5

Clearing the Smoke on Cannabis

Medical Use of Cannabis and Cannabinoids – An Update

Harold Kalant, M.D. Ph.D.
Department of Pharmacology and Toxicology, University of Toronto, and Centre for Addiction and Mental Health

Amy J. Porath-Waller, Ph.D.
Director, Research and Policy, CCSA

This is the fifth in a series of reports that reviews the effects of cannabis use on various aspects of human functioning and development. This report on the medical use of cannabis and cannabinoids provides an update of a previous report with new research findings that validate and extend our current understanding of this issue. Other reports in this series address the effects of chronic cannabis use on cognitive functioning and mental health, maternal cannabis use during pregnancy, cannabis use and driving, and the respiratory effects of cannabis smoking. This series is intended for a broad audience, including health professionals, policy makers and researchers.

Canadian Centre **on Substance Abuse**
Centre canadien **de lutte contre les toxicomanies**

Partnership. Knowledge. Change.
Collaboration. Connaissance. Changement.

Key Points

- Healthcare practitioners need access to the best available scientific evidence to help patients make informed decisions about the medical use of cannabis and cannabinoids. There is a great need for well-designed prospective clinical trials in Canada that assess the efficacy of cannabis and cannabinoids in treating various conditions.
- Evidence suggests that cannabis and cannabinoids are effective for the relief of nausea and vomiting, and certain types of pain, as well as the stimulation of appetite. However, there is insufficient research to promote cannabis and cannabinoids as a primary or first line option for these symptoms.
- More research is needed to determine the risks associated with the medical use of cannabis. However, research on chronic cannabis use has linked it to risks and harms such as reduced cognitive functioning and negative respiratory symptoms.
- Patients who ingest cannabis for medical purposes are not assured the reliable, standardized and reproducible dose they would otherwise receive from using cannabinoid products delivered in controlled doses (e.g., capsules, oral sprays).
- Research is currently examining the efficacy of potential therapeutic uses of cannabinoid products for conditions such as multiple sclerosis, psychiatric disorders, epilepsy, inflammatory diseases, cancer, obesity, glaucoma and neurodegenerative disorders. Although findings from this research are either mixed or insufficient to draw conclusions, there is promising research emerging for the treatment of some of these conditions.

Background

After alcohol, cannabis (also referred to as marijuana), is the most widely used psychoactive substance in Canada. According to the 2013 Canadian Tobacco, Alcohol and Drug Use Survey (CTADS), 10.6% of Canadians aged 15 years and older reported using cannabis in the past year (Statistics Canada, 2015), virtually unchanged from 10.2% in 2012. The use of cannabis is generally more prevalent among young people, with 22.4% of youth aged 15 to 19 and 26.2% of young adults aged 20 to 24 reporting past year use. Approximately 28% of Canadians aged 15 and older who used cannabis in the past three months reported that they used this drug every day or almost daily.

A growing body of evidence suggests that using cannabis may impact several aspects of people's lives, including mental and physical health, cognitive functioning, ability to drive a motor vehicle, and pre- and post-natal development among offspring (McInnis & Porath-Waller, 2016; Porath-Waller, 2015; Beirness & Porath-Waller, 2015; McInnis & Plecas, 2016). However, cannabis and some of its derivatives also have a long history of use as a medicine in many parts of the world. Very thorough and extensively referenced monographs on the subject of medical cannabis have been published by Ben Amar (2006), Health Canada (2013a) and the World Health Organization (Madras, 2015).

The 2011 Canadian Alcohol and Drug Use Monitoring Survey (CADUMS) reported that 17.7% of those aged 15 years and older who used cannabis said they used it for medical reasons (Health Canada 2013b). Several general population surveys have asked Canadians about their self-reported use of cannabis for medical purposes. Although dated, the results from a 1998 survey in Ontario revealed that in the year preceding the survey, 1.9% of adults aged 18 years and older reported using cannabis for a medical reason, compared to 6.8% reporting non-medical use (Adlaf, Begin, & Sawka, 2005). According to results from the 2004 Canadian Addiction Survey, of the 14% of Canadians aged 15 years and older who reported using cannabis in the past year, 29% indicated that they used cannabis or hashish to treat pain, nausea, glaucoma, multiple sclerosis, depression or another medical condition (Ogborne, Smart, & Adlaf, 2000).

