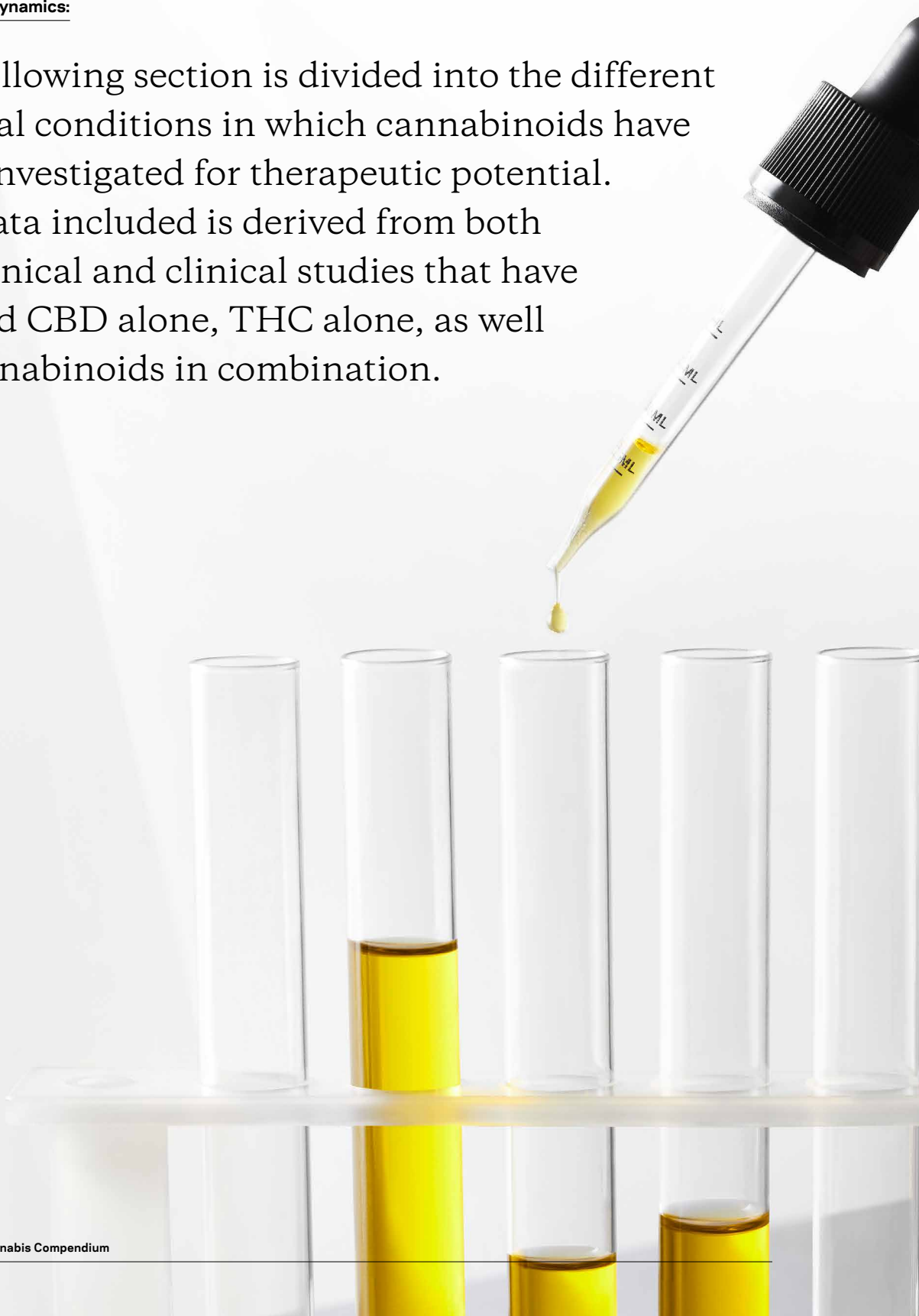
Table 3.2:
Bioavailability of CBD and THC after oral administration or inhalation

Cannabinoid	Route of Administration	
	Oral	Inhalation
CBD (% bioavailability)	13- 19% in dogs[30]	Inhalation from a cannabis cigarette found CBD bioavailability to be 11-45% in humans[45]
THC (% bioavailability)	In humans, 6 ± 3% (ranging from 4-24%)[35,36] when consumed in a cookie and 10-20% when administered in sesame oil[37]	Bioavailability of THC in humans reported values range from 10-37%[35,36,46] Significant differences were found between heavy and light consumers with bioavailability for heavy consumers being 23 ± 16%[36] and 27 ± 10%[46] versus bioavailability for light consumers being 10 ± 7%[36] and 14 ± 1%[46]


200 mL
± 5%
150
100
50

4 Pharmacodynamics:

The following section is divided into the different medical conditions in which cannabinoids have been investigated for therapeutic potential. The data included is derived from both pre-clinical and clinical studies that have utilized CBD alone, THC alone, as well as cannabinoids in combination.



For pre-clinical studies, CBD and THC are most commonly administered intraperitoneally (IP), with a few studies covering administration orally, topically or intravenously (IV). Various concentrations of the cannabinoids have been incorporated into vehicles of ethanol[63], DMSO[64], cremophor EL:ethanol: saline (1:1:18)[65,66], propylene glycol:water:ethanol[60] and methanol[67].

For clinical studies, the most common routes of administration are inhalation, oral ingestion and oromucosal sprays. These studies have examined the efficacy of phytocannabinoid extracts high in either CBD or THC or balanced concentrations (such as Sativex®, GW Pharmaceutical's oromucosal THC:CBD extract spray), as well as synthetic THC [such as nabilone, dronabinol and Namisol® (Echo Pharmaceuticals)], in a wide variety of different medical conditions. Aurora® extracts are from top quality cannabis plants and, as such, they likely have different characteristics when compared to the pharmaceutical industry's cannabinoid-like synthetics. The focus of the following data is on the cannabis plant and its extracts rather than the synthetic cannabinoids.

4.1

Mechanisms of action:

Drugs (such as CBD or THC) mainly interact with receptors, ion channels, enzymes and/or transporters. How they interact with their targets determines what type of cellular response and thus, overall physiological response, drugs elicit when consumed. The different ways a drug may interact with its targets are defined in **Table 4.1** and visually represented in **Figure 4.1**.

Table 4.1:

Pharmacological terms of how drugs interact with protein targets

Agonist	Drug binds and activates the target protein leading to a cellular response
Antagonist	Drug binds and does not activate the target protein, preventing activation by agonists
Partial Agonist	Drug binds and activates the target protein but even if 100% of the proteins are bound, the response is submaximal
Inverse Agonist	Drug binds and reduces the activity of the target protein, leading to the opposite effect of an agonist
Negative Allosteric Modulator	Drug binds to a site on the target protein different from where an agonist would bind, resulting in a change in the protein's structure that reduces or inhibits the activation of the protein by agonists

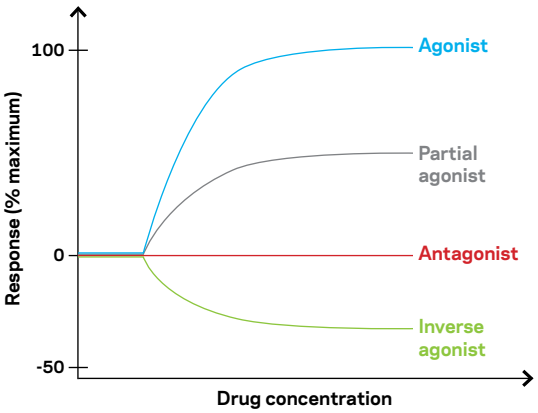


Figure 4.1:
How drugs interact with different protein targets

4.1.1
CBD:

CBD's exact mechanism(s) of action has yet to be conclusively determined, however, it has been found to interact with a number of different targets.

CBD has been shown to be an agonist[68-70], partial agonist[71], inverse agonist[72], antagonist[73] and a negative allosteric modulator[71,74] of CB_1 and CB_2 receptors. Additionally, there is evidence that CBD acts as antagonist at GPR55[75] and an agonist at TRPV1 channels[76-78], peroxisome proliferator-activated receptors-γ ($PPAR\gamma$)[68,79-81], serotonin-1A ($5HT_{1A}$) receptors[82-84] and adenosine (A) receptors[85]. CBD may also elevate anandamide levels through inhibition of fatty acid amide hydrolase (FAAH)[86] and/or inhibition of n-acyl phosphatidyl ethanolamine-specific phospholipase D[87], either directly act as anti-oxidant[76,88] or by enhancing the activity of endogenous anti-oxidant systems[89,90] and modulating caspase 3 activity[68,76,91].

CBD's ability to interact with a wide range of cellular targets is likely why it has been shown to have a number of different physiological effects. It is also probable that CBD's concentration and the absence or presence of other phytocannabinoids and/or terpenes influence CBD's interaction with these different cellular targets.

4.1.2
THC:

THC's physiological effects have most commonly been tied to partial agonism at CB_1[72,92-94] and CB_2[81,92,94-96] receptors. However, THC has also been shown to have anti-oxidant properties, scavenging free radicals[88].

4.2 Anxiety:

Anxiety is a feeling of unease and fear that we experience in response to stress[97]. While occasional anxiety is an expected part of life, when anxiety doesn't go away it can interfere with daily activities such as school and work, and negatively affect our interactions with others[97]. Left untreated, anxiety can lead to repeated episodes of panic attacks and major anxiety disorders[97].

There is evidence, though limited, that acute dosages of CBD prior to an anxiety inducing event have anxiolytic effects[98-101] and thus, CBD may be useful in treating individuals with anxiety. However, chronic treatment of CBD to treat anxiety has yet to be examined extensively in either pre-clinical or clinical studies.

4.2.1
CBD:

Acute CBD has shown anxiolytic effects in a number of animal models[69,77,82,102-106]. Specifically, in research supported by Aurora®, CBD was found to significantly reduce anxiety in an animal model of neuropathic pain[77]. Alternatively, CBD was found to be ineffective in non-stressed mice after chronic administration, indicating that there are potentially different mechanisms underlying the anxiolytic effects of acute versus chronic CBD exposure as well as efficacy in different models of anxiety[106].

In humans, acute doses of CBD (300-600 mg) have been shown to reduce subjective anxiety in a number of studies[98-101]. Furthermore, CBD's anxiolytic effects

were shown to be similar to ipsapirone, a known anxiolytic, in healthy participants required to give an impromptu speech[100]. Additionally, a high CBD cultivar was reported by patients as one of the top three MedReleaf® cultivars that improved their anxiety disorders[107].

The anxiolytic effects of CBD have been tied to CB_1, CB_2 and $5HT_{1A}$ receptor agonism[69,77,82], indicating potentially a number of different mechanisms of action leading to an overall reduction in anxiety.

Conversely, a systematic review encompassing 79 randomly controlled trials found very low-quality evidence of benefit for cannabinoid therapies in treating anxiety[108]. However, this study did not differentiate between different cannabinoid-based therapies (i.e. synthetic cannabinoids versus phytocannabinoids) or take into account different THC:CBD ratios.

Overall, more investigation is required to conclusively determine if phytocannabinoids, and in particular, CBD, could be effective in relieving anxiety.

4.3 Autism spectrum disorder:

Autism spectrum disorder (ASD) is a developmental disorder that is characterized by difficulty with communication and interaction with other people, restricted interests and repetitive behaviours and symptoms that hurt the person's ability to function properly in school, work and other areas of life[109]. It is labeled a spectrum disorder as there is a wide range of different symptoms and severities of symptoms between individuals with ASD[109]. Symptoms are usually apparent within the first two years of life though a person could be diagnosed at any stage of their life[109]. Current treatment plans include behavioural and communication-based approaches, diet changes, medication and complementary and alternative medicine[109]. At this time, no one treatment option can cure and/or treat the core symptoms of ASD[109].

From primarily observational studies, there is evidence that CBD extracts may be efficacious in treating many of the different symptoms of ASD in children and adolescents[110-112]. However, the number of studies is limited and have all utilized different CBD extracts. Overall, there is a need for interventional clinical trials examining the efficacy of phytocannabinoid-derived therapies in patients with ASD.

4.3.1
CBD:

In support of the hypothesis that CBD could be useful in treating ASD, studies that have shown CBD improves social behaviours in rodent models of psychosis[113,114] and reduces aggressive behaviours in mice[115] have been referenced.

This hypothesis has been examined in humans as well, though primarily through observational studies. CBD has been found to improve behavioural outbreaks, anxiety, communication and disruptive behaviours in ASD patients[110]. Furthermore, the use of CBD has been determined to be as efficacious as the conventional treatments outlined in the scientific literature for treating hyperactivity, self-injury and rage attacks, sleep problems and anxiety in individuals with ASD[111]. Additionally, overall quality of life, positive mood, ability to dress and shower independently, sleep and concentration have all been found to be significantly improved with CBD treatment[112]. Moreover, CBD as an adjunct therapy in ASD patients was found to reduce the use of other medications and relieve the personal stress levels of caregivers[110].

Mechanistically, CBD has been shown to reduce GABAergic (GABA) signaling in the pre-frontal and basal ganglia regions of the brain, leading to the hypothesis that altered GABA signaling contributes to ASD[116]. Thus, CBD may have potential as a treatment for ASD due to its ability to normalize GABA signaling[116].

4.4 Cancer:

Cancer is characterized by abnormal cell growth leading to a primary tumor which may or may not lead to the cancer cells spreading to other secondary sites (metastatic cancer)[117]. Current therapies include chemotherapy, radiation and/or surgery[117]. However, these treatments are not always successful and have significant, serious side effects[117]. Thus, there is ongoing investigation into new and better therapies.

Both CBD and THC alone, as well as in combination, have been examined as possible anti-neoplastic agents in a variety of different cancer cell lines, as well as some tumor animal models. Overall, the results show significant efficacy for each CBD and THC alone as well as the potential for synergistic activity when the phytocannabinoids are combined with each other and/or with currently used chemotherapies. However, while there is substantial pre-clinical evidence, the clinical data is still lacking and robust, interventional clinical trials are needed in order to fully elucidate the efficacy of phytocannabinoids in treating different cancers.

4.4.1

CBD:

CBD has been shown to induce apoptosis in human breast[76,118-120], prostate[76], colorectal[68,76,121-123], gastric[76,124], glioma[125-127], lung[128] and pancreatic[75] cancer cells.

CBD has also shown anti-cancer properties *in vivo*, reducing tumor size in glioma[127], breast[76,120], colorectal[121,122] and lung[128] cancer cell-derived xenograft tumor rodent models. Furthermore, in breast metastatic cancer cell animal models, CBD reduced the number of metastatic cancer cells[76,120]. CBD also reduced colon polyp development (precursor to colon cancer growth) in colon cancer animal models[68,121]. And finally, in a pancreatic ductal adenocarcinoma (PDAC) animal model, CBD not only prolonged survival to a similar extent as gemcitabine (one of a few drugs approved for PDAC in humans), but it also had an synergistic effect with gemcitabine; CBD and gemcitabine treated mice lived almost twice as long as ones treated with either drug alone and three times as long as mice treated with vehicle[75].

The above findings suggest that CBD has the potential to prevent cancer proliferation. CBD's anti-neoplastic mechanism of action has been tied to a wide range of different protein targets which include: CB_1 receptor agonism[68,121], CB_2 receptor agonism[68,76,121,127], TRPV1 channel activation[68,76], cyclooxygenase-2 (COX-2) up-regulation[128], $PPAR_Y$ up-regulation and increased activation[68,118,128], GPR55 antagonism[75] and the stimulation or indirect increase in levels of reactive oxygen species production[68,76,122,123,127]. Furthermore, CBD has been suggested to prevent drug resistance to well-used cancer treatments. In the PDAC mouse model and pancreatic cancer cell lines, CBD prevented the resistance to gemcitabine[75] and in cancer cells overexpressing the ABCG2 transporter, CBD enhanced the potency of topotecan (a chemotherapy drug whose efficacy is hampered by overactive ABCG2 transporters)[129]. Additionally, CBD alone inhibited proliferation of two oxaliplatin (a commonly used chemotherapy to treat colorectal cancer) resistant colorectal cancer cell lines (DLD-1 and colo205) while CBD combined with oxaliplatin significantly reduced tumor size and volume of subcutaneously injected oxaliplatin resistant colorectal cancer cells in mice in comparison to the untreated animals while neither treatment alone had any affect[123]. And lastly, both pure and CBD extract have been shown to reduce the activity of glycoprotein P, a transporter tied to chemotherapy drug resistance, suggesting another mechanism of action by which CBD may be beneficial in treating cancer[21].

4.4.2

THC:

THC has been shown to reduce cell viability via autophagy and apoptosis of human breast cancer (ER+/PR+, HER2+ and triple negative breast

cancer)[119,130 131], endometrial[132], glioblastoma[23,126] and hepatocellular[95,133] cancer cell lines. Like CBD, THC has also been shown to reduce cancer cell migration through the down-regulation of proteins required for the alterations that occur prior to metastasis[132] and reduce cell viability in an synergistic manner with temozolomide (a therapeutically used chemotherapy drug)[23].

THC has also been shown to have effects *in vivo*, leading to decreased tumor volume in subcutaneous tumor xenograft rodent models derived from glioblastoma[23,134] and hepatocellular[95,133] cancer cells.

THC's anti-neoplastic mechanism of action has been tied to CB_2 receptor activation and the induction of reactive oxygen species production[126].

4.4.3

Cannabinoids in combination:

The current evidence indicates that there is a synergistic anti-cancer effect not only between CBD and THC but also when they are combined with some current chemotherapies[23,126,130]. For instance, a THC cannabis extract was more potent at reducing the viability of breast cancer cell lines than purified THC[130] and the combination of THC and CBD reduced glioblastoma cell growth in a greater than additive manner (synergistic effect) in two separate studies[23,126]. This synergistic activity was also seen in an *in vivo* study using a xenograft tumor rodent model derived from glioblastoma cells which found THC and CBD combined limited tumor growth while alone neither had any effect[23].

In subcutaneous and intracranial xenograft tumor rodent models derived from glioblastoma cancer cells, combining THC:CBD and temozolomide significantly limited tumor growth while neither THC:CBD or temozolomide alone had any effect[134]. Interestingly, this synergistic effect was not reported when THC:CBD was combined with BCNU, a different chemotherapeutic[134], suggesting that cannabinoids do not have greater than additive effects with all chemotherapies.

Overall, there is a substantial body of pre-clinical evidence that CBD and THC, either alone or together, have anti-cancer effects. Importantly however, it must be noted that there is lack of evidence for the efficacy of phytocannabinoids in treating cancer in humans. Thus, there is a strong need for interventional clinical trials to examine if phytocannabinoids show as robust anti-neoplastic effects in humans as they do in pre-clinical models. Additionally, the above-mentioned studies have examined solely tumor-based forms of cancer and so, further work must occur to understand if phytocannabinoids are able to treat non-tumor forming cancers.

4.5 Cardiovascular function:

Cardiovascular diseases are the leading cause of death worldwide[135] and thus, new different treatment options are being investigated in order to reduce the mortality rates of the various cardiovascular related medical conditions. From pre-clinical work, there is some evidence that CBD may provide cardioprotection against coronary arterial occlusions[136,137] and diabetic-induced cardiomyopathy[90] though this research has yet to move into the clinic.

4.5.1

CBD:

CBD has shown cardioprotective effects in models of coronary arterial occlusions by limiting the development of arrhythmias[136] and reducing infarct size and inflammation[137]. The cardioprotective effects of CBD were blocked with A1 receptor antagonism, indicating that CBD may be mitigating its effects via activation of these receptors[136]. Furthermore, in an animal model of diabetic-induced cardiomyopathy, CBD conferred cardioprotection by enhancing endogenous anti-oxidant mechanisms and decreasing inflammation and thus, preventing cell death[90].

4.6 Depression:

Major depressive disorder or clinical depression includes symptoms such as persistent sad, anxious or "empty" mood, feelings of hopelessness, pessimism, guilt, worthlessness, helplessness, restlessness and/or having trouble sitting still, difficulties with concentration and sleeping and/or thoughts of death or suicide[138]. These symptoms alter how an individual feels, thinks and is able to handle daily life such as sleeping, eating or working[138].

There is some pre-clinical evidence that CBD may have therapeutic potential in treating depression[69,84,106,139-141] however, clinical studies are required to fully elucidate the matter.

4.6.1

CBD:

CBD has shown anti-depressive effects in a number of different animal models of depression[69,84,106,139-141]. Moreover, CBD's anti-depressive effects were similar to imipramine's, an anti-depressant[84]. However, as mentioned above, data from interventional clinical trials is currently lacking. From one of MedReleaf®'s longitudinal patient reported outcomes studies, it was found that patients reported that a high CBD cultivar was one of the top three MedReleaf® cultivars that improved their depression[107].

An interesting finding from these animal studies is that CBD appears to have an inverse U shape dose response regarding its potential anti-depressive actions[69,84,106,139,140]. The inverse U shape (∩) dose response relationship differs from more traditional, linear dose-response relationships in that as the dose increases, the resultant effects reach their maximum and then the effects begin to decrease (i.e. a non-linear dose-response relationship). Thus, more pre-clinical and clinical studies will need to be undertaken in order to further elucidate the dose-response relationship of CBD as it pertains to its anti-depressive effects.