According to Health Canada's Office of Medical Cannabis, licensed producers reported they had 53,649 Canadian clients registered for marijuana for medical use (personal communication, May 16, 2016). A total of 361,076 shipments had been made as of March 31, 2016, with 58% to clients in Ontario, 13% in Alberta and 6% in British Columbia. As of January 31, 2016, there were 6,395 healthcare practitioners out of a total of more than 80,500 who were practising in Canada (Canadian Medical Association, 2016) who had provided medical documents for registered clients under the *Marihuana for Medical Purposes Regulations* (MMPR).

This report—the fifth in a series reviewing the effects of cannabis use on various aspects of human functioning and development (see Beirness & Porath-Waller, 2015; McInnis & Plecas, 2016; Porath-Waller, 2015; McInnis & Porath-Waller, 2016)—examines the research on the medical use of cannabis and cannabinoids. Following a review of the evidence, this report discusses implications for policy and practice.

Cannabis is a greenish or brownish material consisting of the dried flowering, fruiting tops and leaves of the cannabis plant, Cannabis sativa*. Hashish or cannabis resin is the dried brown or black resinous secretion of the flowering tops of the cannabis plant. The acute effects of cannabis include euphoria and relaxation, increased sociability and heightened sensation, but also changes in perception, time distortion, deficits in attention span and memory, body tremors, and impaired motor functioning. It is a controlled substance under the* Controlled Drugs and Substances Act*—meaning that it is illegal to grow, possess, distribute or sell cannabis. There is an exception for those possessing cannabis for medical purposes as supported by a physician. Since July 2015, licensed producers can supply cannabis for medical purposes in fresh, dried and oil forms (Health Canada, 2015). As of August 24, 2016, under the* Access to Cannabis for Medical Purposes Regulations*, Canadians with a medical document are able to produce a limited amount of cannabis for their own medical purposes or designate someone to produce it for them. The Canadian government elected in 2015 has indicated its intention to introduce legislation in spring 2017 to legalize and regulate cannabis for non-medical use. The relationship between medical and non-medical markets is anticipated to be specified in the regulatory framework.*

Cannabis as a Medicine

The use of cannabis as a medical agent has a long history in both folk and professional medicine (Kalant, 2001). Its modern era began in the mid-19th century, when O'Shaughnessy (1843) described the use of crude cannabis preparations in India for the treatment of muscle spasms and convulsions. Later observations recorded its use in Indian folk medicine for the relief of a wide variety of disease symptoms, including pain, diarrhea, fever, anxiety, sleeplessness and lack of appetite (Kalant, 1972). O'Shaughnessy sent samples of Indian cannabis to London, where they were analyzed and used to prepare standardized extracts that were incorporated into the British and American pharmacopoeias of recognized drugs and medicinal preparations, leading to the wide use of cannabis in medical practice in many parts of the world.

In the 20th century, however, the medical use of cannabis gradually decreased because of its unreliability, which resulted from the variable composition of the extracts and their limited shelf life. Cannabis was largely replaced by purified single drugs, both natural and synthetic, with more reliable potency and stability. For example, a variety of natural and synthetic opium-like drugs replaced cannabis as pain relievers, and barbiturates replaced cannabis as sleep-inducers and anti-convulsants. When cannabis was made illegal in many countries between the years 1923 and 1952, this move provoked relatively little opposition because the drug had largely fallen out of use by that time.

The revival of interest in cannabis in Western countries in the 1960s was related principally to its nonmedical use by young people to produce euphoria and facilitate social interaction (the "high"). However, as scientific interest revived, the exploration of its potential therapeutic uses was renewed, and has increased greatly since the discovery of the endocannabinoid system and its widespread physiological activity in many different body organs and tissues, described later in this report.