CBD has shown synergistic effects with fluoxetine (a selective serotonin reuptake inhibitor) but not with desipramine (a selective noradrenaline reuptake inhibitor) and the anti-depressive effects were blocked only by serotonin depletion not noradrenaline depletion in animal models[141]. Thus, CBD's anti-depressive actions are likely linked to serotonin-based mechanisms, either a direct activation of $5HT_{1A}$ receptors[84,139], allosteric modulation of $5HT_{1A}$ receptors and/or increased levels of anandamide to activate $5HT_{1A}$ receptors[141]. CBD has also been shown to increase glutamate in the ventromedial prefrontal cortex, a process that may be part of the anti-depressive mechanism of action[139]. Furthermore, CBD's anti-depressive effects were shown to be independent of neurogenesis by Sales et al.[141].

4.7 Epilepsy:

Epilepsy is one of the most common neurological conditions among persons of all ages and is characterized by abnormal brain activity which results in seizures, unusual behaviour, and can lead to loss of awareness[142]. Pediatric patients suffering from prolonged seizures are at risk for lifelong developmental and intellectual delays[25].

In particular, there have been multiple trials in patients with severe, treatment-resistant epilepsy, such as Dravet and Lennox-Gastaut Syndrome, investigating the possibility that CBD can reduce seizure frequency and severity. Overall, these trials have shown CBD to be a potential therapy for the treatment of severe epilepsy with a tolerable side effect profile (most commonly, adverse events were rated as mild-moderate)[25,143,152-161,144,162,145-151].

Epilepsy is an area Aurora® is actively investigating. CanniMed® is currently involved in an ongoing clinical trial examining the efficacy of CanniMed® 1:20 (1 mg/ml THC:20 mg/ml CBD) oil in children with treatment-resistant epileptic encephalopathy[157,163]. The protocol for the clinical

trial was published in July 2018[163] and a paper of the preliminary results was recently published by Huntsman et al. in *Frontiers of Neurology*[157].

Huntsman et al. published preliminary data from 7 pediatric patients with either Lennox-Gastaut or Dravet Syndrome[157]. CanniMed® 1:20 at a 5-6 mg/kg/day CBD equivalent dose was found to reduce daily seizure frequency >25% in 6 patients, with 4 of these patients experiencing a >50% reduction[157]. At a 10-12 mg/kg/day CBD equivalent dose, CanniMed® 1:20 led to a 74% reduction in mean seizure frequency with 3 patients becoming seizure free from treatment with CanniMed® 1:20 (one patient was seizure free at the 8-9 mg/kg/day CBD equivalent dose while two others were seizure free at the 10-12 mg/kg/day CBD equivalent dose)[157]. All patients showed improvements in their quality of life in childhood epilepsy questionnaire (QOLCE-55) scores, especially in the cognitive, social and emotional function subscales[157]. Electroencephalogram (EEG) encephalopathy rating scales increased by 1 point for 5/7 patients, with 1 patient having an increase by 2 points and the final 7th patient showing no improvement as they had had normal ratings at baseline[157]. In the last month of the trial, patients were weaned off CanniMed® 1:20 and their reduction in seizure frequency remained consistent, with 3 having continuous improvement, though no other changes to their medications occurred[157]. QOLCE-55 scores did decrease during the weaning period, however, they remained greater than baseline[157].

Additionally, MedReleaf® is in partnership with the Ontario Brain Institute, University of Toronto, University Hospital London and Toronto Western Hospital for a clinical trial examining a cannabis extract's efficacy in treating adult epilepsy.

4.7.1

CBD:

CBD has been shown to have potent anti-epileptic effects in both animal models[164-167] and clinical trials in patients with severe, treatment-resistant epilepsy, such as Dravet and Lennox-Gastaut syndrome[25,143-162]. Furthermore, CBD has been shown to have a tolerable side effect profile in these clinical trials, with the most common adverse events rated as mild-moderate[25,143-162].

In particular, CBD has been shown to significantly reduce convulsive seizure frequency in comparison to placebo and more patients to achieve >50% reduction in overall seizure frequency compared to placebo[25]. Additionally, two open-label extension trials (using Epidiolex®) have recently published their interim analyses showing reductions in seizure frequency caused by CBD in patients with Lennox-Gastaut Syndrome or Dravet Syndrome stay consistent over 48 weeks, as do the minimal side effects[147,148]. Furthermore, in an expanded access program for Epidiolex®, 53% of patients with Lennox-Gastaut Syndrome and Dravet Syndrome reported a ⩾50% reduction in major motor seizures and 46% reported a ⩾50% reduction in total seizures at week 12 in comparison to baseline, with similar results through week 96[156]. For the patients with treatment-resistant epilepsies other than Lennox-Gastaut Syndrome or Dravet Syndrome included in this expanded access program, results were similar, with 52% reporting a ⩾50% decrease in major motor seizures and 51% reporting a ⩾50% decrease in total seizure at week 12 in comparison to baseline[156]. And again, these reductions stayed relatively consistent throughout the 96 weeks[156].

Cognitive function was examined in a portion of the patients with treatment-resistant epilepsy enrolled in the open label expanded access program for Epidiolex® via assessing cognitive function at baseline and at a 1 year mark[161]. Martin et al. found no significant changes in cognitive function nor any correlation between cognitive function and CBD dosage or between cognitive function and seizure severity after 1 year of Epidiolex® use[161]. Furthermore, quality of life (QOL) was examined in a different cohort of patients enrolled in the open label access program using Epidiolex® and was found to significantly improve from baseline at the 1-year checkpoint[159]. Interestingly, there was

no significant association between the QOL improvement and number of adverse events, an usual finding as typically a reduction in adverse events is correlated to improved QOL[159]. Thus, the authors suggested that CBD may have independent effects on improving QOL other than decreasing the number of adverse events[159].

From pre-clinical work, the anti-epileptic effects of CBD have been shown to be the result of an increase in inhibitory neurotransmission and a decrease in excitatory neurotransmission through GPR55 antagonism, independent of CB_1 receptors[164]. However, CBD's exact anti-epileptic mechanism of actions have yet to be fully characterized and thus, more investigation is still required.

In the majority of the above-mentioned trials, the treatment arm has been Epidiolex® (GW Pharmaceutical), an oral CBD solution. The abundance of positive data from these trials examining the efficacy of Epidiolex® led to its approval in the USA by the FDA in June 2018 for use in Lennox-Gastaut and Dravet Syndrome patients greater than 2 years old[168]. While the above clinical trials are extremely positive, they do have some limitations. For instance, the clinical trials have primarily utilized Epidiolex®, a pure CBD oral solution, however, Huntsman et al. found a 1:20 THC:CBD extract was also effective at reducing seizure frequency and may perhaps be more potent than Epidiolex®[157]. Thus, more work is required to fully understand the effects of both THC and CBD on limiting seizures in treatment resistant epilepsies in order to determine the optimal effective THC:CBD ratio that would minimize the risk of adverse events.

4.7.2

CBD dosages, plasma levels and correlation to seizure reductions:

There have recently been a number of studies examining the relationship between cannabinoid dose, cannabinoid concentrations in the blood and efficacy in reducing seizures. For instance, Huntsman et al. reported that steady state trough CBD and CBC concentrations increased proportionally to greater CanniMed® 1:20 doses thus, CBD and CBC showed a typical linear relationship for dose to plasma concentrations[157]. However, one of the participants did show a non-linear increase in CBD levels at the highest dose of 10-12 mg/kg/day CBD equivalent dose, suggesting that perhaps at high doses CBD shows non-linear pharmacokinetics[157]. At 5-6 mg/kg/day CBD equivalent dose, when 4/7 participants had a >50% reduction in daily seizure frequency, the steady state trough CBD concentrations ranged from 14.8-24.4 ng/ml[157]. At the 10-12 mg/kg/day CBD equivalent dose, when 5/7 participants had a >50% reduction in seizure frequency and 3/7 were seizure free, the steady state trough CBD concentrations ranged from 42.5-124.47 ng/ml and 54.8-78.9 ng/ml, respectively[157]. Thus, the authors recommended a starting dose of 5-6 mg/kg/day CBD equivalent dose of 1:20 whole plant extracts to be titrated up to 10-12 mg/kg/day[157].

Moreover, Szaflarski et al. found a significant difference in CBD dose (Epidiolex®) and plasma concentrations for responders versus non-responders with treatment resistant epilepsies when examining their entire patient cohort, which included both pediatric and adult patients[155]. However, when they compared within the pediatric cohort or adult cohort independently, they found no significant differences in CBD dosages or plasma concentrations between responders and non-responders[155]. Overall, the study reported effective CBD dosages and plasma concentrations were significantly higher in the adult cohort in comparison to the pediatric cohort and showed a positive linear relationship between an increased CBD dose, and subsequently plasma concentration, and seizure control[155].

Alternatively, Pietrafusa et al. found no significant differences in CBD daily dosage between responders and non-responders to a 98-99% CBD extract in children with developmental and epileptic encephalopathy[158].

4.7.3

THC:

THC alone has been shown to have anti-epileptic effects in two different epilepsy animal models[166].

4.7.4

Cannabinoids in combination:

In two different epilepsy animal models, the combination of THC and CBD showed synergistic anti-epileptic effects so that lower concentrations of each could be used to achieve significant reduction of seizure behaviours[166]. Furthermore, as outlined above, Huntsman et al. found CanniMed® 1:20 (at a 10-12 mg/kg/day CBD equivalent dose) caused a 74% reduction in mean seizure frequency with 3 patients becoming seizure free[157].

Overall, while there have been studies examining the relationship between cannabinoid dosage, cannabinoid plasma concentration and response, the results vary between studies, making any conclusions difficult. This variation may be due to the different CBD therapies utilized, different types of epilepsies included in the different studies and/or the smaller sample size in some of the studies. Thus, more investigation is still required to conclusively determine the most effective THC:CBD ratio and dosage for treating different types of treatment-resistant epilepsies.

4.8 Harm reduction:

As evidence begins to show efficacy for cannabis in treating pain, it has been suggested that medical cannabis could be used as a replacement for opioids prescribed for pain management and/or reduce opioid consumption in general. This is of interest as North America is currently in the midst of an opioid crisis. According to the Canadian Federal Government, there were at least 2,694 accidental apparent opioid-related deaths from January to September 2017, which correlates to an annual death rate of about 9.8/100,000 (up from 2016's estimated opioid-related death rate of 7.2/100,000)[169].

In the USA, more than 130 people die per day from an opioid overdose, with this number increasing[170]. From July 2016 to September 2017 in 52 areas across 45 states the number of opioid overdoses increased by 30% while increasing by 54% in urban centres of 16 states[170]. Preliminary evidence currently supports the hypothesis that cannabis use can reduce the consumption, and related harms, of chronic opioid use[171]. There is also emerging evidence that cannabis use may lead to a reduction in other pharmaceuticals such as benzodiazepines and non-opioid analgesics[172-177].

There is also a small body of evidence that CBD may reduce the use of other substances of abuse such as alcohol[178] and nicotine cigarettes[179,180].

Overall, the data is compelling that cannabis use may limit the consumption of other pharmaceuticals, such as opioids, and substances of abuse. However, at this time, the data is primarily from survey-based and retrospective studies or from animal studies. Thus, there is a need for placebo-controlled, interventional clinical trials to examine if cannabinoid-derived therapies are viable harm reduction tools.

4.8.1

CBD:

Animal data has shown that CBD can reduce self-administration of substances of abuse, such as ethanol[178,181], cocaine[104] and methamphetamine[182]. Furthermore, CBD was shown to reduce the relapse behaviour for animals dependent on ethanol[178] and methamphetamine[182] after periods of abstinence.

This above animal work is supported by findings in humans that have found CBD reduced the number of cigarettes smoked[179] as well as the salience and pleasantness of cigarette cues after overnight abstinence[180]. Acute CBD treatment also decreased cue-induced cravings and anxiety as well as limited general cravings at 24 hours and continued to do

so 7 days post CBD administration in participants dependent on heroin[183]. Furthermore, in a double-blind randomized, placebo-controlled trial in patients with heroin use disorder, acute CBD (400 or 800 mg Epidiolex®) significantly reduced the cravings and anxiety in response to drug cues and abolished the drug cue induced heart rate, temperature and salivary cortisol levels in comparison to the placebo group[184]. However, a dose-dependent effect was not determined as the 400 and 800 mg CBD doses had very similar effects[184].

4.8.2

Cannabinoids in combination:

A number of survey-based and retrospective studies indicate cannabis is being used by patients as a substitute for conventional pharmaceuticals, such as opioids[172-177]. For instance, a survey collecting data from chronic pain patients (n=1321), found that 80% of the respondents were substituting and/or replacing prescribed pharmaceuticals for cannabis (2 ± 1.4 substitutions), with 72% of these respondents replacing opioids[175]. In these studies, patients reported that medical cannabis improved their overall quality of life, managed their symptoms better and caused less adverse events than their previously prescribed pharmaceuticals[172,173,175]. Additionally, by using cannabis, patients reported reductions in their daily opioid dosages and even ceased to use opioids entirely[172,173]. In Vigil et al. (n=37), 40.5% of patients prescribed opioids stopped using them while 83.5% reduced their daily dosage after adding cannabis to their medical regime[172].

Data collected from the USA showed opioid related mortality and addiction rates were reduced in states with medical cannabis policies in comparison to states who do not have medical cannabis policies[185-187]. USA data also shows that adults fatally injured between the ages of 21 and 40 years old in states prior to their operational medical cannabis laws had greater odds of opioid positivity than drivers of the same age in states with active medical cannabis laws[187]. Additionally, the presence of medical cannabis policies reduced hospitalizations due to opioid dependence or abuse by 13% and opioid related overdoses by 11% while there was no significant associations with hospitalizations due to cannabis dependence or abuse[186]. In Bachhuber et al., active medical cannabis laws were associated with a 24.8% decrease in fatalities due to opioid overdose in comparison to states without medical cannabis laws[185].

Furthermore, Medicare- and Medicaid-filled opioid prescriptions were significantly decreased in states in the USA post-legalization of medical and/or recreational cannabis in comparison to the number filled prior to legalization of cannabis[188-190].

In patients with chronic pain, after 3 months of using 10 mg capsules of 1:1 THC:CBD and a vapour pen inhaler with 20:1 THC:CBD for break through pain, pain ratings were reduced from miserable to annoying[191]. Opioid use in these patients also decreased from 79.94 morphine equivalents per day to 19.65 (26/29 patients stopped opioid use all together while the remaining 3 reduced their intake by 75%)[191].

Furthermore, real world data from chronic pain patients (n=800) who used Sativex® for 12 weeks found that Sativex® (7.1 ± 1.4 sprays per day by week 9) led to a discontinuation of maintenance and rescue analgesic medications[177]. The number of patients using rescue medications significantly decreased from 81.4% to 50.1% and the average number of analgesic maintenance treatments were reduced from 3.2 ± 1 to 2.8 ± 1.2[177]. However, while overall there was a significant reduction in rescue and maintenance medications in patients with chronic pain, the effect was greatest in patients suffering from neuropathic pain[177]. Specifically, in the neuropathic pain patient cohort, 61.2% and 46.7% reduced their rescue and maintenance treatments, respectively, and the proportion of neuropathic pain patients no longer using rescue analgesics increased to 42.7% from 15.5%[177]. In the mixed pain cohort, the use of Sativex® led to 30.5% and 19.3% of patients decreasing rescue and maintenance treatments, respectively, while the number of patients no longer using rescue medications increased from 23.3% to 41%[177].

And finally, in the nociceptive pain cohort only 5.6% and 9.3% reduced their rescue and maintenance treatments, respectively, and the percentage of patients using rescue medications stayed constant[177]. Overall, patients reported cessation of rescue non-opioids and NSAIDs most often (41.3%, 41.2%, 37.9% and 28.3% stopped NSAIDS, non-opioids, mild-opioids and strong opioids, respectively)[177]. Specifically, 16.9 ± 6.7% of neuropathic pain patients and 6.4 ± 3.5% of mixed pain patients reduced their maintenance medications[177]. However, nociceptive pain patients on average increased their analgesic maintenance treatments[177]. Furthermore, neuropathic pain patients had the highest discontinuation rates for the maintenance analgesics, reducing non-opioid analgesics by 30.5%, strong opioids by 21.8%, mild opioids by 16.7% and anti-depressants by 13.4%[177]. This data indicates that cannabinoid-based medications may be most effective in reducing the use of analgesics in chronic pain patients with neuropathic pain rather than nociceptive pain.

Furthermore, it appears the replacement of other pharmaceuticals with cannabis is not solely found in medical cannabis consumers but also recreational consumers. For instance, a survey of 1000 adult cannabis consumers found that 65% of them were using cannabis to relieve pain symptoms and 74% were using cannabis as a sleep aid[192]. 80% and 83% of patients using cannabis for pain and sleep, respectively, stated cannabis was "very or extremely helpful" in treating their specific medical symptoms[192]. 88% of the consumers using cannabis to treat pain reported decreasing or stopping their opioid analgesics while 87% of consumers using cannabis to help them sleep said they limited or stopped their over-the-counter sleep aids[192].

Alternatively, a prospective study of people with chronic, non-cancer pain prescribed opioids and using cannabis found no evidence that cannabis improved patient outcomes[193]. Cannabis use did not lead to opioid sparing or reduce pain, with patients using cannabis reporting greater pain and lower self-efficacy in managing their pain than patients who did not use it[193]. However, this study was conducted in Australia, where cannabis is still illegal[193]. Thus, the authors suggested perhaps patients with the highest pain severity were the ones seeking out an illegal substance and their pain would have been worse without cannabis[193].

Overall, there is optimism that cannabis and cannabinoid-derived therapies may help to reduce the use of pharmaceuticals, such as opioids, and associated hospitalizations and mortalities, however, further investigation through clinical trials is required to fully elucidate the topic.

4.9 Inflammatory bowel disease:

Inflammatory bowel disease (IBD), of which there are two types (Crohn's disease and Ulcerative Colitis), is the result of chronic inflammation in parts of the gastrointestinal tract with symptoms such as diarrhea, fever and fatigue, abdominal pain and cramping, bloody stools, reduced appetite and unintended weight loss[194]. There are a variety of currently available treatment options that when used, aim to decrease gastrointestinal inflammation to reduce IBD symptoms. Due to CBD's potential anti-inflammatory effects, there has been interest in CBD as a potential treatment for IBD. While there is some pre-clinical and clinical work that supports the hypothesis that cannabinoid-derived therapies could be used to treat IBD, two large scale Cochrane reviews examining the evidence for cannabis in treating both Crohn's disease and Ulcerative Colitis determined that there was not enough evidence to make any conclusions on efficacy in either medical condition and that further studies are required to elucidate the matter[195,196].

4.9.1

CBD:

In animal models, CBD has been shown to reduce colon inflammation[70,197,198]. In these models, CBD's actions have been tied to the activation of CB_1 receptors and interestingly, CBD had no effect on healthy gut motility, which would be beneficial if used therapeutically[70].

4.9.2

Cannabinoids in combination:

In a retrospective observational study in 30 patients with Crohn's disease, there was significant improvement in disease symptoms (indicated via a reduced Harvey Bradshaw index score) with cannabis treatments, as well as a significant reduction in the use of other medications[199]. Alternatively, in another study of 21 patients (n=11 treatment group and n=10 placebo), while cannabis use did not lead to a significant induction of remission in comparison to placebo in patients with Crohn's disease, it did cause 10/11 patients to achieve significant clinical benefits (reduced pain and increased appetite and overall satisfaction with treatment) in comparison to patients provided the placebo[200].

However, two different Cochrane reviews examining the evidence surrounding cannabis for the treatment of Crohn's disease or Ulcerative Colitis concluded that there is currently a lack of scientific data for either medical condition and that further studies are required to make any conclusions on the efficacy of cannabis in treating either Crohn's disease[195] or Ulcerative Colitis[196].

4.10 Multiple sclerosis:

MS is a central nervous system autoimmune disease that leads to symptoms such as spasticity, weakness, pain, fatigue, lack of coordination, cognitive impairment and altered mood[201]. There is currently no cure though there are treatment options to mitigate disease symptoms[201]. There is evidence that Sativex® may be efficacious in treating many MS-related symptoms[53,202-206].

4.10.1

Cannabinoids in combination:

Sativex® has shown efficacy in reducing spasticity[202-205], pain[53,206] and sleep disturbances[205,206] in patients with MS. In a systematic review (>10,000 abstracts) it was reported that there was conclusive or substantial evidence of efficacy for cannabis-based therapies in relieving patient-reported MS spasticity symptoms, though only limited evidence for reducing clinician-measured MS spasticity symptoms[207]. Alternatively, a systematic review encompassing 79 randomly controlled trials found moderate-quality evidence of benefit for cannabinoid therapies in treating MS spasticity symptoms[108].