Cannabinoids

The major pharmacologically active constituents of cannabis (called "cannabinoids") were isolated, chemically identified and synthesized by Adams and Baker (1940), and the detailed molecular structure was clarified in the 1960s (Gaoni & Mechoulam, 1964). Since the early 1990s there has been a rapid advance in knowledge of how and where in the body these cannabinoids act to produce their effects. As a result, there is now vastly increased scientific literature dealing in part with current therapeutic uses of cannabis and cannabinoids, and in even larger part with possible future developments for medical uses.

Cannabis contains hundreds of known chemicals, more than 100 of which belong to the cannabinoid group (Madras, 2015) that share a common chemical structure first found in some constituents of the cannabis plant. Those found in the cannabis plant are called *phytocannabinoids* or natural cannabinoids. One example is Δ9-tetrahydrocannabinol (THC), which is the primary psychoactive component of the cannabis plant responsible for the "high" from ingesting or inhaling cannabis. Cannabidiol (CBD), another natural cannabinoid, contributes to many of the pharmacological actions of cannabis, but does not produce the high. Other natural cannabinoids include cannabigerol, cannabivarin and cannabichromene, some of which have potentially beneficial therapeutic effects, but are present in cannabis in much lower concentrations than THC and CBD, and therefore make only a very minor contribution to the actions of whole cannabis. Other cannabinoids are synthetic (i.e., made in a laboratory), but are functionally similar to THC or other natural cannabinoids. Some of them, including dronabinol (Marinol®) and nabilone (Cesamet®), are used therapeutically. However, other synthetic cannabinoids (e.g., Spice, K2) have been used recreationally, but not medically.

Until recently, most of the interest in medical uses of cannabis was focused on the actions of THC, but now there is growing interest in potential medical uses of CBD, which does not have the psychoactive effects of THC and appears to have a number of therapeutic benefits.

- *The cannabis plant produces marijuana (cannabis herb) and hashish (cannabis resin).*
- *Cannabinoids are chemicals found in the cannabis plant or synthesized chemically. A few account for most of the known actions of cannabis on mental and bodily functions.*
- *Δ9-tetrahydrocannabinol (THC) is the cannabinoid with the greatest psychoactive effect, but cannabidiol (CBD) shows considerable promise of usefulness for medical purposes.*

The Endocannabinoid System

The cannabinoids produce their effects by binding to *cannabinoid receptors* that are found throughout the human body. There are two types of cannabinoid receptors that are named CB_1 and CB_2. The highest concentration of the CB_1 receptor is found in the brain, located on brain

cells (neurons) where activity signals are passed from one brain cell to another. Their function is to regulate the level of activity of brain cells. The CB_1 receptor is also located widely throughout the body at lower concentrations, on various cells primarily responsible for inflammation and immunity.[1]

Unlike CB_1 receptors, CB_2 receptors are present in the brain, mostly on support cells (also known as glial cells), in smaller numbers than elsewhere in the body. CB_2 receptors can be found on immune cells, inflammatory cells and also on cancer cells. The human body produces substances called endocannabinoids[2] that act on CB_1 and CB_2 receptors, but are chemically different from THC and some other plant cannabinoids that also act on CB_1 and CB_2 receptors.

The endocannabinoids, the enzymes that form them and break them down, and the receptors, together make up what is called the *endocannabinoid system* (Pacher, Batkai, & Kunos, 2008; Pertwee et al., 2010; Micale, Di Marzo, Sulcova, Wotjak, & Drago, 2013; Mechoulam & Parker, 2013; Kalant, 2014; Vemuri & Makriyannis, 2015). This system is widely distributed throughout the body, acting to regulate the activity of different kinds of cells and tissue.

When plant cannabinoids enter the human body, they act on the receptors of the endocannabinoid system, but more strongly and for a much longer time than the human-produced endocannabinoids do. Plant cannabinoids can lead to sustained alterations that can produce both therapeutic effects and unwanted side-effects (Kalant, 2014). Since the endocannabinoid system is so widely distributed throughout the body, cannabinoids can cause a number of changes in body functions. Therefore, the use of cannabinoids for therapeutic action is almost always accompanied to some degree by side-effects.