The primarily positive evidence surrounding Sativex®'s efficacy in reducing spasticity and neuropathic pain has led to its approval as an adjunct therapy to treat spasticity and neuropathic pain in adult patients suffering from MS[53,54].

4.11 Nausea and vomiting:

Nausea and vomiting are symptoms tied to a wide range of different medical conditions and/or side effects from various medications, such as chemotherapy[208]. There is evidence that cannabis-derived CBD and THC alone as well as together, may be effective in reducing nausea and/or vomiting. The majority of the evidence in this area has been generated through the use of the synthetic THCs, dronabinol and nabilone, both of which are approved for treating nausea and vomiting due to chemotherapy in the USA[209,210] while only nabilone is approved for the indication in Canada[211]. To date, direct comparisons of efficacy between the synthetic cannabinoids and phytocannabinoids has yet to be carried out. Thus, more research is required to determine if cannabis extracts are as or more effective than the synthetic cannabinoids for treating nausea and vomiting symptoms and to determine which type of cannabinoid is most effective for these particular symptoms.

4.11.1

CBD:

There is some evidence from pre-clinical models that CBD[212,213] can reduce nausea.

4.11.2

THC:

For THC, the results are mixed, with some animal studies reporting THC reduces nausea[214,215] while others show no effect[216].

4.11.3

Cannabinoids in combination:

In humans, the use of Sativex®, as an adjunct therapy, provided symptomatic relief of chemotherapy-induced nausea and vomiting in 71% of patients in comparison to 22% of patients receiving the placebo[217].

Furthermore, a systematic review (>10,000 abstracts) found conclusive or substantial evidence of efficacy for cannabis-based therapies in treating chemotherapy-induced nausea and vomiting[207]. However, another systematic review encompassing 79 randomly controlled trials found low-quality evidence of benefit for cannabinoid therapies in treating nausea and vomiting due to chemotherapy[108].

4.12 Neuroprotection:

Neuroprotection "is an effect that may result in salvage, recovery or regeneration of the nervous system, its cells, structure and function"[218]. There is evidence for CBD conferring neuroprotection in response to ischemia, as well as against neurodegenerative diseases, such as Parkinson's, Huntington's and Alzheimer's disease, in both *in vitro* and *in vivo* pre-clinical experiments. Furthermore, CBD may induce neuritogenesis (the process of forming of new outgrowths, which extend from the neuronal body), which would be beneficial in neurodegenerative diseases characterized by neuronal loss[219].

In general, there is more work to be done to fully elucidate the efficacy of cannabinoids as neuroprotective agents, especially through clinical trials, as primarily, the currently available data is from pre-clinical research. There is some evidence that neuropsychiatric symptoms in patients with dementia can be mitigated through the use of dronabinol (synthetic THC)[220,221] or a THC extract[222]. However, a direct comparison of efficacy against neuropsychiatric symptoms in patients with dementia between the synthetic THC, dronabinol and THC cannabis extract have yet to be carried out.

4.12.1 Alzheimer's disease and dementia:

There are two types of Alzheimer's disease: familial and sporadic. Sporadic is the more common version and is the combined result of genetics, environmental influences and lifestyle choices. Familial is less common (~1%) and is characterized by autosomal dominant mutations in the amyloid precursor protein (APP) or presenilin 1 and 2 (PS1 and PS2) genes[223]. Mutated genes lead to the accumulation of neurofibrillary tangles (from hyperphosphorylated tau proteins) and senile plaques (lesions comprised of amyloid-ß (Aß) aggregates, activated astrocytes and dystrophic neuritis)[224] that induce neuroinflammation, glial cell overactivation and oxidative stress, leading to neurodegeneration and cognitive decline[223]. While the least common form in the general public at large, familial Alzheimer's disease is the most commonly studied by pre-clinical researchers as the model is easier to generate (isolated neurons and/or animals are exposed to Aß). Alternatively, a popular transgenic mouse model of Alzheimer's disease with mutant APP and PS1 genes, leading to the overproduction of Aß and subsequently, senile plaque development, is also commonly used[225]. Therefore, while the least common in the general public, familial Alzheimer's disease models allow for the study of the pathology of the disease as well as the ability to identify new pharmacological targets/therapies. In these models of Alzheimer's disease, CBD has shown promise as a potential therapy for promoting neuronal survival and memory retention. However, it has yet to be investigated if these effects translate to humans with Alzheimer's disease or if CBD would have the same effects in the sporadic version of Alzheimer's disease.

CBD:

CBD has been shown to prevent an Aß-induced cellular toxicity in a number of different studies through the reduction of inflammatory markers, the number of activated astrocytes, hyperphosphorylated tau, oxidative stress and DNA fragmentation[64,91,226,227]. However, though conferring neuroprotection, CBD did not alter fibril formation and was unable to reverse damage caused by preformed Aß fibrils[226,227]. This suggests that CBD may only confer neuroprotective effects early on in disease progression[226,227]. CBD has also been shown to limit the activation, migration and inflammatory response to Aß in cultured astrocytes[80,228] and promote cell survival in neurons overexpressing amyloid precursor protein[229].

CBD *in vivo*, has been reported to protect against inflammation[80,224,228], glial cell activation[80,228] and prevent memory impairment[228,230,231] in a number of different pre-clinical Alzheimer's disease mouse models.

The anti-inflammatory and pro-survival effects of CBD have been tied generally to the activation of $PPAR_Y$[79,80,226,229] but CBD may also be acting as an agonist at CB_1, CB_2 and/or A_2 receptors[228], inhibiting caspase 3 activity and/or as a direct anti-oxidant[91] to elicit these effects.

4.12.1.2

THC:

From pre-clinical research, acute and chronic THC exposure was shown to significantly reduce Aß production and aggregation in cultured cells[232].

Furthermore, a THC extract (1.65% potency from Cannabliss®) significantly decreased the neuropsychiatric symptoms, including delusions, agitation/aggression, apathy, irritability, aberrant motor behaviour, in a small study of 10 patients with Alzheimer's disease[222].

4.12.1.3

Cannabinoids in combination:

The combination of THC and CBD has also shown neuroprotective effects in Alzheimer's disease mouse models. In pre-clinical models of Alzheimer's disease, treatment with THC:CBD has been shown to reduce inflammation, number of activated glial cells and tau and amyloid plaque deposition[89,231]. THC:CBD treatment also enhanced the activity of endogenous anti-oxidant systems and autophagy of plaques[89,231] and prevented memory impairment in mouse models of Alzheimer's disease[231,233].

4.12.2 Huntington's disease:

Huntington's disease is caused by a mutation in the *HTT* gene resulting in the formation of a mutated protein, huntingtin[234]. The disease is characterized by poor coordination (difficulty walking), issues with swallowing, irritability, depression, involuntary twitching or jerking movements (called chorea) and difficulty with speaking, learning new information and/or decision making[234]. Current treatments are able to mitigate the symptoms but there is no cure and disease progression cannot be slowed or stopped[234]. There is limited pre-clinical evidence that CBD[235] and tetrahydrocannabinolic acid (THCA)[236] may each provide neuroprotection in models of Huntington's disease and there is conflicting clinical evidence of the efficacy of Sativex® in treating the motor and dystonia symptoms of the disease[237,238]. Overall, the area is understudied and requires more evidence for any conclusions about efficacy of cannabinoid-derived therapies in treating the symptoms of Huntington's disease.

4.12.2.1

CBD or THCA:

There is limited data on the efficacy of cannabinoids for treating the symptoms of Huntington's disease. In pre-clinical models, CBD[235] as well as THCA[236] have shown neuroprotection. THCA in particular, improved the behavioural symptoms in an animal model of Huntington's disease[236].

4.12.2.2

Cannabinoids in combination:

Currently the results in humans are mixed what effect cannabinoid-derived therapies have in patients with Huntington's disease[237,238]. A small study of two patients found that Sativex® improved motor and dystonia scores[237], while a larger, double-blind randomized, placebo-controlled cross-over trial of 25 patients found that Sativex® had no effect[238].

4.12.3 Ischemia/reperfusion injury:

A cerebral ischemic/reperfusion injury (ischemic stroke) is caused by blood arteries in the brain becoming blocked or significantly narrowed, which cuts off blood and oxygen to areas of the brain, leading to neuronal death[239]. There is some pre-clinical evidence that CBD may reduce neuronal death induced by ischemic strokes, however, the current evidence is limited and has yet to be translated into clinical studies.

4.12.3.1

CBD:

CBD has been shown to promote neuronal survival through limiting inflammation and oxidative stress[85,240-242]. CBD has also been shown to reduce infarct size induced by cerebral ischemia in a number of different pre-clinical models[240,243-245]. The conferred neuroprotection by CBD was also shown to prevent memory and motor impairment seen in the untreated animals in different cerebral ischemia models[240,245].

CBD's mechanism of action in limiting cerebral ischemic damage is not clear, though it has been tied to the activation of CB_2, $5HT_{1A}$, A_1 and A_2 receptors[85,241,243,244]. Interestingly, Pazos *et al.* suggested that CB_2 and $5HT_{1A}$ receptors may form heterodimers, which would explain why antagonism of those individual receptors either partially or fully prevent CBD's effects in the outlined ischemic model but also in the other medical conditions outlined in this compendium[241].

4.12.4 Parkinson's disease:

Parkinson's disease is a neurodegenerative disease characterized by loss of dopaminergic neurons and dopamine signaling leading to the development of tremors, impaired balance, muscle rigidity, difficult sleeping and stiffness[246]. There is some, though limited, evidence from pre-clinical and clinical studies that CBD may reduce some of the symptoms associated with Parkinson's disease. In general, more evidence is required to determine if CBD is efficacious in treating the symptoms of Parkinson's disease.

4.12.4.1

CBD:

CBD has been shown to limit dopamine and tyrosine hydroxylase depletion[247,248], oxidative stress[247,248] and catalepsy[249] in different animal models of Parkinson's disease. Furthermore, in humans, CBD has been reported to reduce the psychotic symptoms[250], improve overall quality of life[251] and limit or abolish rapid eye movement (REM) sleep behaviour events[252] in patients with Parkinson's disease. However, to date CBD has not been shown to have any effect on motor function or any other symptoms of the disease[250,251].

From the pre-clinical work, CBD's neuroprotection in a model of Parkinson's disease was found to occur via activation of $5HT_{1A}$ receptors[249].

4.12.5 Traumatic brain injury:

Traumatic brain injuries (TBI) commonly occur when an external force injures the brain and can cause abnormal brain function[253]. Symptoms of a TBI are dependent on the severity of the injury and as such, symptom duration ranges from acute to chronic[253]. There are currently no standard treatments for TBIs though a number of different medical interventions may be utilized in order to prevent any secondary insults from occurring as a result of the initial trauma[253]. There is general

optimism for CBD's possible role in mitigating the long-term disruption in brain function and being helpful in reducing the duration and severity of symptoms caused by TBIs. This is based on CBD's anti-inflammatory and neuroprotective effects seen in other neurodegenerative medical conditions[254]. However, to date, the evidence is limited and scientific investigation from both pre-clinical and clinical studies is required to determine if the optimism is warranted.

4.12.5.1

CBD:

In a mouse model of minor TBI (mTBI), CBD significantly improved tactile withdrawal thresholds (an indicator of improved allodynia) and social interactions, reduced rearing behaviour and aggressiveness as well as mitigating mTBI-induced depressive symptoms[255]. This study showed that CBD may improve the social, mental and pain response symptoms caused by mTBI as well as the increased tendency towards aggression[255].

Belardo et al. also found that mTBI mice had significantly enhanced glutamate and d-aspartate levels and reduced GABA in the prefrontal cortexes day 14 post-injury[255]. CBD treatment for the 14 days post-injury period normalized these altered levels so that there was no difference in glutamate, d-aspartate or GABA levels between the vehicle treated sham mice and the CBD treated mTBI mice[255]. These findings shed some light on the potential mechanisms of action of CBD as well as the changes that occur as a result of an mTBI.

4.13 Pain/inflammation:

Pain is a distressing sensory and emotional experience caused by intense stimuli. As it is often linked to underlying conditions, it leads to more frequent physician visits and decreased quality of life. There are two major categories of pain. Tissue damage triggers sudden pain, also known as acute, while long-term, persistent pain is known as chronic. Different types of chronic pain are neuropathic (complex, chronic pain, that may be accompanied by tissue injury, that affects nerve fibres leading to incorrect signaling) and nociceptive (pain from a physical trauma).

In animal models of pain, thermal and mechanical sensitivity are measured to examine: hyperalgesia (an abnormally enhanced sensitivity to painful stimuli) and allodynia (painful responses to non-painful stimuli). Thermal sensitivity is normally measured via an apparatus that focuses a beam of radiant heat to the bottom of a paw and then the time it takes for the paw to be withdrawn is measured[256,257]. Longer latency to withdraw times indicate less thermal sensitivity and thus, reduced pain responses[256,257]. Mechanical sensitivity is normally measured via the use of von Frey Filaments. Each filament delivers a specifically calibrated number of grams force to a paw and withdrawal threshold is measured, with higher tolerated grams force indicating decreased pain responses[258].

In clinical trials, pain responses are measured using von Frey Filaments, cold pressor tests (holding a hand in ice water for as long as possible)[259] and a number of different validated surveys[260].

There is evidence from pre-clinical and clinical studies that CBD and THC alone as well as in combination may be effective in treating different types of pain. A systematic review encompassing 79 random controlled trials found moderate-quality evidence of benefit for cannabinoid therapies in treating chronic neuropathic pain and cancer pain[108] while a second, systematic review of >10,000 abstracts found conclusive or substantial evidence of efficacy for cannabis-based therapies in treating chronic pain[207].

Examining the efficacy of cannabinoid-based therapies in treating different types of pain is a focus for Aurora®, with many studies, ranging from pre-clinical, to survey-based, to interventional

clinical trials, currently ongoing or completed in this area. For instance, Aurora® has recently published Canadian Cannabis Clinic patient intake data in *Cannabis and Cannabinoid Research*[261].

The Canadian Cannabis Clinics are a group of 27 clinics in Canada that aim to provide their patients with the highest level of care and improve their quality of life through education on the therapeutic use of cannabis. The clinics' staff physicians, licensed nurse practitioners and counsellors have expertise in prescribing medical cannabis. When a patient is new to the Canadian Cannabis Clinics, they complete an intake interview that collects the primary medical complaint they are requesting medical cannabis for and many patients also complete validated questionnaires testing for anxiety, depression and drug and alcohol abuse. This intake interview data provides demographic and clinical data from patients who sought cannabis as a medical therapy from the Canadian Cannabis Clinics. The data set recently published included data collected from 10,269 adult patients between April 2014 and June 2016[261]. However, it did not include patient data past their intake interview so dose, efficacy, route of administration of cannabis consumption, and ratio of THC:CBD data is not included in this particular publication[261]. The reported demographics from this cohort can be found in Table 4.2[261].

Table 4.2:
Patient demographics[261]

		Patients (% or mean ± SD)
Sex	Male	54.3
	Female	45.7
Age (years)	Male	51.2 ± 14.6
	Female	52.5 ± 14.8

Canadian Cannabis Clinic patients were primarily seeking medical cannabis to treat[261]:

1) Pain: 66% were treating chronic general or musculoskeletal pain
2) Osteoarthritis: determined to be the most common (33.7%) musculoskeletal pain condition
3) Anxiety: 50.7% of patients were classified as having moderate to severe anxiety, according to the validated Generalized Anxiety Disorder 7-item (GAD-7) scale
4) Depression: 32.6% of patients had moderate to severe depression, characterized by Patient Health Questionnaire (PHQ-9)

The analysis of patient intake interview data collected from the Canadian Cannabis Clinics indicates that individuals with pain and co-morbid anxiety and depression are the most likely to seek out medical cannabis as an additional therapy, and that these patients are greater than 50 years of age[261]. This data is supported by a recent report that the most common medical condition USA patient's report using medical cannabis for is chronic pain[262].

As evidence begins to show efficacy for cannabis in treating pain, it has been suggested that medical cannabis could be used as a replacement for opioids prescribed for pain management, with preliminary evidence supporting this hypothesis[171]. Findings related to cannabis as an opioid sparing means can be found in Section 4.8: Harm reduction. Additionally, while opioid-induced hyperalgesia is a well described and studied phenomenon[263,264], to date, cannabinoid-induced hyperalgesia has yet to be reported.

Overall, the scientific evidence supports the hypothesis that cannabinoid-based therapies are useful in treating chronic pain. However, these studies differ in the route of administration of the cannabis treatment, THC:CBD ratio, cannabinoid dosages and duration of treatment. Many pain and cannabis studies also lack a placebo control and are open label. Thus, there is a need for further large-scale, robust, interventional clinical trialsto fully examine how effective cannabinoid-based therapies are in treating chronic pain. Furthermore, real world data of Sativex® use by chronic pain patients reported by Ueberall et al. appears to

indicate Sativex® is more effective at relieving the symptoms of chronic neuropathic pain versus chronic nociceptive pain[177]. This study indicates the need to determine not only what ratio of THC:CBD is most effective at relieving pain symptoms but also what type(s) of pain will be most responsive to cannabinoid-based therapies.

4.13.1

CBD:

CBD has been shown to reduce thermal and mechanical hyperalgesia and/or allodynia in pre-clinical neuropathic and inflammatory models[21,77,256,265-269]. For instance, in an inflammatory mouse model of pain, CBD significantly enhanced withdrawal thresholds to von Frey Filaments and the amount of weight bearing in the inflamed hind limb[258]. In a neuropathic rat model, CBD significantly limited thermal and mechanical hyperalgesia in a dose-dependent manner, with the hyperalgesia abolished by the highest dose of 20 mg/kg CBD[256]. Interestingly, CBD reduced the mechanical sensitivity found in paclitaxel-induced neuropathic pain, but had no effect against vincristine-induced mechanical sensitivity[265], pointing to potential differences in the neuropathic pain induced by these chemotherapies. Furthermore, CBD extracts have been found more efficacious than CBD isolates in treating thermal hyperalgesia[21] and graft versus host disease[81] in pre-clinical studies. Alternatively, CBD showed no analgesic effects against two different models of nociception in both mice[269] and rats[270]. These conflicting reports indicate a need to further examine the mechanism(s) of action of CBD in reducing pain and may also suggest that CBD is not as effective at limiting nociceptive pain as neuropathic pain.

CBD has shown anti-inflammatory effects in cultured immune[81] and skin[271] cells and pre-clinical models of osteoarthritis[258], graft versus host disease[81], paw-inflammation[266,272] and monoarthritis[267].

CBD's anti-hyperalgesic effects have been linked to the activation of TRPV1 channels[21,77,78,258], $5HT_{1A}$ receptors[273], CB_1 and CB_2 receptors[269] and $PPAR_Y$[81].

4.13.2

THC:

THC has been shown to diminish mechanical allodynia in paclitaxel- and vincristine-induced neuropathic pain (but not oxaliplatin-induced neuropathic pain)[265] and in an eye model of neuropathic pain[273]. Additionally, THC prolonged the latency for tail withdrawal from cold water in rats, indicating THC-induced analgesic effects[274].

CanniMed® has previously supported research examining the efficacy of phytocannabinoids in treating pain. For instance, in a paw inflammation animal model, THC alone and in combination with cannabidiolic acid (CBDA), provided by CanniMed®, at subthreshold doses (that had no effect alone) reduced edema and hyperalgesia in a CB_1 receptor sensitive manner[275].

In humans, while the data is limited for high THC-based products derived from cannabis, a longitudinal patient reported outcome study by MedReleaf® found that two out of the three top cultivars patients associate with pain improvement at a 10 month follow-up were high THC cultivars[107].

4.13.3

Cannabinoids in combination:

From pre-clinical research in rodents, low doses of THC and CBD have been shown to have a synergistic effect on reducing paclitaxel- or oxaliplatin-induced mechanical sensitivity but had no effect on vincristine-induced mechanical sensitivity[265]. Thus, again, there appears to be a difference in the mechanisms of chemotherapy-induced neuropathic pain and the efficacy of cannabinoids against different types of pain.

Clinical trials (both interventional and observational) examining cannabis as a therapy for treating pain report mostly positive effects on pain symptoms. These studies have utilized different cannabis products and routes of administration as well as

examining the efficacy of cannabis in different pain conditions, making comparisons between studies difficult.

Inhaled cannabis (1–8% THC) significantly reduced neuropathic pain in HIV patients, causing a significantly greater number of patients to achieve clinically meaningful pain relief with cannabis use than without[276,277]. Furthermore, pain patients using a Syqe® Inhaler with 3.08 ± 0.02 mg THC in a 15.1 ± 0.1 mg cannabis dose found a significant improvement in pain symptoms 20 minutes after inhalation with pain returning around 90 minutes post-inhalation[278].

Bellnier et al. examined the efficacy of combining different formulations and dosages. Chronic pain patients (n=29) were provided 10 mg capsules of 1:1 THC:CBD to be taken every 8–12 hours and a vapour pen inhaler with 20:1 THC:CBD for break-through pain (1–5 puffs every 15 minutes until relief was achieved every 4–6 hours as needed) to use for 3 months[191]. The use of these cannabis medications was found to significantly improve quality of life and reduce paroxysmal, surface and deep pain[191]. Furthermore, pain ratings went from miserable to annoying and opioid use decreased from 79.94 morphine equivalents per day to 19.65 (26/29 patients stopped opioid use all together while the remaining 3 reduced their intake by 75%)[191].

CanniMed® has also provided cannabis for two pain-related clinical trials: a chronic non-cancer pain trial (median daily dose of 2.5 g/day of 12.5% THC; administered orally and/or inhaled based on patient preference)[279] and a chronic neuropathic pain trial (25 mg of 9.4% THC; inhaled)[280]. These trials both showed that cannabis use significantly improves pain symptoms, sleep, and overall quality of life in patients suffering from chronic pain[279,280]. In the chronic, non-cancer pain trial, cannabis treatment also significantly reduced the sensory components of pain (tension-anxiety and depression-dejection)[279].

Sativex® has also been extensively examined for efficacy in treating pain symptoms. Sativex® has been shown to significantly reduce pain symptoms in a number of trials[53,281-283]. For instance, in a 5 week[284] as well as a 15 week[285] trial in patients with neuropathic pain, Sativex® significantly reduced pain and improved sleep. However, two other trials found that while Sativex® improved sleep in neuropathic pain patients, the reduction in pain did not reach significance[281,286]. Real world data from chronic pain patients (n=800) who used Sativex® for 12 weeks found that Sativex® (7.1 ± 1.4 sprays per day by week 9) provided significant pain intensity relief for patients suffering from neuropathic chronic pain and mixed pain, however, it was not effective and/or worsened pain symptoms in patients with nociceptive pain[177]. Additionally, 76.1% of neuropathic pain patients, 24.1% of mixed pain and 1.9% of nociceptive pain patients reported their lives were much better or very much better by using Sativex®. Interestingly, no statistically important correlation was determined between the number of sprays and treatment response[177]. Thus, Sativex® appears to be significantly less effective at relieving the symptoms of nociceptive pain than neuropathic and/or mixed pain[177].

The primarily positive evidence surrounding Sativex®'s efficacy in reducing pain has led to its approval as an adjunct therapy to treat pain in adult patients with advanced cancer who experience moderate to severe pain during the highest tolerate dose of strong opioids, and as an adjunct therapy to treat spasticity and neuropathic pain in adult patients suffering from MS[53,54].

Alternatively, in a fibromyalgia crossover trial, there was no effect on spontaneous or electrical pain after the acute inhalation of 6.3% THC:8% CBD (13.4 mg THC:17.8 mg CBD; Bediol®), <1% THC: 9% CBD (18.4 mg CBD; Bedrolite®) or 22% THC: <1% CBD (22.4 mg THC; Bedrocan®)[62]. However, significantly more participants had a >30% reduction in spontaneous pain after inhalation of 6.3% THC:8% CBD (13.4 mg THC:17.8 mg CBD; Bediol®) in comparison to placebo[62].

Overall, there is a need for further placebo-controlled, interventional clinical trials examining the efficacy

of cannabinoid-based therapies in treating different types of pain. However, the above-mentioned positive data indicates cannabinoid-based therapies have the potential to alleviate pain symptoms in a number of different medical conditions.

4.14 Post-traumatic stress disorder:

Post-traumatic stress disorder (PTSD) is a mental health disorder caused by experiencing one or more traumatic life events[287]. PTSD is characterized by symptoms that include intrusive memories (recurrent and unwanted memories of the event and emotional distress when something is similar to the traumatic event), negative changes in thinking and mood (depression and anxiety), changes in physical and emotional reactions (on guard, difficult sleeping or concentrating, angry) and avoidance of the traumatic event[287].

To study PTSD in pre-clinical models, animals are exposed to traumatic events, such as predators and electrical foot shocks, and their contextual conditioned fear responses (freezing behaviours, heart rate, blood pressure) and/or anxiety levels are measured[288]. For clinical trials, validated surveys are the most common way to determine PTSD symptom levels.

Currently, there is some pre-clinical evidence that CBD may be beneficial in treating PTSD but there is a need for interventional clinical trials to fully elucidate this matter. To date, the efficacy of cannabis in treating PTSD in humans has been primarily through observational studies.

4.14.1

CBD:

Several studies have shown that CBD reduced anxiety in a number of pre-clinical models of PTSD[83,288-293]. Furthermore, CBD's reduction of contextual conditioned fear was similar to diazepam, a known anxiolytic[288], and an acute dose of CBD administered immediately after the initial shock test reduced fear responses 22 days post-dose[291]. Alternatively, an acute dose of CBD had no effect on the conditioned fear response in rats to a synthetic form of fox feces[293]. Despite these primarily favourable results, these studies do not provide clarity as to when CBD should be administered to reduce PTSD symptoms. Depending on the study, CBD administered to rodents prior to[289] and after[83,291] the traumatic event have both been shown to be efficacious. Interestingly, only when administered immediately after the traumatic event and not 6 hours following it, did CBD significantly limit the fear response at 1, 7 and 22 days[291]. Thus, while there is potential for CBD as a treatment for PTSD, the optimal time of administration in relation to the traumatic event has yet to be determined.

4.14.2

THC:

MedReleaf® has previously published a number of longitudinal patient reported outcomes studies, of which many have included PTSD-specific patient data[294-298]. For instance, Wan et al. found that MedReleaf®'s PTSD patients associated high THC cultivars as being most effective at improving their symptoms[107].

4.14.3

Cannabinoids in combination:

Due to the overwhelming number of veterans who report using cannabis as means to treat their symptoms[299-301], there is a clear need for interventional clinical trials to examine the efficacy of cannabis-based products in treating PTSD. To date, a large proportion of the data available on the efficacy of cannabis in treating PTSD is rooted in anecdotes and observational studies[301]. For instance, a review of the currently available literature by Betthauser et al. reported that cannabis use relieved symptoms such as anxiety and insomnia and enhanced coping capabilities in veterans with PTSD[300].

Furthermore, from MedReleaf®'s published longitudinal patient reported outcomes studies, cannabis use significantly reduced PTSD symptoms (specifically suicidal thoughts)[297], pain severity[297], the impact of PTSD on social and family life[297],

general mood[295], sleep[295], concentration[295] and overall quality of life[295]. These MedReleaf® patients also reported a 50% decrease in consumption of other PTSD medications when they began using medical cannabis[297].

Thus, while these studies provide evidence that cannabis is reported as efficacious in treating PTSD symptoms by patients, there is a need for placebo, interventional clinical trials to further investigate the efficacy of cannabinoid-derived therapies in treating PTSD.

4.15 Psychosis:

Psychosis is a condition characterized by the inability to distinguish what is real and what is not and includes both positive (delusions, disorganized speech and hallucinations) and negative (limited emotions, speech, ability to perform tasks, socialization and motivation and trouble thinking) symptoms[302]. Other symptoms associated with psychosis include: cognitive dysfunction, mood changes, suicidal thoughts and/or behaviours, substance abuse and sleep issues[302]. Many different mental illnesses may involve an individual suffering from psychosis such as schizophrenia, schizoaffective disorder and depression with psychotic features[302].

It has been reported that schizophrenics have a higher use of cannabis than the general public[303]. In the largest genome-wide association study of lifetime cannabis use it was found that there was "weak evidence for a causal link from cannabis use to schizophrenia" while "much stronger evidence for a causal link from schizophrenia to cannabis use," suggesting that individuals with the genetic predisposition to develop schizophrenia are more likely to use cannabis rather than cannabis use inducing schizophrenia[303]. Risk variants in CADM2 and NCAM1 genes, both of which are cell adhesion molecules part of the immunoglobulin superfamily, showed the strongest correlation to cannabis use and have also been associated with increased risk-taking, alcohol consumption, illicit drug use and psychiatric disorders, such as schizophrenia[303]. Furthermore, the comprehensive review of the current cannabis literature carried out by the United States of America's National Academies of Sciences, Engineering and Medicine, reported cannabis use is "likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater the risk"[207]. Nevertheless, there is some evidence that CBD can alleviate psychotic symptoms in humans and animal models, which is outlined below. Thus, the relationship between cannabis use and the development of psychiatric disorders is not fully understood and requires further investigation. For a more in-depth examination of the evidence surrounding cannabis use and psychosis, see Section 6.2: Cannabis use and psychosis.

4.15.1 CBD:

In pre-clinical models of schizophrenia, CBD reversed the cognitive dysfunction and working memory impairments and improved social behaviours in comparison to the untreated animals[113,114,304].

In humans, 800 mg CBD significantly improved psychiatric symptoms while also showing no serious side effects and less extrapyramidal symptoms, weight gain and prolactin release (predictor of sexual dysfunction) than amisulpride, a known anti-psychotic, in patients with schizophrenia[305]. Additionally, in anti-psychotic naïve patients with a high risk of psychosis, a single dose of CBD altered brain activity so that activity in the striatum, medial temporal cortex and midbrain were at levels between placebo participants and healthy control activity levels, supporting the idea that CBD may be an anti-psychotic[306]. Alternatively, there is also some evidence that CBD is not effective at reducing psychotic symptoms in individuals with schizophrenia[307,308], although McGuire et al. reported that CBD did cause a significant number of patients to be rated as improved overall by their

clinicians[307]. Thus, further investigation is required to determine if CBD is an effective therapy for treating psychosis.

4.16 Sleep:

Sleep is a naturally recurring state in which the body alternates between two distinct modes: REM sleep and non-REM sleep. Sleep is characterized by altered consciousness, relatively inhibited sensory activity, reduced muscle activity, inhibition of nearly all voluntary muscles during REM sleep and reduced interactions with surroundings[309,310]. It is important as sleep helps to restore and maintain mood, memory and cognitive function and plays a large role in the endocrine and immune systems function[309,310]. The brain does remain active during sleep which is thought to play a role in memory consolidation[311].

Cannabis is commonly associated with improving sleep, for instance, 74% of adults surveyed reported using cannabis as a sleep aid[192]. However, robust, interventional clinical trials examining the efficacy of cannabis-derived therapies in aiding sleep are limited and/or show minimal benefits. Overall, this is an area of study that requires extensive research for any conclusions to be made about the therapeutic efficacy of cannabinoid-based therapies in treating sleep disturbances.

4.16.1

CBD:

In rodents, CBD increased the total percentage of time in sleep and the time to reach REM sleep cycle[312].

In humans, CBD has been found to improve sleep problems in patient with ASD[111,112]. However, CBD was found to have no effect on improving sleep in adult psychiatric outpatients[313].

Thus, overall, there is limited data available and so the relationship between CBD and sleep is currently inconclusive.

4.16.2

THC:

One of MedReleaf®'s published longitudinal patient reported outcomes studies found that patients find primarily high-THC cultivars effective in improving sleep disorders[107].

4.16.3

Cannabinoids in combination:

A systematic review (n= >10,000 abstracts) found moderate evidence of efficacy for cannabis-based therapies in treating sleep disturbances associated with sleep apnea, fibromyalgia, chronic pain and MS[207]. Additionally, Sativex® was reported to significantly improve sleep in patients with neuropathic pain in a number of different studies[281,284-286] as well as relieve sleep disturbances in patients with MS[205,206]. However, it should be noted that in these studies Sativex® was also found to improve the underlying condition and so the improved sleep could be the result of the improved condition rather than a direct effect on sleep.

From MedReleaf®'s published longitudinal patient reported outcomes data focusing on PTSD patients, patients reported cannabis use significantly improved their sleep[295]. Furthermore, MedReleaf®'s longitudinal patient reported outcome studies reported 25.7-38.4% of their patients use cannabis for sleep disorders and/or sleep problems[107]. Additionally, from these studies, it was found that the top three most popular cultivars in treating sleep problems were a high THC, a balanced 1:1 THC:CBD and a high CBD[107].

Therefore, it is clear that more research is required to investigate if cannabinoid-based therapies could be efficacious as both a sleep aid in sleep disorders and for sleep improvement in other medical conditions.

5 Adverse events:

Overall, the consumption of cannabis products or phytocannabinoid isolates has been reported to be well-tolerated with predominantly mild to moderate-rated adverse events experienced.

5.1

CBD:

Ewing et al. recently performed a toxicity study on mice examining acute and chronic (10 days) CBD administration[314]. Acute doses were 246, 738, 2460 mg/kg CBD administered via oral gavage so as to be analogous to human doses of 20, 60 and 200 mg/kg CBD, respectively[314]. Chronic doses were 61.5, 184.5 and 615 mg/kg so as to be analogous to human doses of 5, 15 and 50 mg/kg CBD, respectively[314]. In the acute study, 738 and 2460 mg/kg increased aminotransferase serum levels and various cytochrome P450 (CYP450) and glucuronoysyltransferase levels 24 hours post dosing[314]. These doses also reduced appetite and responses to stimuli 4–5 hours post CBD consumption (indicating lethargic behaviour), while these effects were shown up to 24 hours post-dosing with 2460 mg/kg[314]. The 738 mg/kg dose also significantly increased liver to body weight while the 2460 mg/kg dose enhanced reduced glutathione amounts (indicating increased oxidant levels)[314]. In the chronic dosing portion of the study, the 615 mg/kg dose caused significant loss of appetite and body weight along with lethargy, leading to the cessation of this dose on day 3[314]. Analysis of these animals found significantly enhanced liver-to-body weight ratio, reduced kidney-to-body weight ratio and elevated bilirubin and CYP450 and glucuronoysyltransferase enzymes, indicating liver and kidney damage[314]. Chronic dosing of 61.5 and 184.5 mg/kg for 10 days resulted in no significant changes to bilirubin or aminotransferases, though 50 different genes tied to liver function (including those related to CYP450 and glucuronoysyltransferases) were dysregulated[314]. This study highlights the potential toxicity of higher doses of CBD indicating further investigation of dosages is required in humans.

CBD formulations in clinical trials have been most commonly investigated in patients with treatment-resistant epilepsy. From these clinical trials, the majority of adverse events reported have been deemed mild-moderate, with the most common being: somnolence[25,143,145,146,149,150,154,156,157,160,161], diarrhea and vomiting[144,149,150,154,156,157,159,161,315] and dizziness[316]. Furthermore, the above mild-moderate adverse events, particularly somnolence, diarrhea and vomiting, have stayed consistent in the interim analyses published from two extension trials (one in Dravet Syndrome patients and one in Lennox-Gastaut Syndrome patients) at week 48 of these extension trials[147,148] and in Laux et al., an expanded access program, over 96 weeks[156].

Supporting the evidence from epilepsy trials, in ASD patients, the most common adverse events for high-CBD oral extracts (mean doses were reported as 3.8 ± 2.6 mg/kg CBD:0.22 ± 0.14 mg/kg THC[110], 79.5 ± 61.5 mg CBD:4 ± 3 mg THC[112] and 90 mg CBD:7 mg THC[111]) were somnolence, restlessness and changes in appetite[110-112].

Laux et al. found 91% of Lennox-Gastaut Syndrome and Dravet Syndrome patients enrolled in their expanded access program over 96 weeks reported some type of adverse event, with 41% of these events characterized as serious[156]. The most common serious adverse events were convulsions (14%), status epilepticus (increased seizures; 9%), pneumonia (5%) and pyrexia (4%)[156]. Five other epilepsy studies have also reported status epilepticus with CBD as an adjunct anti-epileptic[112,147-149,153] and while a sixth study also reported it, they deemed that CBD was not the cause of the status epilepticus[150].

Another common serious adverse event reported from the epilepsy clinical trials has been elevated liver aminotransferase levels. However, it is likely not CBD directly causing this effect but rather CBD in combination with other anti-epileptic drugs, in particular valproate. The elevated liver aminotransferase levels have been found to be reversible once CBD was tapered, discontinued or concomitant anti-epileptic drug doses were decreased[144-148,150,152,153,158]. In a meta-analysis of four epilepsy trials examining CBD's efficacy as an anti-epileptic agent, concomitant valproate use with CBD was found to have the greatest risk for hepatic injury due to increased transaminase levels[25]. In a trial examining CBD in refractory epilepsy children (1–17 years old), aminotransferase

levels became elevated in 3/26 patients who were taking both CBD and valproate, however, reducing the CBD dose did normalize the aminotransferase levels[152]. Differing from previous studies, these patients had been receiving CBD alone and then valproate was added to their treatment regimen, while previous studies have added CBD to an existing treatment regimen of valproate[152]. Additionally, aminotransferase enzyme levels were unaltered in patients who were not taking valproate in Devinsky et al.'s study[147] and in Laux et al.'s study 22/152 patients experience elevated aminotransferase levels >3 times the upper limit, of which 82% of these patients were concomitantly taking valproate[156]. Furthermore, Pietrafusa et al. reported 22.2% of their patients had abnormal hepatic transaminase levels and all were taking valproate[158] while Gaston et al. found patients on both CBD and valproate had significantly higher transaminase levels than patients on CBD without valproate[160]. Thus, it is likely that the combination of CBD and valproate, regardless of which drug was administered first, could lead to elevated aminotransferase levels. Therefore, patients should be monitored closely, and CBD and/or valproate dosages adjusted as required.

In a longer trial examining CBD as a treatment for refractory epilepsy (mean duration of treatment was 21 months; dose 9–25 mg/kg/day), where patients ranged from 1–17 years old, clinically significant weight loss in 30.75% of the patients was observed at around month 6 of chronic CBD treatment while diarrhea and reduced appetite was recorded within the first 3 months[152]. In some children the change was due more to stagnation in weight gain versus true weight loss, as lack of appropriate weight gain in children is classified as a failure to thrive[152]. Weight loss was also reported in 14/264 (5.3%) patients in the extension trial for Dravet Syndrome patients[147].

CBD (400 and 800 mg) in combination with IV fentanyl was found to have no adverse effects and to be well tolerated, indicating that CBD would likely be safe when used as an add-on therapy for pain and/or a means to reduce opioid use (either medically or recreationally)[317].

1000 mg of CBD per day for 6 weeks in schizophrenic patients led to no effect on weight, liver function, inflammatory markers, sleep or prolactin (low prolactin levels indicate sexual dysfunction); 15/44 patients taking CBD and 16/44 patients with placebo had adverse events and all were deemed mild-moderate[307].

From the literature above, in general, CBD has been shown to be well tolerated, with minimal serious adverse events, found after the consumption of a wide range of doses and in a number of different medical conditions. However, extensive toxicology studies for CBD to determine its therapeutic window have yet to be carried out and the safety of longitudinal CBD treatment has not been significantly investigated.

5.2

THC:

The number of clinical trials examining the efficacy of cannabis plant-based THC products is limited thus, capturing adverse event reports is also limited. In general, it appears high-THC products are well tolerated with mild-moderate adverse events primarily being reported[44,281,282].

Given the limited data, MedReleaf® recently investigated the safety and tolerability of acute doses of either 5 or 10 mg THC extract administered as oral capsules in healthy participants[44]. The study reported no significant changes in cognition, heart rate and blood pressure with primarily mild-moderate adverse events such as somnolence, fatigue and euphoric mood[44]. Shelef et al. also reported no change in weight, glucose levels, systolic blood pressure and diastolic blood pressure after four weeks of treatment with a THC extract (1.65% THC Cannabliss®) in 10 patients with Alzheimer's disease[222].

THC's effects on cognitive impairment and/or cardiovascular function may be influenced by the route of administration. Spindle et al. showed that vaping a high-THC dried flower led to significantly greater feelings of paranoia and impairment than when the THC dried flower was smoked[318].

Furthermore, while smoking and vaping of cannabis increased heart rate from baseline, only smoking significantly increased systolic blood pressure[318].

5.3

Cannabinoids in combination:

As found when either high-CBD or high-THC product is used, the adverse events reported from the use of cannabis (or cannabinoids in combination) have been deemed mild-moderate in severity[279,282,285]. Commonly reported adverse events are: dry mouth[191], dizziness[56,177,277,282,316], gastrointestinal issues[279,282,285], nervous system disorders[279,316] and drowsiness[55,177,277,282].

A median daily dose of 2.5 g of inhaled cannabis per day (12.5% THC and unspecified CBD percentage) for a year, reduced pain and caused no significant difference in the number of reported serious adverse events or in hematological, biochemical, liver, renal and endocrine function in comparison to the group who did not use cannabis[279].

Real world patient data of Sativex® as an add-on therapy in patients with chronic pain (n=800) reported that Sativex® was well tolerated over a 12-week period with most adverse events being reported as mild (81.6%) or moderate (16.5%)[177]. 4 events were characterized as a serious adverse event over the 12 weeks and no deaths occurred[177]. Importantly, only 4% discontinued Sativex® due to adverse events (reported as mouth discomfort, dizziness/fatigue and somnolence)[177]. Furthermore, there was no pattern of intentional misuse, evidence of abuse or deliberate overdoses during the study[177].