Medically Used Preparations and Methods of Administration

In Canada, cannabis for medical purposes is legally accessed through the *Access to Cannabis for Medical Purposes Regulations* (ACMPR). Because the cannabis accessed through this program is monitored and standardized, it is less risky to use than cannabis that is obtained illegally, which can be contaminated with unknown substances and have varying levels of THC and other cannabinoids. In addition, there are several other cannabinoid products available for medical use in Canada. The forms of cannabinoids that are used or tested as medicines by physicians, and their routes of administration, are mainly the following:

- **Dronabinol:** Synthetic THC in oral pill form that has been marketed as Marinol®. It is still used in the United States and elsewhere, but has been withdrawn from the Canadian market by its manufacturer for unstated reasons, and it is not known whether it will be restored;
- **Nabilone:** A synthetic derivative of THC in oral pill form that is marketed as Cesamet®;
- **Nabiximols:** A standardized extract of a cannabis strain containing equal proportions of THC and CBD that is marketed under the name Sativex®. It is used in a special dispenser that sprays a standard volume per dose on to the inside of the cheek or under the tongue. Food can delay absorption by this route (Stott, White, Wright, Wilbraham, & Guy, 2013);
- **Plant-derived cannabis preparations made by government-licensed producers:**[3] Licensed producers provide cannabis in quantities up to those indicated in the medical documents submitted by the client. Delivery takes place via postal mail. The products sold by the different licensed producers vary considerably from each other with respect to the concentrations of cannabinoids they contain, but each must be of reliably constant composition and purity. In most of them, the main cannabinoid component is THC, but its concentration in different strains of cannabis varies from as little as 1.4% to as much as 25% or more with 1% or less of CBD. They are most commonly smoked, but can also be used in vaporizers that do not heat the cannabis enough to cause combustion, but deliver the cannabinoids as a smokeless vapour (Solowij, Broyd, van Hell, & Hazekamp, 2014).
- Dried cannabis can also be brewed in boiling water and drunk as a tea, or taken by mouth as “edibles” such as cookies, brownies or candies containing cannabis as an ingredient. It can also be extracted with alcohol or with a

[1] For example, on smooth muscle cells in the walls of blood vessels, intestine and urinary bladder; on secretory cells in the stomach and intestine linings, liver, pancreas and other glands.

[2] For example, anandamide (AEA) and 2-arachidonoylglycerol (2-AG).

[3] As outlined in the ACMPRs, plant-derived cannabis preparations include dried cannabis as well as oils. Authorized individuals can also produce their own cannabis products for personal use or designate a grower to do so, but there is limited data about the preparations and methods of administration in this context.

fatty material such as olive oil or melted butter, yielding a concentrated extract with much higher cannabinoid content than the original plant material. Some of these special administration forms are produced by licensed producers, whereas others are made at home by the clients. Edibles currently constitute 28% of the "medical marijuana" sold in Colorado, New Mexico, Oregon and Washington (Pacula, Jacobson, & Maksabedian, 2016), and have the advantage of avoiding the irritant effects of smoke in the airways. Dosage is more difficult in edibles due to the greater potential for uneven distribution of cannabinoids in the final product.

- Cannabis oil, produced by steam distillation of cannabis, has much higher cannabinoid concentration than the original cannabis. As a medication, some clients apply it to the skin and rub it in for relief from local pain of muscular or skeletal origin. However, scientific studies show that although THC in the oil can diffuse through the skin, it does so at only one-tenth the rate of CBD, and is so slow that THC concentrations in the rest of the body are probably too low to have any significant effect (Stinchcomb, Valiveti, Hammell, & Ramsey, 2004). In contrast, the diffusion of CBD is possibly rapid enough to produce pharmacological effects both locally where it is applied and also elsewhere in the body (Liput, Hammell, Stinchcomb, & Nixon, 2013). The oil can also be taken orally in food or inhaled from a vaporizer.
- Cannabidiol is the main cannabinoid in cannabis that does not produce a high. It is not yet available in Canada for medical use by itself, but a preparation of 99% pure plant-derived CBD called Epidiolex® is currently undergoing extensive clinical and laboratory testing in several countries, and will probably become available for clinical use in the fairly near future. However, some of the products already marketed by licensed producers under the ACMPR contain much more CBD than THC.