A significant reduction in systolic blood pressure was reported 90 minutes post inhalation of 3.08 ± 0.02 mg THC in a 15.1 ± 0.1 mg dose of cannabis via a Syqe® Inhaler, while diastolic blood pressure and heart rate were unaltered[278]. Furthermore, cannabis use was shown to be an independent predictor of heart failure and cerebrovascular accident from data obtained from the USA's National Inpatient Sample database; cannabis consumers had a significant increase in rates of heart failure, cerebrovascular accident, coronary artery disease, sudden cardiac death and hypertension in comparison to non-cannabis consumers[319]. Thus, the long-term effects of cannabis consumption, including examining the differences between THC:CBD ratios and specific routes of administration, on cardiovascular health still requires investigation.

Health Canada recommends for women to not use cannabis when pregnant and/or breastfeeding. Supporting this recommendation, a comprehensive review by the USA's National Academies of Sciences, Engineering and Medicine found there is substantial evidence to conclude smoking cannabis while pregnant significantly reduces birth weight[207]. Additionally, in a cellular model of placental function, THC exposure induced significant stress and dysfunction that could translate to a diminished placental size and efficiency *in vivo*[320]. Moreover, recently published data indicates cannabis use by males could negatively affect fertility and fetal and childhood development. Murphy et al. found that cannabis use (greater than weekly for at least 6 months) significantly reduced sperm concentration and induced epigenetic changes in the sperm of male cannabis users in comparison to males who did not consume cannabis[321]. These epigenetic changes were primarily deregulated methylation (most commonly hypomethylation) in the hippo-signaling pathways (involved with organ development, cell proliferation and apoptosis) and pathways involved with cancer development[321]. These findings were also similarly replicated in rats who had been administered THC versus ones who had not[321]. While the authors did not examine if these methylation changes would lead to non-viable embryos and/or viable embryos with altered developmental trajectories, it may indicate that both women and men who are attempting to conceive should abstain from cannabis consumption[321].

In a cohort of 14–21 year old adolescents and young adults (n=781; n=634 non-users and n=147 users), no significant differences in brain structure were found between users and non-users of cannabis via MRI scanning[322]. Furthermore, no age interactions between brain structure and cannabis use was found[322]. However, this study was limited by their cohort being primarily non-users, as this may have affected the results[322]. A similar lack of cannabis-induced changes on brain structure was reported between older adults who were currently cannabis users (n=28, mean 69.8 years, 36% female) versus older adults who were non-users (n=28, mean 66.8 years 61% females)[323]. Interestingly, age was associated with the strongest effect on brain structure changes in the hippocampus; age had a negative association with gray matter and a positive association with cerebral spinal fluid volume[323]. Additionally, there was no significant difference in cognitive performance between the cannabis users and non-users group, though the cannabis non-users did report a significantly greater number of depressive symptoms[323].


29/42
KIMAX
USA
1000ml

6 Contraindications:

According to Health Canada's Information for Health Care Professionals document[324], clinical guidelines do not currently exist for monitoring patients using medical cannabis. However, Health Canada recommends that cannabis with high THC:CBD ratios not be prescribed for individuals who are under the age of 25, unless the benefit/risk ratio is considered favourable by the physician[324].

Furthermore, cannabis use in general is not recommended if a person has a history of hypersensitivity to cannabinoids or smoke, psychosis, substance abuse, respiratory disease and/or severe cardiovascular, cerebrovascular, renal or liver disease[324]. Cannabis should be used with caution in patients receiving concomitant therapy with sedative-hypnotics or other psychoactive drugs and smoking cannabis is not recommended for patients with respiratory diseases[324]. Furthermore, Health Canada does not recommend cannabis to be used by women of childbearing age without reliable contraception, who are breastfeeding, pregnant and/or planning to become pregnant[324]. The Society of Obstetricians and Gynaecologists of Canada also recommends not using cannabis during pregnancy or breastfeeding[325].

6.1

Cannabis use in adolescents:

It has been recommended that younger individuals do not consume cannabis as it has been suggested that the frequent use of cannabis at a young age leads to cognitive impairment later in life[326,327]. However, a meta-analysis of 69 studies investigating cannabis use in adolescents and young adults found that while frequent cannabis use correlated to a significant negative effect in cognitive functioning this effect was small, and "of questionable clinical significance"[328]. Furthermore, there was no significant long-term effect of cannabis-induced cognitive impairment 72 hours or longer post cannabis consumption[328]. Additionally, there was no effect of age; either the age of the participants or the age at which participants began to use cannabis[328]. Meier et al. followed 181 boys from adolescence through adulthood (recruitment of 13-19 year olds who were followed until they were 30-36 years old) and identified four cannabis user groups: non users/ infrequent users, desisters, escalators and chronic-relatively frequent users[329]. Through the use of an MRI, Meier et al. reported no significant changes (volume and/or thickness) in brain structure in any subcortical or cortical regions examined between any of the four cannabis user groups[329]. Therefore, more work is required to gain clarity on the effects of cannabis use during adolescence and young adulthood.

6.2

Cannabis use and psychosis:

The use of cannabis has been suggested to induce psychosis that converts into schizophrenia or bipolar disorder[330] thus, the recommendation that individuals with a personal or family history of psychiatric disorders do not consume cannabis. This recommendation is supported by the findings from a comprehensive review of the current cannabis literature carried out by the United States of America's National Academies of Sciences, Engineering and Medicine, that reported cannabis use is "likely to increase the risk of developing schizophrenia and other psychoses; the higher the use, the greater the risk"[207]. Furthermore, an observational study that collected data from 11 sites across Europe on 901 patients after they experienced their first psychotic episode along with 1247 population controls, found the greatest predictors of whether an individual would develop psychosis was daily cannabis use and the use of high-THC cannabis[331]. Daily cannabis use increased the risk of developing psychosis by 3.2 times while the use of high-THC cannabis increased the likelihood of doing so by 1.6 times[331]. However, these findings were largely criticized by the larger scientific community, most notably by Gillespie et al.[332], Sommer and Brink[333], Linman[334], and Clark[335] through correspondence letters to the Lancet Psychiatry, who all took issue with the Di Forti et al.'s interpretation of their data[331].

Conversely, findings from the largest genome-wide association study of lifetime cannabis use showed "weak evidence for a causal link from cannabis use to schizophrenia" with "much stronger evidence for a causal link from schizophrenia to cannabis use," suggesting that individuals with the genetic predisposition to develop schizophrenia are more likely to use cannabis rather than cannabis use inducing schizophrenia[303]. Supporting this conclusion is the finding that cannabis use in people with schizophrenia may be associated with improved

learning and memory[207]. Risk variants in CADM2 and NCAM1 genes, both of which are cell adhesion molecules part of the immunoglobulin superfamily, showed the strongest correlation to cannabis use and have also been associated with increased risk-taking, alcohol consumption, illicit drug use and psychiatric disorders like schizophrenia[303]. These findings indicate there may be a strong genetic component linking alcohol, illicit drug, cannabis use and the development of psychiatric disorders[303].

There is a need for further investigation into the genetic predisposition of mental illness and cannabis use to fully understand why significantly more individuals with mental illnesses consume cannabis and the implications of cannabis use and mental illness.

6.3
Cannabis-drug interactions:

6.3.1
CBD:

CBD has been shown to inhibit liver metabolic enzymes, such as CYP450[336-339] and carboxylesterase 1 (CES 1)[340]. Thus, CBD may alter the pharmacology of other phytocannabinoids (such as THC) as well as other pharmaceuticals, alcohol and other non-pharmaceutical drugs.

From animal studies, CBD has been shown to have PK interactions with topiramate, oxcarbazepine, gabapentin, tiagabine and pregabalin and pharmacodynamic interactions with levetiracetam[167]. However, in an open label expanded access program utilizing Epidiolex® (maximum dose was 50 mg/kg/day) in treatment resistant epilepsy patients, seizure frequency and severity was significantly decreased independently of other anti-epileptics, such as clobazam, rufinamide, topiramate, zonisamide and eslicarbazepine[162]. Thus, the authors concluded their findings indicated no drug-CBD interactions altered either the effects of CBD or the other anti-epileptics in this cohort[162].

Geffrey et al. examined the drug-drug interaction between clobazam, a drug known to be primarily metabolized by CYP3A4 into norclobazam, and CBD in children with epilepsy and found norclobazam levels were increased by a mean of 500 ± 300% when clobazam and CBD were taken together, even though clobazam dosages were decreased throughout the 36 weeks[151]. In general, over the 36 weeks, the concomitant use of CBD and clobazam was well-tolerated once the clobazam dose was reduced in order to improve the adverse events[151]. Gaston et al. reported serum levels of topiramate, rufinamide and n-desmethylclobazam (the active metabolite of clobazam) increased significantly with the addition of CBD treatment in both pediatric and adult patients with treatment-resistant epilepsy enrolled in an open label expanded access program with Epidiolex®[160]. Patients in this study had to reduce their clobazam dosages, and subsequently serum clobazam levels were decreased, due to a need to limit the adverse event of sedation experienced in patients concomitantly taking clobazam and CBD[160]. In Wheless et al., the concomitant use of CBD and clobazam increased both CBD and 7-OH-CBD plasma concentrations as well as clobazam and norclobazam plasma concentrations thus, CBD and clobazam showed bi-directional drug interaction behaviour in this study[33]. Furthermore, Laux et al. found that 38% of patients on clobazam and CBD reported somnolence while only 18% of patients solely on CBD did so and that 46% of patients on clobazam reduced their dosage throughout the 96 week reporting period[156]. Huntsman et al.'s recent publication from using CanniMed® 1:20 in children with epileptic encephalopathy also supports a CBD-clobazam drug interaction[157]. Steady state trough concentrations of the other anti-epileptics patients were also using were unchanged with the exception of clobazam, which increased with the addition of the CanniMed® 1:20 treatment[157]. Furthermore, 3 patients reduced clobazam concentrations throughout the study which mitigated the adverse events they were experiencing[157]. However, neither CBD, CBC nor THC levels were significantly altered in patients who were concomitantly taking clobazam and CanniMed® 1:20[157].

From an open-label expanded access program utilizing Epidiolex® in treatment-resistant epilepsy patients, it was reported that adult patients experienced elevated serum levels of zonisamide and eslicarbazepine with the addition of the CBD treatment, indicating potential CBD-drug interactions between CBD and those two anti-epileptics as well[160]. Alternatively, Gaston et al. found that seizure frequency and severity were reduced independently of any concomitantly used anti-epileptics (including clobazam, rufinamide, topiramate, zonisamide and eslicarbazepine) in patients with treatment-resistant epilepsy administered Epidiolex® (maximum dose was 50 mg/kg/day) in an open label expanded access program[162]. Together, these studies indicate that elevated serum levels of some anti-epileptics may not correspond to any significant physiological effects.

Therefore, there is the potential for CBD to interact with well used anti-epileptics, such as clobazam, but the significance of this interaction has yet to be elucidated and more work in this area is required. In general, from the studies above, it appears that any adverse events as a result of CBD and clobazam drug interactions are relatively mild and reversible, when doses of either are reduced.

Many studies have reported elevated aminotransferase enzyme levels with CBD administration[25,147,156,160], particularly when it is concomitantly taken with valproate (see Section 5: Adverse events). Reduction of either valproate or CBD typically leads to normalization of the levels indicating some interaction between these two compounds. Patients themselves appear to self-titrate valproate dosages in response to experiencing adverse events, as seen in an expanded access program for Epidiolex®[156] where 52% of treatment-resistant epileptic patients reduced valproate throughout the 96 week reporting period[156]. Interestingly, very few patients in this study also taking levetiracetam reduced its dosage, indicating that perhaps there is little drug interaction between CBD and levetiracetam[156].

CBD has also been shown to alter the metabolism of THC, likely through the inhibition of CYP450 enzymes that metabolize THC and its active metabolite, 11-OH-THC[336-339,341]. In rats, chronic treatment of CBD for 7 consecutive days prior to treatment with THC was found to significantly enhance THC and reduce THC-COOH blood levels compared to when THC was administered alone[342] and in humans, peak THC concentration was significantly greater after inhalation of the 11% THC:11% CBD in comparison to the 11% THC:<1% CBD product[341]. These studies support the hypothesis that CBD inhibits enzymes responsible for THC metabolism[342]. Additionally, it has been proposed that the presence of CBD in cannabis-based products is able to reduce the negative effects of THC, such as anxiety, impaired cognition and acute psychosis[343]. Overall, there is mixed and limited data to support this hypothesis[343]. Boggs et al. reviewed the subject in 2018 and concluded there were "many unanswered questions about the potentially interactive effect of the cannabis constituents, CBD and THC" and that additional research was required to fully "evaluate [the] claims and establish potential mechanisms of action"[343]. Thus, further scientific investigation is required to fully elucidate the PK and PD interactions of CBD and THC.

CBD has also been shown to inhibit CES 1 *in vivo*, which is a hepatic esterase that is responsible for 80–95% of the total hydrolytic activity in the liver, including the hydrolysis of pharmaceutical pro-drugs into their active metabolites (i.e. angiotensin converting enzyme inhibitors used to treat hypertension, diabetes, congestive heart failure[344])[340]. Thus, there is the potential for CBD-drug interactions that depend on CES 1 hydrolysis for either activation and/or clearance.

6.3.2

THC:

THC and its metabolites may interact with other pharmaceuticals as they have been shown to bind extensively to plasma proteins[41,345-347]. Thus, there is potential for THC-drug interactions between THC and its metabolites and other drugs which also bind to plasma proteins.

THC and its metabolites (though to a lesser extent) have been shown to inhibit CES 1 *in vivo*, a hepatic esterase that is responsible for 80–95% of the total hydrolytic activity in the liver, which includes the hydrolysis of pharmaceutical pro-drugs into their active metabolites (i.e. angiotensin converting enzyme inhibitors used to treat hypertension, diabetes and congestive heart failure[344]) [340]. Thus, there is the potential for THC-drug interactions that depend on CES 1 hydrolysis for either activation and/or clearance.

6.4

CBD and impaired hepatic function:

The PK parameters of an acute dose of 200 mg CBD (Epidiolex®) was examined in individuals with normal hepatic function and mildly, moderately and severely impaired hepatic function[34]. Time to peak plasma concentration and volume of distribution was not significantly different between the groups[34]. However, CBD's mean absorption and clearance rate were significantly increased for the moderately and severely impaired hepatic function groups in comparison to the normal hepatic function group[34]. The reported elimination half-lives were not significantly different between the groups though the authors did highlight that the values were increased as the hepatic function worsened[34]. Thus, this study showed that CBD dosages may need to be adjusted in patients with impaired hepatic function in comparison to patients with normal hepatic function.

7 Warnings:

The use of cannabis may involve risk to an individual's health, some of which may not be known or fully understood. Furthermore, studies supporting the safety and efficacy for cannabis for therapeutic purposes are limited and do not meet the standard required by the Food and Drug Regulations for marketed drugs in Canada. (Health Canada 2020)

8 Glossary:

Agonist: drug binds and activates the target protein leading to a cellular response
Allodynia: painful responses to non-painful stimuli
Amisulpride: anti-psychotic medication
Antagonism: drug binds and does not activate the target protein, preventing activation by agonists
Bioavailability: the percentage of drug consumed that reaches the systemic circulation and is able to have an effect on the body
Buccal absorption: absorption of a drug into the systemic circulation through the cheek mucosa by placing the drug between the gum and your cheek
Cannabidiol (CBD): non-intoxicating phytocannabinoid that may reduce pain, anxiety and inflammation and which is a potent anti-epileptic
Cannabinoids: a class of compounds of which there are three types (endocannabinoids, phytocannabinoids and synthetic cannabinoids)
Clearance rate: volume of plasma the drug is removed from per unit of time
Clinical studies: research conducted in humans
Clobazam: an anti-epileptic drug
Cold pressor tests: holding a hand in ice water for as long as possible
Cultivar: plant variety developed by humans for a specific use such as production of grain or fruit, or flower colour or growth habitat)
Decarboxylate: a chemical reaction which removes a carboxyl group from a molecule, releasing carbon dioxide
Desipramine: a selective noradrenaline reuptake inhibitor used to treat depression
Dronabinol: synthetic THC
Elimination half-life: how long it takes for half of the dose to leave the body
Endocannabinoids: physiological signaling molecules which are part of the endocannabinoid system and involved with regulating different physiological functions
Endocannabinoid system: physiological system that regulates many crucial physiological functions in the body and contributes significantly to the maintenance of homeostasis, which is a state of steady internal conditions
Epidiolex®: GW Pharmaceuticals' 100 mg/ml CBD oral solution
First pass metabolism: metabolism of an orally consumed drug that occurs in the liver after it was absorbed in the intestine before it reaches the systemic circulation
Flavonoids: phenolic compounds with anti-oxidant properties that are found in many different plants, including cannabis
Fluoxetine: a selective serotonin reuptake inhibitor used to treat depression
Genotype: A unique set of genes that is shared in a clonal lineage, which is not transmitted to the progeny if a plant from this clonal lineage produces seed and is the best term to use when referring to a specific clonal lineage (what is often inaccurately called "strains" in the cannabis space).
Hemp: a variety of cannabis that has high amounts of CBD and negligible amounts of THC (<0.3% or <0.2% THC depending on the country)
Hyperalgesia: an abnormally enhanced sensitivity to painful stimuli
Imipramine: a tricyclic antidepressant used to treat depression
Intoxication: a condition that follows the administration of a psychoactive substance and results in disturbances in the level of consciousness, cognition, perception, judgement, affect, or behaviour, or other psychophysiological functions and responses
Inverse agonist: drug binds and reduces the activity of the target protein, leading to the opposite effect of an agonist
Ipsapirone: a known anxiolytic
Nabilone: synthetic analogue of THC
Negative allosteric modulator: drug binds to a site on the target protein different from where an agonist would bind, resulting in a change in the protein's structure that reduces or inhibits the activation of the protein by agonists
Neuritogenesis: the process of forming of new outgrowths, which extend from the neuronal body
Neuropathic pain: complex, chronic pain, that may be accompanied by tissue injury, that affects nerve fibres leading to incorrect signaling

Neuroprotection: an effect that may result in salvage, recovery or regeneration of the nervous system, its cells, structure and function
Nociceptive pain: pain from a physical trauma
Norclobazam: clobazam's active metabolite
Oromucosal absorption: absorption of a drug into the systemic circulation through the oral mucosa by placing it under the tongue or on the inside of the cheek
Oral administration: ingestion of a drug so that it is first absorbed by the small intestine where it passes through the liver and undergoes first pass metabolism prior to entry into the systemic circulation where it can have physiological effects
Paclitaxel: chemotherapy drug
Partial agonist: drug binds and activates the target protein but even if 100% of the proteins are bound the response is submaximal
Phylogeny: the evolutionary history of an individual, group or species
Phytocannabinoids: cannabinoids derived from cannabis plants which when consumed, interact with different targets within the body, most of which are part of the endocannabinoid system, to cause physiological effects
Plasma half-life: how long it takes for half of the dose to leave the plasma into tissue
Pre-clinical studies: experiments performed with cultured cells and animal models
Sativex®: GW Pharmaceuticals' oromucosal THC:CBD extract spray containing equal concentrations of tetranabinex (27 mg/ml THC extract) and nabidiolex (25 mg/ml CBD extract), residual cannabinoids (5%) and other extracted compounds, such as terpenes and flavonoids
Secondary metabolite: organic compounds produced by organisms that are not directly necessary for growth, development or reproduction
Sublingual absorption: absorption of a drug into the systemic circulation by placing it under the tongue to absorb through the tissue
Synergistic effect: when the effect of multiple drugs have a greater than additive effect when they are applied together
Synthetic cannabinoids: man-made cannabinoids, similar chemically to THC but are not found in nature and when consumed, interact with different targets within the body, most of which are part of the endocannabinoid system, to cause physiological effects
Temozolomide: a therapeutically used chemotherapy drug
Terpenes: are the largest group of phytochemicals found in many different plants and herbs, such as cannabis, and may have therapeutic effects of their own as well as enhance the effects of phytocannabinoids
Δ^9-tetrahydrocannabinol (THC): the predominant intoxicating phytocannabinoid and has therapeutic potential as an analgesic, anti-inflammatory and anti-emetic
Time to peak plasma concentration: how long it takes for the drug to reach its highest concentration in the systemic circulation after consumption
Topical application: application of a drug to the skin where it will have local effects in the area it is applied but it does not absorb through the skin to enter the systemic circulation
Topotecan: a chemotherapy drug whose efficacy is hampered by overactive ABCG2 transporters
Transdermal application: application of a drug to the skin where it is absorbed through the skin and enters the systemic circulation to have effects away from the site of application
Variety: a taxonomic rank lower than species and subspecies or a genotype that has yet to be approved for production and sale to the public
Vincristine: chemotherapy drug
Von Frey Filaments: specifically calibrated number of grams force to a paw and withdrawal threshold is measured, with higher tolerated grams force indicating decreased pain responses

9 References:

1. Linnaeus C. Species Plantarum Volume 2. 1753.
2. Potter DJ. OPTIMISATION OF CANNABIS SATIVA L AS A PHYTOPHARMACEUTICAL. A thesis submitted by David Potter JP. 2009;(March).
3. Schultes RE, Klein WM, Plowman T, et al. Cannabis: An example of taxonomic neglect. 1974;23(9):337-367.
4. Lindley J. *Flora Medica: A Botanical Account of All the More Important Plants Used in Medicine, in Different Parts of the World*. Cambridge: Cambridge University Press; 1838.
5. Small E, Cronquist A. A Practical and Natural Taxonomy for Cannabis. *Taxon*. 1976;25(4):405-435.
6. Hillig KW. A chemotaxonomic analysis of terpenoid variation in Cannabis. *Biochem Syst Ecol*. 2004;32(10):875-891.
7. Hillig KW. Genetic evidence for speciation in Cannabis (Cannabaceae). *Genet Resour Crop Evol*. 2005;52(2): 161-180.
8. Rahn B. Sativa vs. Indica: An Overview of Cannabis Types.
9. Ursing BM, Ursing JB, Dijkshoorn L. Strain, clone and species: comments on three basic concepts of bacteriology. *J Med Microbiol*. 2015;49(5):397-401.
10. Mcneill J, Barrie FR, Buck WR, et al. International Code of Nomenclature for algae, fungi, and plants. *Koeltz Sci Books*. 2012:1-140.
11. Spencer RD, Cross RG. The International Code of Botanical Nomenclature (ICBN), the International Code of Nomenclature for Cultivated Plants (ICNCP), and the cultigen. *Taxon*. 2007;56(3):938-940.
12. Small E. Chapter 7: Fiber. In: *Cannabis A Complete Guide*.; 2017:91-139.
13. Small E. Chapter 8: Oilseed. In: *Cannabis A Complete Guide*.; 2017:143-176.
14. Hemp and the hemp industry Frequently Asked Questions - Canada.ca.
15. Remarks at the National Industrial Hemp Council 2019 Hemp Business Summit - 08/13/2019 | FDA.
16. Hughes B, European Monitoring Centre for Drugs and Drug Addiction. Cannabis legislation in Europe.
17. Perrotin-Brunel H, Verpoorte R, Witkamp G-J, et al. Decarboxylation of Δ9-tetrahydrocannabinol: Kinetics and molecular modeling. *J Mol Struct*. 2010;987(1-3):67-73.
18. Degenhardt F, Stehle F, Kayser O. *The Biosynthesis of Cannabinoids*. Elsevier Inc.; 2017.
19. Russo EB. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. *Br J Pharmacol*. 2011;163(7):1344-1364.
20. Baron EP. Medicinal Properties of Cannabinoids, Terpenes, and Flavonoids in Cannabis, and Benefits in Migraine, Headache, and Pain: An Update on Current Evidence and Cannabis Science. *Headache Curr*. 2018;July/ Augus:1139-1186.
21. Comelli F, Giagnoni G, Bettoni I, et al. Antihyperalgesic effect of a Cannabis sativa extract in a rat model of neuropathic pain: mechanisms involved. *Phyther Res*. 2008;22(8):1017-1024.
22. Gallily R, Yekhtin Z, Ond L, et al. Overcoming the Bell-Shaped Dose-Response of Cannabidiol by Using Cannabis Extract Enriched in Cannabidiol. *Pharmacol Pharm*. 2015;6:75-85.
23. Torres S, Lorente M, Rodríguez-Fornés F, et al. A combined preclinical therapy of cannabinoids and temozolomide against glioma. *Mol Cancer Ther*. 2011;10(1):90-103.
24. WHO. WHO | Acute intoxication. WHO.

25. Lattanzi S, Brigo F, Trinka E, et al. Efficacy and Safety of Cannabidiol in Epilepsy: A Systematic Review and Meta-Analysis. *Drugs*. 2018;78(17): 1791-1804.
26. Aizpurua-Olaizola O, Elezgarai I, Rico-Barrio I, et al. Targeting the endocannabinoid system: future therapeutic strategies. *Drug Discov Today*. 2017;22(1):105-110.
27. De Petrocellis L, Di Marzo V. An introduction to the endocannabinoid system: from the early to the latest concepts. *Best Pract Res Clin Endocrinol Metab*. 2009;23(1):1-15.
28. Minister of Health HC, Health Canada. *Health Effects of Cannabis*; 2017.
29. Millar SA, Stone NL, Yates AS, et al. A Systematic Review on the Pharmacokinetics of Cannabidiol in Humans. *Front Pharmacol*. 2018;9:1365.
30. Samara E, Bialer M, Mechoulam R. Pharmacokinetics of cannabidiol in dogs. *Drug Metab Dispos*. 1988;16(3):469-472.
31. Taylor L, Gidal B, Blakey G, et al. 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*. 2018;32(11):1053-1067.
32. Pellesi L, Licata M, Verri P, et al. Pharmacokinetics and tolerability of oral cannabis preparations in patients with medication overuse headache (MOH)—a pilot study. *Eur J Clin Pharmacol*. 2018;74(11):1427-1436.
33. Wheless JW, Dlugos D, Miller I, et al. Pharmacokinetics and Tolerability of Multiple Doses of Pharmaceutical-Grade Synthetic Cannabidiol in Pediatric Patients with Treatment-Resistant Epilepsy. *CNS Drugs*. 2019;33(6):593-604.
34. Taylor L, Crockett J, Tayo B, et al. A Phase 1, Open-Label, Parallel-Group, Single-Dose Trial of the Pharmacokinetics and Safety of Cannabidiol (CBD) in Subjects With Mild to Severe Hepatic Impairment. *J Clin Pharmacol*. 2019;59(8):1110-1119.
35. Ohlsson A, Lindgren JE, Wahlen A, et al. Plasma delta-9 tetrahydrocannabinol concentrations and clinical effects after oral and intravenous administration and smoking. *Clin Pharmacol Ther*. 1980;28(3):409-416.
36. Lindgren J-E, Ohlsson A, Agurell S, et al. Clinical Effects and Plasma Levels of A 9-Tetrahydrocannabinol (A 9-THC) in Heavy and Light Users of Cannabis. *Psychopharmacology (Berl)*. 1981;74:208-212.
37. Wall M, Sadler B, Brine D, et al. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. *Clin Pharmacol Ther*. 1983;34(3):352-363.
38. De Vries M, van Rijckevorsel DCM, Vissers KCP, et al. Tetrahydrocannabinol Does Not Reduce Pain in Patients With Chronic Abdominal Pain in a Phase 2 Placebo-controlled Study. *Clin Gastroenterol Hepatol*. 2017;15(7):1079-1086.e4.
39. Nadulski T, Pragst F, Weinberg G, et al. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of Delta9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. *Ther Drug Monit*. 2005;27(6):799-810.
40. Vandrey R, Herrmann ES, Mitchell JM, et al. Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes. *J Anal Toxicol*. 2017;41(2):83-99.

41. Hunt CA, Jones RT. Tolerance and disposition of tetrahydrocannabinol in man. *J Pharmacol Exp Ther*. 1980;215(1).
42. Łebkowska-Wieruszewska B, Stefanelli F, Chericoni S, et al. Pharmacokinetics of Bedrocan®, a cannabis oil extract, in fasting and fed dogs: An explorative study. *Res Vet Sci*. 2018;123(July 2018):26-28.
43. Birnbaum AK, Karanam A, Marino SE, et al. Food effect on pharmacokinetics of cannabidiol oral capsules in adult patients with refractory epilepsy. *Epilepsia*. 2019;60(8):1586-1592.
44. Lunn S, Diaz Pa, O'Hearn S, et al. Human pharmacokinetic parameters of orally administered THC capsules are altered by fed versus fasted conditions and sex differences. *Cannabis Cannabinoid Res*. 2019;Submitted.
45. Ohlsson A, Lindgren JE, Andersson S, et al. Single-dose kinetics of deuterium-labelled cannabidiol in man after smoking and intravenous administration. *Biomed Environ Mass Spectrom*. 1986;13(2):77-83.
46. Ohlsson A, Lindgren J-E, Wahlén A, et al. Single dose kinetics of deuterium labelled Δ1-tetrahydrocannabinol in heavy and light cannabis users. *Biol Mass Spectrom*. 1982;9(1):6-10.
47. Goulle J, Saussereau E, Lacroix C. Delta-9-tetrahydrocannabinol pharmacokinetics. *Ann Pharm Françaises*. 2008;66(4):232-234.
48. Chiang C-W, Barnett G, Perez-Reyes M, et al. Kinetic Study of Smoking Marijuana. *J Pharmacokinet Biopharm*. 1982;10(5):495-506.
49. Hunault C, Van Eijkeren J, Mensinga T, et al. Disposition of smoked cannabis with high Δ(9)-tetrahydrocannabinol content: a kinetic model. *Toxicol Appl Pharmacol*. 2010;246(3):148-153.
50. Johansson E, Halldin MM, Agurell S, et al. Terminal elimination plasma half-life of delta 1-tetrahydrocannabinol (delta 1-THC) in heavy users of marijuana. *Eur J Clin Pharmacol*. 1989;37(3):273-277.
51. Kelly P, Jones RT. Metabolism of Tetrahydrocannabinol in Frequent and Infrequent Marijuana Users. *J Anal Toxicol*. 1992;16(4):228-235.
52. Sattar M, Sayed OM, Lane ME. Oral transmucosal drug delivery – Current status and future prospects. *Int J Pharm*. 2014;471(1-2):498-506.
53. Rog D, Nurmikko T, Young C. Oromucosal Δ9-tetrahydrocannabinol/ cannabidiol for neuropathic pain associated with multiple sclerosis: An uncontrolled, open-label, 2-year extension trial. *Clin Ther*. 2007;29(9):2068-2079.
54. Fact sheet - Sativex (Tetranabinex and Nabidiolex) - Canada.ca.
55. Stott C, White L, Wright S, et al. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. *Springerplus*. 2013;2(1):236.
56. Stott CG, White L, Wright S, et al. A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. *Eur J Clin Pharmaco*l. 2013;69(4):825-834.
57. Challapalli PVN, Stinchcomb AL. In vitro experiment optimization for measuring tetrahydrocannabinol skin permeation. *Int J Pharm*. 2002;241:329-339.
58. Touitou E, I BF, Dany S, et al. Transdermal delivery of tetrahydrocannabinol. *Int J Pharm*. 1988;43:9-15.
59. Scheuplein RJ. Mechanism of Percutaneous Absorption. *J Invest Dermato*l. 1966;48(1):79-88.

60. Valiveti S, Hammell DC, Earles DC, et al. In Vitro / In Vivo Correlation Studies for Transdermal D 8 -THC Development. *J Pharm* Sci. 2004;93(5):1154-1164.
61. Touitou E, Fabin B. Altered skin permeation of a highly lipophilic molecule : tetrahydrocannabinol. 1988;43:17-22.
62. van de Donk T, Niesters M, Kowal MA, et al. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain*. 2019;160(4):860-869.
63. Mannila J, Järvinen T, Järvinen K, et al. Precipitation Complexation Method Produces Cannabidiol/ß-Cyclodextrin Inclusion Complex Suitable for Sublingual Administration of Cannabidiol. *J Pharm Sci*. 2007;96(2):312-319.
64. Esposito G, De Filippis D, Carnuccio R, et al. The marijuana component cannabidiol inhibits ß-amyloid-induced tau protein hyperphosphorylation through Wnt/ß-catenin pathway rescue in PC12 cells. *J Mol Med*. 2006;84(3):253-258.
65. Deiana S, Watanabe A, Yamasaki Y, et al. Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Δ9-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive–compulsive behavi. *Psychopharmacology* (Berl). 2012;219(3):859-873.
66. Ward SJ, McAllister SD, Kawamura R, et al. Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy. *Br J Pharmacol*. 2014;171(3):636-645.
67. Ahmed KT, Amin R, Shah P, et al. Motor neuron development in zebrafish is altered by brief (5-hr) exposures to THC (Δ 9-tetrahydrocannabinol) or CBD (cannabidiol) during gastrulation. *Sci Rep*. 2018;8:10518.
68. Aviello G, Romano B, Borrelli F, et al. Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer. *J Mol Med*. 2012;90(8):925-934.
69. Breuer A, Haj CG, Fogaça M V, et al. Fluorinated Cannabidiol Derivatives: Enhancement of Activity in Mice Models Predictive of Anxiolytic, Antidepressant and Antipsychotic Effects. *PLoS One*. 2016;11(7):e0158779.
70. Capasso R, Borrelli F, Aviello G, et al. Cannabidiol, extracted from Cannabis sativa, selectively inhibits inflammatory hypermotility in mice. *Br J Pharmacol*. 2008;154(5):1001-1008.
71. Tham M, Yilmaz O, Alaverdashvili M, et al. Allosteric and orthosteric pharmacology of cannabidiol and cannabidiol-dimethylheptyl at the type 1 and type 2 cannabinoid receptors. *Br J Pharmaco*l. 2019;176(10):1455-1469.
72. Petitet F, Jeantaud B, Reibaud M, et al. Complex pharmacology of natural cannabivoids: Evidence for partial agonist activity of Δ9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. *Life Sci*. 1998;63(1):PL1-PL6.
73. Thomas A, Baillie GL, Phillips AM, et al. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol*. 2009;150(5):613-623.
74. Chung H, Fierro A, Pessoa-Mahana CD. Cannabidiol binding and negative allosteric modulation at the cannabinoid type 1 receptor in the presence of delta-9-tetrahydrocannabinol: An In Silico study. *PLoS One*. 2019;14(7):e0220025.

75. Ferro R, Adamska A, Lattanzio R, et al. GPR55 signalling promotes proliferation of pancreatic cancer cells and tumour growth in mice, and its inhibition increases effects of gemcitabine. *Oncogene*. 2018;37(49):6368-6382.
76. Ligresti A, Moriello AS, Starowicz K, et al. Antitumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma. *J Pharmacol Exp Ther*. 2006;318(3):1375-1387.
77. De Gregorio D, McLaughlin RJ, Posa L, et al. Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain. *Pain*. 2019;160(1):136-150.
78. Costa B, Giagnoni G, Franke C, et al. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. *Br J Pharmacol*. 2004;143(2):247-250.
79. Vallée A, Lecarpentier Y, Guillevin R, et al. Effects of cannabidiol interactions with Wnt/ß-catenin pathway and PPARγ on oxidative stress and neuroinflammation in Alzheimer's disease. *Acta Biochim Biophys Sin* (Shanghai). 2017;49(10):853-866.
80. Esposito G, Scuderi C, Valenza M, et al. Cannabidiol reduces Aß-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement. *PLoS One*. 2011;6(12):e28668.
81. Khuja I, Yekhtin Z, Or R, et al. Cannabinoids Reduce Inflammation but Inhibit Lymphocyte Recovery in Murine Models of Bone Marrow Transplantation. *Int J Mol Sc*i. 2019;20(3):E668.
82. Resstel LBM, Tavares RF, Lisboa SFS, et al. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol*. 2009;156(1):181-188.
83. Campos AC, Ferreira FR, Guimarães FS. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: Possible involvement of 5HT1A receptors. *J Psychiatr Res*. 2012;46(11):1501-1510.
84. Zanelati T V, Biojone C, Moreira FA, et al. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. *Br J Pharmacol*. 2010;159(1):122-128.
85. Castillo A, Tolón MR, Fernández-Ruiz J, et al. The neuroprotective effect of cannabidiol in an in vitro model of newborn hypoxic–ischemic brain damage in mice is mediated by CB2 and adenosine receptors. *Neurobiol Dis*. 2010;37(2):434-440.
86. Bisogno T, Hanus L, De Petrocellis L, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmaco*l. 2001;134(4):845-852.
87. Leishman E, Manchanda M, Thelen R, et al. Cannabidiol's Upregulation of N -acyl Ethanolamines in the Central Nervous System Requires N -acyl Phosphatidyl Ethanolamine-Specific Phospholipase D. *Cannabis Cannabinoid Res*. 2018;3(1):228-241.
88. Hacke AC, Lima D, de Costa F, et al. PROBING THE ANTIOXIDANT ACTIVITY OF Δ 9 - TETRAHYDROCANNABINOL AND CANNABIDIOL IN CANNABIS SATIVA EXTRACTS. *Analyst*. 2019;144(16):4952-4961.

89. Casarejos MJ, Perucho J, Gomez A, et al. Natural Cannabinoids Improve Dopamine Neurotransmission and Tau and Amyloid Pathology in a Mouse Model of Tauopathy. *J Alzheimer's Dis*. 2013;35(3):525-539.
90. Rajesh M, Mukhopadhyay P, Bátkai S, et al. Cannabidiol attenuates cardiac dysfunction, oxidative stress, fibrosis, and inflammatory and cell death signaling pathways in diabetic cardiomyopathy. *J Am Coll Cardiol*. 2010;56(25):2115-2125.
91. Iuvone T, Esposito G, Esposito R, et al. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem*. 2004;89(1):134-141.
92. Iwamura H, Suzuki H, Ueda Y, et al. In vitro and in vivo pharmacological characterization of JTE-907, a novel selective ligand for cannabinoid CB2 receptor. *J Pharmacol Exp Ther*. 2001;296(2):420-425.
93. Pertwee R. The diverse CB 1 and CB 2 receptor pharmacology of three plant cannabinoids: D. *Br J Pharmacol*. 2008;153:199-215.
94. Rinaldi-Carmona M, Barth F, Héaulme M, et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. *FEBS Lett*. 1994;350(2-3):240-244.
95. Vara D, Salazar M, Olea-Herrero N, et al. Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy. *Cell Death Differ*. 2011;18(7):1099-1111.
96. Pertwee RG. Cannabinoid pharmacology: the first 66 years. *Br J Pharmacol*. 2006;147(S1):S163-S171.
97. NIH. Anxiety at a Glance | NCCIH.
98. Bergamaschi MM, Queiroz RHC, Chagas MHN, et al. Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology*. 2011;36(6):1219-1226.
99. Crippa J, Derenusson GN, Ferrari TB, et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. *J Psychopharmacol*. 2011;25(1):121-130.
100. Zuardi AW, Cosme RA, Graeff FG, et al. Effects of ipsapirone and cannabidiol on human experimental anxiety. *J Psychopharmacol*. 1993;7(Suppl 1):82-88.
101. Crippa J, Zuardi AW, Garrido GEJ, et al. Effects of Cannabidiol (CBD) on Regional Cerebral Blood Flow. *Neuropsychopharmacology*. 2004;29(2):417-426.
102. Guimarães FS, Chiaretti TM, Graeff FG, et al. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology (Berl)*. 1990;100(4):558-559.
103. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. *J Pharmacol Exp Ther*. 1990;253(3):1002-1009.
104. Luján MÁ, Castro-Zavala A, Alegre-Zurano L, et al. Repeated Cannabidiol treatment reduces cocaine intake and modulates neural proliferation and CB1R expression in the mouse hippocampus. *Neuropharmacology*. 2018;143:163-175.
105. Rock E, Limebeer CL, Petrie GN, et al. Effect of prior foot shock stress and Δ9-tetrahydrocannabinol, cannabidiolic acid, and cannabidiol on anxiety-like responding in the light-dark emergence test in rats. *Psychopharmacology (Berl)*. 2017;234(14):2207-2217.

106. Schiavon AP, Bonato JM, Milani H, et al. Influence of single and repeated cannabidiol administration on emotional behavior and markers of cell proliferation and neurogenesis in non-stressed mice. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2016;64:27-34.
107. Wan B angela, Diaz P, Blake A, et al. Efficacy of different varieties of medical cannabis in relieving symptoms. *J Pain Manag*. 2017;10(4):375-383.
108. Whiting PFP, Wolff RRFR, Deshpande S, et al. Cannabinoids for Medical Use A Systematic Review and Meta-analysis. *JAMA - J Am Med Assoc*. 2015;313(24):2456-2473.
109. NIH. NIMH » Autism Spectrum Disorder.
110. Aran A, Cassuto H, Lubotzky A, et al. Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study. *J Autism Dev Disord*. 2019;49(3):1284-1288.
111. Barchel D, De-Haan T, Stolar O, et al. Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities. *Front Pharmacol*. 2019;9:1521.
112. Schleider LB-L, Mechoulam R, Saban N, et al. Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy. *Sci Reports 2019* 91. 2019;9(1):200.
113. Osborne AL, Solowij N, Babic I, et al. Improved Social Interaction, Recognition and Working Memory with Cannabidiol Treatment in a Prenatal Infection (poly I:C) Rat Model. *Neuropsychopharmacology*. 2017;42(7):1447-1457.
114. Stark T, Ruda-Kucerova J, Iannotti FA, et al. Peripubertal cannabidiol treatment rescued behavioral and neurochemical abnormalities in MAM model of schizophrenia. *Neuropharmacology*. 2019;146:212-221.
115. Hartmann A, Lisboa SF, Sonego AB, et al. Cannabidiol attenuates aggressive behavior induced by social isolation in mice: Involvement of 5-HT1A and CB1 receptors. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2019;94:109637.
116. Ajram L, Heasman M, Edden RAE, et al. Effects of cannabidiol on brain excitation and inhibition systems; a randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder. *Neuropsychopharmacology*. 2019;44(8):1398-1405.
117. WHO. WHO: Cancer.
118. Sultan AS, Marie MA, Sheweita SA. Novel mechanism of cannabidiol-induced apoptosis in breast cancer cell lines. *The Breast*. 2018;41:34-41.
119. McAllister SD, Christian RT, Horowitz MP, et al. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. *Mol Cancer Ther*. 2007;6(11):2921-2927.
120. Murase R, Kawamura R, Singer E, et al. Targeting multiple cannabinoid anti-tumour pathways with a resorcinol derivative leads to inhibition of advanced stages of breast cancer. *Br J Pharmacol*. 2014;171(19):4464-4477.
121. Romano B, Borrelli F, Pagano E, et al. Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. *Phytomedicine*. 2014;21(5):631-639.