Uses of Cannabis and Cannabinoids as Medicine

1. Current and Approved Uses

(a) Nausea and vomiting

In many countries, including Canada, cannabis and individual cannabinoids are approved for relief and prevention of nausea and vomiting caused by anti-cancer and anti-HIV chemotherapy. This action is exerted through the endocannabinoid system (Sharkey, Darmani, & Parker, 2014), and might be effective against nausea due to some other causes, such as diffuse cancer (Hernandez, Sheyner, Stover, & Stewart, 2015).

(b) Appetite stimulation

Cannabis and cannabinoids are also approved for stimulation of appetite in AIDS patients with a severe loss of body weight. However this action, exerted through CB_1 receptors, mainly increases intake of carbohydrates, not of protein, and is therefore not very effective for restoration of tissue mass. A recent clinical trial (Andries, Frystyk, Flyvbjerg, & Stoving, 2014) found that dronabinol was also moderately effective in stimulating appetite in patients with severe anorexia nervosa, although the trial was only of four weeks duration so additional research is needed to speak to long-term efficacy.

(c) Pain relief

In Canada, Sativex® is approved for the relief of neuropathic pain (pain due to disease of the nervous system), of pain and spasticity (muscular stiffness) due to multiple sclerosis, and of severe pain due to advanced cancer. Sativex is undergoing clinical trials in the United States and is available on a limited basis by prescription in the United Kingdom and Spain. Numerous studies have confirmed the efficacy of smoked or vaporized cannabis or of oral cannabinoids in relieving neuropathic pain (Boychuk, Goddard, Mauro, & Orellana, 2015; Fine & Rosenfeld, 2014; Lynch & Campbell, 2011; Serpell et al., 2014; Wallace, Marcotte, Umlauf, Gouaux, & Atkinson, 2015; Wilsey et al., 2013), in both short-term and longer-term trials (Aggarwal, 2013; Johnson, Lossignol, Burnell-Nugent, & Fallon, 2013; Ware, Wang, Shapiro, & Collet, 2015). However, doses of oral dronabinol or smoked cannabis that were high enough to give a significant relief of pain also had significant psychoactive effects that some consider to be indicative of risk of addiction (Issa et al., 2014), and some clinicians regard the pain-relieving effect of cannabis as insufficient to outweigh its adverse effects (Saxon & Browne, 2014).

Though some individuals who use cannabis say they use it to relieve headache, there is still no valid clinical evidence that cannabis or cannabinoids are effective against ordinary headache or migraine (McGeeney, 2013). There is laboratory evidence that CB_2 receptors are involved in the regulation of joint pain, as in arthritis (Fukuda et al., 2014), but so far there is little or no clinical evidence of the useful analgesic effect of CB_1 or CB_2 receptor agents in arthritis in humans. However, CBD, which acts through different receptors, might have useful pain-relieving effects in some types of arthritis (see below under anti-inflammatory actions).

2. Proposed Uses

In contrast to the above-reviewed evidence on the clinical efficacy of cannabinoids for approved uses, much of the current research literature deals with **proposed** therapeutic uses for cannabis or cannabinoids. In this latter case, the evidence of efficacy is generally less clear, but there is great variation between the different applications with respect to the amount and quality of their scientific support.

(a) Multiple sclerosis

A number of clinical studies have found cannabis or cannabinoids to be moderately effective in the relief of neurogenic pain (pain caused by illness or damage to the nervous system) in multiple sclerosis (Jawahar, Oh, Yang, & Lapane, 2013; Koppel et al., 2014; Langford et al., 2013). The findings have been less consistent with respect to the effects on spasticity. In most of the earlier studies, patients reported subjective relief of the sensation of spasm, but objective measures of spasticity did not reveal any significant improvement (Zajicek & Apostu, 2011). However, in more recent studies, either smoked cannabis or nabiximols oral spray gave objective evidence of decreased spasm as well as of relief of pain (Corey-Bloom et al., 2012; Flachenecker, Henze, & Zettl, 2014; Koehler, Feneberg, Meier, & Pollmann, 2014; Lorente-Fernandez et al., 2014; Serpell, Notcutt, & Collin, 2013). In long-term treatment continuation studies, the benefits have continued for up to a year in some patients. However, a substantial percentage of patients did not show clear benefit or dropped out of continued treatment because of adverse effects. The reason for the discrepancy of findings between the earlier and the later studies is not yet clear, but one possible explanation is that the use of combined THC–CBD preparations decreased the side effects of THC and permitted the use of higher doses, with correspondingly better effect (Zajicek et al., 2013).

(b) Epilepsy

Basic laboratory studies of isolated brain tissue have provided evidence that the endocannabinoid system is involved in controlling the activity of brain cells (Hofmann & Frazier, 2013). Exogenous cannabinoids (i.e., those not produced in the body) reduce the excitability and spontaneous activity of brain cells, though different plant cannabinoids act by different mechanisms (Iannotti et al., 2014). THC acts through CB_1 receptors, whereas CBD and some other cannabinoids, such as cannabidivarin, act through receptors in the inflammation system. They all decrease the activity of the nerve cells on short exposure, but chronic exposure to THC reduces the number of CB_1 receptors and can cause , rather than prevent, seizures (Blair et al., 2009). The availability of CBD-enriched cannabis strains and extracts has enabled some parents to try them in children with severe epilepsy that failed to respond to conventional treatment (Hussain et al., 2015). A number of case reports and interviews of parents indicated that up to 70% of the children treated had a 50% or greater reduction of seizure frequency (Geffrey, Pollack, Bruno, & Thiele, 2015; Porter & Jacobson, 2013; Press, Knupp, & Chapman, 2015; Saade & Joshi, 2015). These encouraging observations have led to the initiation of properly designed clinical trials with a cannabis extract containing 99% pure CBD (Epidiolex®) for the treatment of different types of childhood epilepsy, which are currently in progress in the United States and elsewhere. However, there is not yet sufficient evidence available from well-designed clinical trials to permit recommendation of cannabis or CBD for treatment of epilepsy (Friedman & Devinsky, 2015).

(c) Cancer

Although the anti-cancer effect of cannabinoids has been intensively studied in cell cultures (test-tube studies) and in animals with tumours, no firm conclusions about their clinical use are yet possible. It has been confirmed repeatedly that THC and various other cannabinoids binding to CB_1 and CB_2 cannabinoid receptors, and CBD acting through different mechanisms, can promote cancer cell death, or retard or prevent the growth of cancer cells of various types, including lung, prostate, pancreas, colon and brain cancer (Dando et al., 2013; De Petrocellis et al., 2013; Haustein, Ramer, Linnebacher, Manda, & Hinz, 2014; Macpherson, Armstrong, Criddle, & Wright, 2014; Zogopoulos, Korkolopoulou, Patsouris, & Theocharis, 2015). The cannabinoids also reduce the ability of cancer cells to invade surrounding normal tissues and to metastasize (i.e., give rise to colonies of cancer cells in many different tissues at a distance from the original cancer site). It has also been suggested that some actions of endocannabinoids might reduce the risk of mutations that give rise to cancer cells (Alexander, Smith, & Rosengren, 2009; Freimuth, Ramer, & Hinz, 2010). Cannabinoids have been shown to inhibit the growth of new blood vessels that are necessary to provide enough oxygen and food to support the rapid growth of cancer cells (Ramer & Hinz, 2015). All of these actions have raised hopes that cannabinoids or derivatives of them might become important anti-cancer drugs.