122. Jeong S, Yun HK, Jeong YA, et al. Cannabidiol-induced apoptosis is mediated by activation of Noxa in human colorectal cancer cells. *Cancer Lett*. 2019;447:12-23.
123. Jeong S, Kim BG, Kim DY, et al. Cannabidiol Overcomes Oxaliplatin Resistance by Enhancing NOS3- and SOD2-Induced Autophagy in Human Colorectal Cancer Cells. *Cancers (Basel)*. 2019;11(6):E781.
124. Zhang X, Qin Y, Pan Z, et al. Cannabidiol Induces Cell Cycle Arrest and Cell Apoptosis in Human Gastric Cancer SGC-7901 Cells. *Biomolecules*. 2019;9(302):1-17.
125. Kosgodage US, Uysal-Onganer P, MacLatchy A, et al. Cannabidiol Affects Extracellular Vesicle Release, miR21 and miR126, and Reduces Prohibitin Protein in Glioblastoma Multiforme Cells. *Transl Oncol*. 2019;12(3):513-522.
126. Marcu JP, Christian RT, Lau D, et al. Cannabidiol Enhances the Inhibitory Effects of 9-Tetrahydrocannabinol on Human Glioblastoma Cell Proliferation and Survival. *Mol Cancer Ther*. 2010;9(1):180-189.
127. Massi P, Vaccani A, Ceruti S, et al. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther*. 2004;308(3):838-845.
128. Ramer R, Heinemann K, Merkord J, et al. COX-2 and PPAR-γ confer cannabidiol-induced apoptosis of human lung cancer cells. *Mol Cancer Ther*. 2013;12(1):69-82.
129. Holland Ml, Lau DTT, Allen JD, et al. The multidrug transporter ABCG2 (BCRP) is inhibited by plant-derived cannabinoids. *Br J Pharmacol*. 2007;152(5):815-824.
130. Blasco-Benito S, Seijo-Vila M, Caro-Villalobos M, et al. Appraising the "entourage effect": Antitumor action of a pure cannabinoid versus a botanical drug preparation in preclinical models of breast cancer. *Biochem Pharmaco*l. 2018;157:285-293.
131. Takeda S, Yoshida K, Nishimura H, et al. Δ(9)-Tetrahydrocannabinol disrupts estrogen-signaling through up-regulation of estrogen receptor ß (ERß). *Chem Res Toxicol*. 2013;26(7):1073-1079.
132. Zhang Y, Zheng W, Shen K, et al. Δ9-tetrahydrocannabinol inhibits epithelial-mesenchymal transition and metastasis by targeting matrix metalloproteinase-9 in endometrial cancer. *Oncol Lett*. 2018;15(6): 8527-8535.
133. Vara D, Morell C, Rodríguez-Henche N, et al. Involvement of PPARγ in the antitumoral action of cannabinoids on hepatocellular carcinoma. *Cell Death Dis*. 2013;4(5):e618.
134. López-Valero I, Torres S, Salazar-Roa M, et al. Optimization Of A Preclinical Therapy Of Cannabinoids In Combination With Temozolomide Against Glioma. *Biochem Pharmacol*. 2018;157:275-284.
135. WHO. WHO: Cardiovascular diseases (CVDs).
136. Gonca E, Darıcı F. The effect of cannabidiol on ischemia/reperfusion-induced ventricular arrhythmias: the role of adenosine A1 receptors. *J Cardiovasc Pharmacol Ther*. 2015;20(1):76-83.
137. Durst R, Danenberg H, Gallily R, et al. Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury. *Am J Physiol Circ Physiol*. 2007;293(6):H3602-H3607.
138. Depression | CAMH.

139. Linge R, Jiménez-Sánchez L, Campa L, et al. Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors. *Neuropharmacology*. 2016;103:16-26.
140. Sales AJ, Fogaça M V., Sartim AG, et al. Cannabidiol Induces Rapid and Sustained Antidepressant-Like Effects Through Increased BDNF Signaling and Synaptogenesis in the Prefrontal Cortex. *Mol Neurobiol*. 2019;56(2):1070-1081.
141. Sales AJ, Crestani CC, Guimarães FS, et al. Antidepressant-like effect induced by Cannabidiol is dependent on brain serotonin levels. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2018;86:255-261.
142. WHO. WHO: Epilepsy.
143. Hausman-Kedem M, Menascu S, Kramer U. Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents - An observational, longitudinal study. *Brain Dev*. 2018;40(7):544-551.
144. Thiele EAA, Marsh EDD, French JAA, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* (London, England). 2018;391(10125):1085-1096.
145. Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. *N Engl J Med*. 2018;378(20):1888-1897.
146. McCoy B, Wang L, Zak M, et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. *Ann Clin Transl Neurol*. 2018;5(9):1077-1088.
147. Devinsky O, Nabbout R, Miller I, et al. Long-term cannabidiol treatment in patients with Dravet syndrome: An open-label extension trial. *Epilepsia*. 2019;60(2):294-302.
148. Thiele E, Marsh E, Beldzinska-Mazurkiewicz M, et al. Cannabidiol in patients with Lennox-Gastaut syndrome: Interim analysis of an open-label extension study. *Epilepsia*. 2019;60(3):419-428.
149. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *Lancet Neurol*. 2016;15(3):270-278.
150. Devinsky O, Cross JH, Laux L, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N Engl J Med*. 2017;376(21):2011-2020.
151. Geffrey AL, Pollack SF, Bruno PL, et al. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia*. 2015;56(8):1246-1251.
152. Sands TTT, Rahdari S, Oldham MSS, et al. Long-Term Safety, Tolerability, and Efficacy of Cannabidiol in Children with Refractory Epilepsy: Results from an Expanded Access Program in the US. *CNS Drugs*. 2019;33(1):47-60.
153. Szaflarski JP, Bebin EM, Comi AM, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. *Epilepsi*a. 2018;59(8):1540-1548.
154. Szaflarski JP, Bebin EM, Cutter G, et al. Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study. *Epilepsy Behav*. 2018;87:131-136.

155. Szaflarski JP, Hernando K, Bebin EM, et al. Higher cannabidiol plasma levels are associated with better seizure response following treatment with a pharmaceutical grade cannabidiol. *Epilepsy Behav*. 2019;95:131-136.
156. Laux LC, Bebin EM, Checketts D, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatmentresistant Lennox-Gastaut syndrome or Dravet syndrome: Expanded access program results. *Epilepsy Res*. 2019;154:13-20.
157. Huntsman RJ, Tang-Wai R, Alcorn J, et al. Dosage Related Efficacy and Tolerability of Cannabidiol in Children With Treatment-Resistant Epileptic Encephalopathy: Preliminary Results of the CARE-E Study. *Front Neurol*. 2019;10:716.
158. Pietrafusa N, Ferretti A, Trivisano M, et al. Purified Cannabidiol for Treatment of Refractory Epilepsies in Pediatric Patients with Developmental and Epileptic Encephalopathy. *Pediatr Drugs*. 2019;21(4):283-290.
159. Gaston TE, Szaflarski M, Hansen B, et al. Quality of life in adults enrolled in an open-label study of cannabidiol (CBD) for treatment-resistant epilepsy. *Epilepsy Behav*. 2019;95:10-17.
160. Gaston TE, Bebin EM, Cutter GR, et al. Interactions between cannabidiol and commonly used antiepileptic drugs. *Epilepsia*. 2017;58(9):1586-1592.
161. Martin RC, Gaston TE, Thompson M, et al. Cognitive functioning following long-term cannabidiol use in adults with treatment-resistant epilepsy. *Epilepsy Behav*. 2019;97:105-110.
162. Gaston TE, Bebin EM, Cutter GR, et al. Drug–drug interactions with cannabidiol (CBD) appear to have no effect on treatment response in an open-label Expanded Access Program. *Epilepsy Behav*. 2019;98(Pt A):201-206.
163. Reithmeier D, Tang-Wai R, Seifert B, et al. The protocol for the Cannabidiol in children with refractory epileptic encephalopathy (CARE-E) study: a phase 1 dosage escalation study. *BMC Pediatr*. 2018;18(1):221.
164. Kaplan JS, Stella N, Catterall WA, et al. Cannabidiol attenuates seizures and social deficits in a mouse model of Dravet syndrome. *Proc Natl Acad Sci USA*. 2017;114(42):11229-11234.
165. Patra PH, Barker-Haliski M, White HS, et al. Cannabidiol reduces seizures and associated behavioral comorbidities in a range of animal seizure and epilepsy models. *Epilepsia*. 2018;(October):1-12.
166. Samarut É, Nixon J, Kundap UP, et al. Single and Synergistic Effects of Cannabidiol and Δ-9-Tetrahydrocannabinol on Zebrafish Models of Neuro-Hyperactivity. *Front Pharmacol*. 2019;10:226.
167. Socała K, Wyska E, Szafarz M, et al. Acute effect of cannabidiol on the activity of various novel antiepileptic drugs in the maximal electroshock- and 6 Hz-induced seizures in mice: pharmacodynamic and pharmacokinetic studies. *Neuropharmacology*. 2019;158:107733.
168. Commissioner O of the. Press Announcements - FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy.
169. National report: Apparent opioid-related deaths in Canada (released March 2018) - Canada.ca.
170. Vivolo-Kantor AM, Seth P, Gladden RM, et al. Vital Signs : Trends in Emergency Department Visits for Suspected Opioid Overdoses — United States, July 2016–September 2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(9):279-285.

171. Lucas P. Rationale for cannabis-based interventions in the opioid overdose crisis. *Harm Reduct J*. 2017;14(1):58.
172. Vigil JM, Stith SS, Adams IM, et al. Associations between medical cannabis and prescription opioid use in chronic pain patients: A preliminary cohort study. Vrana KE, ed. *PLoS One*. 2017;12(11):e0187795.
173. Boehnke KF, Litinas E, Clauw DJ. Medical Cannabis Use Is Associated With Decreased Opiate Medication Use in a Retrospective Cross-Sectional Survey of Patients With Chronic Pain. *J Pain*. 2016;17(6):739-744.
174. Lucas P, Walsh Z. Medical cannabis access, use, and substitution for prescription opioids and other substances: A survey of authorized medical cannabis patients. *Int J Drug Policy*. 2017;42:30-35.
175. Boehnke KF, Scott JR, Litinas E, et al. Pills to pot: observational analyses of cannabis substitution among medical cannabis users with chronic pain. *J Pain*. 2019;20(7):830-841.
176. Corroon JM, Mischley LK, Sexton M, et al. Cannabis as a substitute for prescription drugs - a cross-sectional study. *J Pain Res*. 2017;10:989-998.
177. Ueberall MA, Essner U, Mueller-Schwefe GH. Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry. *J Pain Res*. 2019;12:1577-1604.
178. Viudez-Martínez A, García-Gutiérrez MS, Navarrón CM, et al. Cannabidiol reduces ethanol consumption, motivation and relapse in mice. *Addict Biol*. 2018;23(1):154-164.
179. Morgan CJA, Das RK, Joye A, et al. Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. *Addict Behav*. 2013;38(9):2433-2436.
180. Hindocha C, Freeman TP, Grabski M, et al. Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal. *Addiction*. 2018;113(9):1696-1705.
181. Viudez-Martínez A, Garcia-Gutierrez MS, Manzanares J. Gender differences in the effects of cannabidiol on ethanol binge drinking in mice. *Addict Biol*. 2019:e12765.
182. Hay GL, Baracz SJ, Everett NA, et al. Cannabidiol treatment reduces the motivation to self-administer methamphetamine and methamphetamine-primed relapse in rats. *J Psychopharmacol*. 2018;32(12):1369-1378.
183. Hurd YL, Yoon M, Manini AF, et al. Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage. *Neurotherapeutics*. 2015;12(4):807-815.
184. Hurd YL, Spriggs S, Alishayev J, et al. 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. *Am J Psychiatry*. 2019:appiajp201918101191.
185. Bachhuber MA, Saloner B, Cunningham CO, et al. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States. *JAMA intern med*. 2014;174(10):1668-1673.
186. Shi Y. Medical marijuana policies and hospitalizations related to marijuana and opioid pain reliever. *Drug Alcohol Depend*. 2017;173:144-150.

187. Kim JH, Santaella-Tenorio J, Mauro C, et al. State Medical Marijuana Laws and the Prevalence of Opioids Detected Among Fatally Injured Drivers. *Am J Public Health*. 2016;106(11):2032-2037.
188. Bradford AC, Bradford WD. Medical Marijuana laws may be associated with a decline in the number of prescriptions for medicaid enrollees. *Health Aff*. 2017;36(5):945-951.
189. Bradford AC, Bradford WD, Abraham A, et al. Association between US state medical cannabis laws and opioid prescribing in the medicare part D population. *JAMA Intern Med*. 2018;178(5):667-673.
190. Wen H, Hockenberry JM. Association of medical and adult-use marijuana laws with opioid prescribing for medicaid enrollees. *JAMA Intern Med*. 2018;178(5):673-679.
191. Bellnier T, Brown GW, Ortega TR. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. *Ment Heal Clin*. 2018;8(3):110-115.
192. Bachhuber M, Arnsten JH, Wurm G. Use of Cannabis to Relieve Pain and Promote Sleep by Customers at an Adult Use Dispensary. *J Psychoactive Drugs*. 2019;0(0).
193. Campbell G, Hall WD, Peacock A, et al. Effect of cannabis use in people with chronic non-cancer pain prescribed opioids: findings from a 4-year prospective cohort study Gabrielle. *Lancet Public Heal*. 2018;3(7):e341-e350.
194. NIH. Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS) | NCCIH.
195. Kafil TS, Nguyen TM, MacDonald JK, et al. Cannabis for the treatment of Crohn's disease. *Cochrane Database Syst Rev*. 2018;(11):CD012853.
196. Kafil TS, Nguyen TM, MacDonald JK, et al. Cannabis for the treatment of ulcerative colitis. *Cochrane Database Syst Rev*. 2018;(11):CD012954.
197. Borrelli F, Aviello G, Romano B, et al. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. *J Mol Med*. 2009;87(11):1111-1121.
198. Schicho R, Storr M. Topical and systemic cannabidiol improves trinitrobenzene sulfonic acid colitis in mice. *Pharmacology*. 2012;89(3-4):149-155.
199. Naftali T, Bar Lev L, Yablekovitz D, et al. Treatment of Crohn's Disease with Cannabis: An Observational Study. *IMAJ*. 2011;13:455-458.
200. Naftali T, Schleider LB-L, Dotan I, et al. Cannabis Induces a Clinical Response in Patients With Crohn's Disease: A Prospective Placebo-Controlled Study. *Clin Gastroenterol Hepatol*. 2013;11:1276-1289.
201. Comparison of Efficacy and Safety of Rimonabant 20mg/Day Versus Placebo in Smoking Cessation - Tabular View - ClinicalTrials.gov.
202. Wade DT, Collin C, Stott C, et al. Meta-analysis of the efficacy and safety of Sativex (nabiximols), on spasticity in people with multiple sclerosis. *Mult Scler*. 2010;16(6):707-714.
203. Markovà J, Essner U, Akmaz B, et al. Sativex® as Add-on therapy Vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial. *Int J Neurosci*. May 2018:1-28.
204. Wade DT, Makela PM, House H, et al. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler*. 2006;12(5):639-645.

205. Wade DT, Makela P, Robson P, et al. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler J*. 2004;10(4):434-441.
206. Rog DJ, Nurmikko TJ, Friede T, et al. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 2005;65(6):812-819.
207. United States of America's National Academies of Sciences E and M. The Health Effects of Cannabis and Cannabinoids : *The Current State of Evidence and Recommendations for Research*.; 2017.
208. Nausea and vomiting - Mayo Clinic.
209. Fda. *Marinol (Dronabinol)*.; 2017.
210. *CESAMET™ (Nabilone)* Capsules.
211. *CESAMET® Capsules*.; 2009.
212. Rock E, Bolognini D, Limebeer CL, et al. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. *Br J Pharmacol*. 2012;165(8):2620-2634.
213. Rock E, Limebeer CL, Mechoulam R, et al. The effect of cannabidiol and URB597 on conditioned gaping (a model of nausea) elicited by a lithium-paired context in the rat. *Psychopharmacology (Berl)*. 2008;196(3):389-395.
214. Rock E, Limebeer CL, Navaratnam R, et al. A comparison of cannabidiolic acid with other treatments for anticipatory nausea using a rat model of contextually elicited conditioned gaping. *Psychopharmacology (Berl)*. 2014;231(16):3207-3215.
215. Parker L, Kwiatkowska M, Mechoulam R. Delta-9-tetrahydrocannabinol and cannabidiol, but not ondansetron, interfere with conditioned retching reactions elicited by a lithium-paired context in Suncus murinus: An animal model of anticipatory nausea and vomiting. *Physiol Behav*. 2006;87(1):66-71.
216. Limebeer CL, Hall G, Parker LA. Exposure to a lithium-paired context elicits gaping in rats: A model of anticipatory nausea. *Physiol Behav*. 2006;88(4-5):398-403.
217. Duran M, Pérez E, Abanades S, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol*. 2010;70(5):656-663.
218. Vajda FJE. Neuroprotection and neurodegenerative disease. *J Clin Neurosci*. 2002;9(1):4-8.
219. Santos NAG, Martins NM, Sisti FM, et al. The neuroprotection of cannabidiol against MPP+-induced toxicity in PC12 cells involves trkA receptors, upregulation of axonal and synaptic proteins, neuritogenesis, and might be relevant to Parkinson's disease. *Toxicol Vitr*. 2015;30(1):231-240.
220. Walther S, Mahlberg R, Eichmann U, et al. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl)*. 2006;185(4):524-528.
221. Woodward MR, Harper DG, Stolyar A, et al. Dronabinol for the Treatment of Agitation and Aggressive Behavior in Acutely Hospitalized Severely Demented Patients with Noncognitive Behavioral Symptoms. *Am J Geriatr Psychiatry*. 2014;22(4):415-419.

222. Shelef A, Barak Y, Berger U, et al. Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study. *J Alzheimer's Dis*. 2016;51(1):15-19.
223. Watt G, Karl T. In vivo Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease. *Front Pharmacol*. 2017;8:20.
224. Esposito G, Scuderi C, Savani C, et al. Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression. *Br J Pharmacol*. 2007;151(8):1272-1279.
225. Cheng D, Low JK, Logge W, et al. Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1ΔE9 mice. *Psychopharmacology (Berl)*. 2014;231(15):3009-3017.
226. Janefjord E, Mååg JL V., Harvey BS, et al. Cannabinoid Effects on ß Amyloid Fibril and Aggregate Formation, Neuronal and Microglial-Activated Neurotoxicity In Vitro. *Cell Mol Neurobiol*. 2014;34(1):31-42.
227. Harvey BS, Ohlsson KS, Mååg JLV, et al. Contrasting protective effects of cannabinoids against oxidative stress and amyloid-ß evoked neurotoxicity in vitro. *Neurotoxicology*. 2012;33(1):138-146.
228. Martín-Moreno AM, Reigada D, Ramírez BG, et al. Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimer's disease. *Mol Pharmacol*. 2011;79(6):964-973.
229. Scuderi C, Steardo L, Esposito G. Cannabidiol Promotes Amyloid Precursor Protein Ubiquitination and Reduction of Beta Amyloid Expression in SHSY5Y APP+ Cells Through PPARγ Involvement. *Phyther Res*. 2014;28(7):1007-1013.
230. Cheng D, Spiro AS, Jenner AM, et al. Long-Term Cannabidiol Treatment Prevents the Development of Social Recognition Memory Deficits in Alzheimer's Disease Transgenic Mice. *J Alzheimer's Dis*. 2014;42(4):1383-1396.
231. Aso E, Sánchez-Pla A, Vegas-Lozano E, et al. Cannabis-based medicine reduces multiple pathological processes in AßPP/PS1 mice. *J Alzheimer's Dis*. 2014;43(3):977-991.
232. Cao C, Li Y, Liu H, et al. The potential therapeutic effects of THC on Alzheimer's disease. *J Alzheimer's Dis*. 2014;42(3):973-984.
233. Aso E, Andrés-Benito P, Ferrer I. Delineating the Efficacy of a Cannabis-Based Medicine at Advanced Stages of Dementia in a Murine Model. Cassano T, ed. *J Alzheimer's Dis*. 2016;54(3):903-912.
234. NIH. Genetics Home Reference: Huntington's Disease.
235. Sagredo O, Ramos JA, Decio A, et al. Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors. *Eur J Neurosci*. 2007;26(4):843-851.
236. Nadal X, del Río C, Casano S, et al. Tetrahydrocannabinolic acid is a potent PPARγ agonist with neuroprotective activity. *Br J Pharmacol*. 2017;174(23):4263-4276.
237. Saft C, von Hein SM, Lücke T, et al. Cannabinoids for Treatment of Dystonia in Huntington's Disease. *J Huntingtons Dis*. 2018;7(2):167-173.
238. López-Sendón Moreno JL, García Caldentey J, Trigo Cubillo P, et al. A double-blind, randomized, cross-over, placebo-controlled, pilot trial with Sativex in Huntington's disease. *J Neurol*. 2016;263(7):1390-1400.

239. Stroke.
240. Santiago AN, Mori MA, Guimarães FS, et al. Effects of Cannabidiol on Diabetes Outcomes and Chronic Cerebral Hypoperfusion Comorbidities in Middle-Aged Rats. *Neurotox Res*. 2019;35(2):463-474.
241. Pazos MR, Mohammed N, Lafuente H, et al. Mechanisms of cannabidiol neuroprotection in hypoxic–ischemic newborn pigs: Role of 5HT1A and CB2 receptors. *Neuropharmacology*. 2013;71:282-291.
242. Barata L, Arruza L, Rodríguez M-J, et al. Neuroprotection by cannabidiol and hypothermia in a piglet model of newborn hypoxic-ischemic brain damage. *Neuropharmacology*. 2019;146:1-11.
243. Mishima K, Hayakawa K, Abe K, et al. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. *Stroke*. 2005;36(5):1077-1082.
244. Hayakawa K, Mishima K, Nozako M, et al. Repeated treatment with cannabidiol but not Δ9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance. *Neuropharmacology*. 2007;52(4):1079-1087.
245. Pazos MR, Cinquina V, Gómez A, et al. Cannabidiol administration after hypoxia–ischemia to newborn rats reduces long-term brain injury and restores neurobehavioral function. *Neuropharmacology*. 2012;63(5):776-783.
246. Understanding Parkinson's - Parkinson Canada.
247. García-Arencibia M, González S, de Lago E, et al. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: Importance of antioxidant and cannabinoid receptor-independent properties. *Brain Res*. 2007;1134(1):162-170.
248. Lastres-Becker I, Fernández-Ruiz J. An overview of Parkinson's disease and the cannabinoid system and possible benefits of cannabinoid-based treatments. *Curr Med Chem*. 2006;13(30):3705-3718.
249. Gomes F V., Del Bel EA, Guimarães FS. Cannabidiol attenuates catalepsy induced by distinct pharmacological mechanisms via 5-HT1A receptor activation in mice. Prog Neuro-Psychopharmacology *Biol Psychiatry*. 2013;46:43-47.
250. Zuardi A, Crippa J, Hallak J, et al. Cannabidiol for the treatment of psychosis in Parkinson's disease. *J Psychopharmacol*. 2009;23(8):979-983.
251. Chagas MHN, Zuardi AW, Tumas V, et al. Effects of cannabidiol in the treatment of patients with Parkinson's disease: An exploratory double-blind trial. *J Psychopharmacol*. 2014;28(11):1088-1098.
252. Chagas MHN, Eckeli AL, Zuardi AW, et al. Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series. *J Clin Pharm Ther*. 2014;39(5):564-566.
253. Traumatic Brain Injury – Causes, Symptoms and Treatments.
254. Schurman LD, Lichtman AH. Endocannabinoids: A Promising Impact for Traumatic Brain Injury. *Front Pharmacol*. 2017;8:69.
255. Belardo C, Iannotta M, Boccella S, et al. Oral Cannabidiol Prevents Allodynia and Neurological Dysfunctions in a Mouse Model of Mild Traumatic Brain Injury. *Front Pharmacol*. 2019;10:352.
256. Costa B, Trovato AE, Comelli F, et al. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556(1-3):75-83.

257. Li H, Kong W, Chambers CR, et al. The non-psychoactive phytocannabinoid cannabidiol (CBD) attenuates pro-inflammatory mediators, T cell infiltration, and thermal sensitivity following spinal cord injury in mice. *Cell Immunol*. 2018;329:1-9.
258. Philpott HT, O'Brien M, McDougall JJ. Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis. *Pain*. 2017;158(12):2442-2451.
259. Allan GM, Finley CR, Ton J, et al. Systematic Review of Systematic Reviews for Medical Cannabinoids Pain, *Nausea and Vomiting, Spasticity, and Harms*. Vol 64. FEBRUARY | FÉVRIER; 2018.
260. Amerongen V, Siebenga P, de Kam Ml, et al. Effect profile of paracetamol, Δ9-THC and promethazine using an evoked pain test battery in healthy subjects. *Eur J Pain* (United Kingdom). 2018;22(7):1331-1342.
261. Eurich DT, Hanlon JG, Boisvenue JJ, et al. A Description of the Medical Cannabis Use in Ontario, Canada. *Cannabis Cannabinoid Res*. 2019;x(X):1-5.
262. Boehnke KF, Gangopadhyay S, Clauw DJ, et al. Qualifying Conditions Of Medical Cannabis License Holders In The United States. *Health Aff* (Millwood). 2019;38(2):295-302.
263. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br J Anaesth*. 2014;112(6):991-1004.
264. Lee M, Silverman SM, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 14(2):145-161.
265. King KM, Myers AM, Soroka-Monzo AJ, et al. Single and combined effects of Δ 9 -tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. *Br J Pharmacol*. 2017;174(17):2832-2841.
266. Gallily R, Yekhtin Z, Hanuš LO. The Anti-Inflammatory Properties of Terpenoids from Cannabis. *Cannabis cannabinoid Res*. 2018;3(1):282-290.
267. Hammell DC, Zhang LP, Ma F, et al. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. *Eur J Pain*. 2016;20(6):936-948.
268. Costa B, Colleoni M, Conti S, et al. Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. *Naunyn Schmiedebergs Arch Pharmacol*. 2004;369(3):294-299.
269. Silva NR, Gomes F V., Fonseca MD, et al. Antinociceptive effects of HUF-101, a fluorinated cannabidiol derivative. *Prog Neuro-Psychopharmacology Biol Psychiatry*. 2017;79:369-377.
270. Javadi-Paydar M, Creehan KM, Kerr TM, et al. Vapor inhalation of cannabidiol (CBD) in rats. *Pharmacol Biochem Behav*. 2019:172741.
271. Sangiovanni E, Fumagalli M, Pacchetti B, et al. Cannabis sativa L. extract and cannabidiol inhibit in vitro mediators of skin inflammation and wound injury . *Phyther Res*. 2019;(April):1-11.
272. Lodzki M, Godin B, Rakou L, et al. Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model. *J Control Release*. 2003;93(3): 377-387.
273. Thapa D, Cairns EA, Szczesniak A-M, et al. The Cannabinoids Δ8THC, CBD, and HU-308 Act via Distinct Receptors to Reduce Corneal Pain and Inflammation. *Cannabis cannabinoid Res*. 2018;3(1):11-20.

274. Kruse LC, Cao JK, Viray K, et al. Voluntary oral consumption of Δ 9 -tetrahydrocannabinol by adolescent rats impairs reward-predictive cue behaviors in adulthood. *Neuropsychopharmacology*. 2019;44(8):1406-1414.
275. Rock E, Limebeer CL, Parker LA. Effect of cannabidiolic acid and Δ9-tetrahydrocannabinol on carrageenan-induced hyperalgesia and edema in a rodent model of inflammatory pain. *Psychopharmacology (Berl)*. 2018;235(11):3259-3271.
276. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology*. 2009;34(3):672-680.
277. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. *Neurology*. 2007;68(7):515-521.
278. Eisenberg E, Ogintz M, Almog S. The Pharmacokinetics, Efficacy, Safety, and Ease of Use of a Novel Portable Metered-Dose Cannabis Inhaler in Patients With Chronic Neuropathic Pain: A Phase 1a Study. *J Pain Palliat Care Pharmacother*. 2014;28(3):216-225.
279. Ware MA, Wang T, Shapiro S, et al. Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *J Pain*. 2015;16(12):1233-1242.
280. Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*. 2010;182(14):E694-701.
281. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain*. 2004;112(3):299-306.
282. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study of the Efficacy, Safety, and Tolerability of THC:CBD Extract and THC Extract in Patients with Intractable Cancer-Related Pain. *J Pain Symptom Manage*. 2010;39(2):167-179.
283. Darkovska-Serafimovska M, Serafimovska T, Arsova-Sarafinovska Z, et al. Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients with malignant diseases. *J Pain Res*. 2018;11:837-842.
284. Nurmikko TJ, Serpell MG, Hoggart B, et al. Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. *Pain*. 2007;133(1):210-220.
285. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain*. 2014;18(7):999-1012.
286. Lichtman AH, Lux EA, McQuade R, et al. Results of a Double-Blind, Randomized, Placebo-Controlled Study of Nabiximols Oromucosal Spray as an Adjunctive Therapy in Advanced Cancer Patients with Chronic Uncontrolled Pain. *J Pain Symptom Manage*. 2018;55(2):179-188. e1.
287. Post-traumatic stress disorder (PTSD) - Symptoms and causes - Mayo Clinic.
288. Resstel LBM, Joca SRL, Moreira FA, et al. Effects of cannabidiol and diazepam on behavioral and cardiovascular responses induced by contextual conditioned fear in rats. *Behav Brain Res*. 2006;172(2): 294-298.

289. Uribe-Mariño A, Francisco A, Castiblanco-Urbina MA, et al. Anti-aversive effects of cannabidiol on innate fear-induced behaviors evoked by an ethological model of panic attacks based on a prey vs the wild snake Epicrates cenchria crassus confrontation paradigm. *Neuropsychopharmacology*. 2012;37(2):412-421.
290. Hsiao YT, Yi PL, Li CL, et al. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. *Neuropharmacology*. 2012;62(1):373-384.
291. Stern CAJ, Gazarini L, Takahashi RN, et al. On disruption of fear memory by reconsolidation blockade: evidence from cannabidiol treatment. *Neuropsychopharmacology*. 2012;37(9):2132-2142.
292. Lemos JI, Resstel LB, Guimarães FS. Involvement of the prelimbic prefrontal cortex on cannabidiol-induced attenuation of contextual conditioned fear in rats. *Behav Brain Res*. 2010;207(1):105-111.
293. Shallcross J, Hámor P, Bechard AR, et al. The Divergent Effects of CDPPB and Cannabidiol on Fear Extinction and Anxiety in a Predator Scent Stress Model of PTSD in Rats. *Front Behav Neurosci*. 2019;13:91.
294. Jin S, Angela Wan B, Chan S, et al. The effect of medical cannabis on alcohol and tobacco use in veterans with post-traumatic stress disorder (PTSD). *J Pain Manag*. 2017;10(4):0-00.
295. Chan S, Blake A, Wolt A, et al. Medical cannabis use for patients with post-traumatic stress disorder (PTSD). *J Pain Manag*. 2017;10(4):385-396.
296. Drost L, Angela Wan B, Blake A, et al. Efficacy of different varieties of medical cannabis in relieving symptoms in post-traumatic stress disorder (PTSD) patients. *J Pain Manag*. 2017;10(4):0-00.
297. Smith PA, Chan S, Blake A, et al. Medical cannabis use in military and police veterans diagnosed with post-traumatic stress disorder (PTSD). *J Pain Manag*. 2017;10(4):397-405.
298. Zaki P, Ganesh V, Wolt A, et al. The use of medical cannabis in common medical conditions excluding cancer. *J Pain Manag*. 2017;10(4):363-374.
299. Davis AK, Lin LA, Ilgen MA, et al. Recent cannabis use among Veterans in the United States: Results from a national sample. *Addict Behav*. 2018;76:223-228.
300. Betthauser K, Pilz J, Vollmer LE. Use and effects of cannabinoids in military veterans with posttraumatic stress disorder. *Am J Heal Pharm*. 2015;72(15):1279-1284.
301. Shishko I, Oliveira R, Moore TA, et al. A review of medical marijuana for the treatment of posttraumatic stress disorder: Real symptom re-leaf or just high hopes? *Ment Heal Clin*. 2018;8(2):86-94.
302. Psychosis | CAMH.
303. Pasman JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat Neurosci*. 2018;21(9):1161-1170.
304. Osborne AL, Solowij N, Babic I, et al. Cannabidiol improves behavioural and neurochemical deficits in adult female offspring of the maternal immune activation (poly I:C) model of neurodevelopmental disorders. *Brain Behav Immun*. 2019.

305. Leweke FM, Piomelli D, Pahlisch F, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl Psychiatry*. 2012;2(3):e94.
306. Bhattacharyya S, Wilson R, Appiah-Kusi E, et al. Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis: A Randomized Clinical Trial. *JAMA Psychiatry*. 2018;75(11):1107-1117.
307. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. *Am J Psychiatry*. 2018;175(3):225-231.
308. Boggs DL, Surti T, Gupta A, et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. *Psychopharmacology (Berl)*. 2018;235(7):1923-1932.
309. FERRI R, MANCONI M, PLAZZI G, et al. A quantitative statistical analysis of the submentalis muscle EMG amplitude during sleep in normal controls and patients with REM sleep behavior disorder. *J Sleep Res*. 2008;17(1):89-100.
310. Brain Basics: Understanding Sleep | National Institute of Neurological Disorders and Stroke.
311. Walker MP, Stickgold R. Sleep-dependent learning and memory consolidation. *Neuron*. 2004;44(1):121-133.
312. Maia L, Machado-de-Sousa JP, Tufik S, et al. Effects of acute systemic administration of cannabidiol on sleep-wake cycle in rats. *J Psychopharmacol*. 2013;27(3):312-316.
313. Linares IMP, Guimaraes FS, Eckeli A, et al. No Acute Effects of Cannabidiol on the Sleep-Wake Cycle of Healthy Subjects: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study. *Front Pharmacol*. 2018;9:315.
314. Ewing LE, Skinner CM, Quick CM, et al. Hepatotoxicity of a Cannabidiol-Rich Cannabis Extract in the Mouse Model. *Molecules*. 2019;24(9):E1694.
315. Szaflarski JP, Martina Bebin E. Cannabis, cannabidiol, and epilepsy — From receptors to clinical response. *Epilepsy Behav*. 2014;41:277-282.
316. Hoggart B, Ratcliffe S, Ehler E, et al. A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. *J Neurol*. 2015;262(1):27-40.
317. Manini AF, Yiannoulos G, Bergamaschi MM, et al. Safety and Pharmacokinetics of Oral Cannabidiol When Administered Concomitantly With Intravenous Fentanyl in Humans. *J Addict Med*. 2015;9(3):204-210.
318. Spindle TR, Cone EJ, Schlienz NJ, et al. Acute Effects of Smoked and Vaporized Cannabis in Healthy Adults Who Infrequently Use Cannabis A Crossover Trial. 2018;1(7):1-14.
319. Kalla A, Krishnamoorthy PM, Gopalakrishnan A, et al. Cannabis use predicts risks of heart failure and cerebrovascular accidents: results from the National Inpatient Sample. *J Cardiovasc Med (Hagerstown)*. 2018;19(9):480-484.
320. Lojpur T, Easton Z, Raez-Villanueva S, et al. Δ9-Tetrahydrocannabinol leads to endoplasmic reticulum stress and mitochondrial dysfunction in human BeWo trophoblasts. *Reprod Toxicol*. 2019;87:21-31.

321. Murphy SK, Itchon-Ramos N, Visco Z, et al. Cannabinoid exposure and altered DNA methylation in rat and human sperm. *Epigenetics*. 2018;00(00):1-14.
322. Scott JC, Rosen AFG, Moore TM, et al. Cannabis use in youth is associated with limited alterations in brain structure. *Neuropsychopharmacology*. 2019;44(8):1362-1369.
323. Thayer RE, York Williams SL, Hutchison KE, et al. Preliminary results from a pilot study examining brain structure in older adult cannabis users and nonusers. Psychiatry Res - *Neuroimaging*. 2019;285:58-63.
324. Canada H. *Information for Health Care Practitioner: Cannabis (Marihuana, Marijuana) and the Cannabinoids*.; 2018.
325. Don T. CANNABIS AND PREGNANCY. :32-33.
326. Solowij N, Jones KA, Rozman ME, et al. Verbal learning and memory in adolescent cannabis users, alcohol users and non-users. *Psychopharmacology* (Berl). 2011;216(1):131-144.
327. Dougherty DM, Mathias CW, Dawes MA, et al. Impulsivity, attention, memory, and decision-making among adolescent marijuana users. *Psychopharmacology (Berl)*. 2013;226(2):307-319.
328. Scott JC, Slomiak ST, Jones JD, et al. Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA psychiatry*. 2018;75(6):585-595.
329. Meier MH, Schriber RA, Beardslee J, et al. Associations between adolescent cannabis use frequency and adult brain structure: A prospective study of boys followed to adulthood. *Drug Alcohol Depend*. 2019;202:191-199.
330. Starzer MSK, Nordentoft M, Hjorthøj C. Rates and predictors of conversion to schizophrenia or bipolar disorder following substance-induced psychosis. *Am J Psychiatry*. 2018;175(4):343-350.
331. Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *The Lancet Psychiatry*. 2019;0(0):1-9.
332. Gillespie NA, Pasman JA, Treur JL, et al. High-potency cannabis and incident psychosis: correcting the causal assumption. *The Lancet Psychiatry*. 2019;6(6):464.
333. Sommer IE, van den Brink W. High-potency cannabis and incident psychosis: correcting the causal assumption. *The Lancet Psychiatry*. 2019;6(6).
334. Linnman C. High-potency cannabis and incident psychosis: correcting the causal assumption. *The Lancet Psychiatry*. 2019;6(6):465-466.
335. Clark CS. High-potency cannabis and incident psychosis: correcting the causal assumption. *The Lancet Psychiatry*. 2019;6(6):e14.
336. Roth MD, Marques-Magallanes JA, Yuan M, et al. Induction and Regulation of the Carcinogen-Metabolizing Enzyme CYP1A1 by Marijuana Smoke and Δ 9 -Tetrahydrocannabinol. *Am J Respir Cell Mol Bio*l. 2001;24(3):339-344.
337. Bornheim LM, Grillo MP. Characterization of Cytochrome P450 3A Inactivation by Cannabidiol: Possible Involvement of Cannabidiol-Hydroxyquinone as a P450 Inactivator. *Chem Res Toxicol*. 1998;11(10):1209-1216.

338. Yamaori S, Ebisawa J, Okushima Y, et al. Potent inhibition of human cytochrome P450 3A isoforms by cannabidiol: Role of phenolic hydroxyl groups in the resorcinol moiety. *Life Sci*. 2011;88(15-16):730-736.
339. Yamaori S, Okamoto Y, Yamamoto I, et al. Cannabidiol, a Major Phytocannabinoid, As a Potent Atypical Inhibitor for CYP2D6. *Drug Metab Dispos*. 2011;39(11):2049-2056.
340. Qian Y, Wang X, Markowitz JS. Inhibition of Carboxylesterase 1 by Major Cannabinoids and Selected Metabolites. *Drug Metab Dispos*. 2019;47(5):465-472.
341. Arkell TR, Lintzeris N, Kevin RC, et al. Cannabidiol (CBD) content in vaporized cannabis does not prevent tetrahydrocannabinol (THC)-induced impairment of driving and cognition. *Psychopharmacology (Berl)*. 2019.
342. Klein C, Karanges E, Spiro A, et al. Cannabidiol potentiates Δ 9-tetrahydrocannabinol (THC) behavioural effects and alters THC pharmacokinetics during acute and chronic treatment in adolescent rats. *Psychopharmacology (Berl)*. 2011;218(2):443-457.
343. Boggs DL, Nguyen JD, Morgenson D, et al. Clinical and Preclinical Evidence for Functional Interactions of Cannabidiol and Δ9-Tetrahydrocannabinol. *Neuropsychopharmacology*. 2018;43(1):142-154.
344. Thomsen R, Rasmussen HB, Linnet K. In vitro drug metabolism by human carboxylesterase 1: Focus on angiotensin-converting enzyme inhibitors. *Drug Metab Dispos*. 2014;42(1):126-133.
345. McCallum NK, Eastwood ME. In vivo binding of delta 1-tetrahydrocannabinol and cannabinol to rat serum proteins. *J Pharm Pharmacol*. 1978;30(6):384-386.
346. Wahlqvist M, Nilsson IM, Sandberg F, et al. Binding of delta-1-tetrahydrocannabinol to human plasma proteins. *Biochem Pharmacol*. 1970;19(9):2579-2584.
347. Widman M, Agurell S, Ehrnebo M, et al. Binding of (+)- and (minus)-delta-1-tetrahydrocannabinols and (minus)-7-hydroxy-delta-1-tetrahydrocannabinol to blood cells and plasma proteins in man. *J Pharm Pharmacol*. 1974;26(11):914-916.

AURORA™ MC


AURORA
TM
MC