However, these actions have been demonstrated by adding cannabinoids to cultures of growing cancer cells, by injecting cannabinoids directly into cancers growing in living animals, and by administering cannabinoids to animals in which cancers have been produced experimentally. Only one small, uncontrolled clinical trial has been carried out in nine patients whose brain cancers had recurred after surgical removal. THC was injected directly into the recurrent brain cancers. Although there was a rapid

decrease of pressure inside the skull and an initial relief of symptoms, the THC treatment did not cure the cancer or slow the rate of its recurrence (Guzman et al., 2006). There are various possible explanations for the apparent lack of success in this human trial compared to the results demonstrated in animals with transplanted cancers or human cancer cells growing in cultures. The most plausible reason might relate to the doses or concentrations of cannabinoid used in the studies. At very low concentrations THC can stimulate cancer cell growth, but the inhibitory action is seen at very high concentrations. For example, in one study with prostate cancer cell cultures (Sarfaraz, Afaq, Adhami, & Mukhtar, 2005), a 50% decrease in cancer cell survival was produced by continuous exposure to a cannabinoid concentration that was about 10 times higher than the peak concentration that would occur in the blood of a human who had smoked a large dose of cannabis. As the successful treatment of cancer requires complete eradication of the cancer cells, the doses of cannabinoids required to accomplish this would evidently be very large. At such high concentrations, the side effects of drugs acting via CB_1 receptors would be intolerable to patients. Therefore current research on anti-cancer actions is focused principally on CBD and on synthetic cannabinoids acting exclusively through CB_2 receptors (Fowler, 2015; Massi, Solinas, Cinquina, & Parolaro, 2013; Zogopoulos et al., 2015). The early findings are encouraging, but they have not yet led to the development of effective treatment for cancer in humans.

(d) Anti-inflammatory actions

The endocannabinoids, as well as THC and other cannabinoids acting through CB_1 receptors, and CBD acting through non-cannabinoid receptors, are all able to decrease the formation and release of chemical factors that give rise to inflammation (Burstein, 2015; Esposito et al., 2013; Koay, Rigby, & Wright, 2014). The endocannabinoid and the inflammatory systems co-exist in most tissues of the body, and the ability of CBD and some other cannabinoids to suppress inflammation reactions has been shown experimentally in such tissues as the endothelial lining of blood vessels (Wilhelmsen et al., 2014), human skin (Olah et al., 2014), human intestinal lining cell cultures (Harvey, Sia, Wattchow, & Smid, 2014) and a mouse model of rheumatoid arthritis (Fukuda et al., 2014). However, the only disease state in which this research has yet progressed to clinical trials is chronic inflammatory bowel disease (Crohn's disease and ulcerative colitis). One double-blind randomized placebo-controlled study found that smoked cannabis improved the symptoms of patients with ulcerative colitis, but did not achieve complete disappearance of the disease process (Irving et al., 2015). In contrast, a different study (Naftali et al., 2013) found complete subsidence of Crohn's disease in 90% of patients treated with THC-rich smoked cannabis, versus 40% of those receiving placebo. Both were fairly small-scale trials, and lasted only eight weeks. The results are encouraging, but much larger and longer-lasting trials are needed to see whether cannabis is a useful therapy in chronic intestinal inflammatory disease.

(e) Uses in psychiatry

Post-traumatic stress disorder

The early use of cannabis for relief of anxiety, tension and sleeplessness is reflected in modern studies with cannabinoids. THC, CBD and THC–CBD combinations have been reported to improve sleep quality and duration as an additional benefit in patients being treated primarily for complaints such as pain, Parkinson's disease, sleep apnoea, anxiety disorders and post-traumatic stress disorder (PTSD) (Johnson et al., 2013; Chagas et al., 2014; Farabi, Prasad, Quinn, & Carley, 2014; Roitman, Mechoulam, Cooper-Kazaz, & Shalev, 2014; Blessing, Goddard, Mauro, & Orellana, 2015), though most studies have been of short duration. A number of studies among military personnel have shown that a high proportion of those with PTSD also use cannabis; that might represent use of cannabis as a form of self-treatment by PTSD patients. There have also been a number of studies of the possible role of endocannabinoid system disturbances in the development of PTSD. THC was found to help prevent the recall of extinguished conditioned fear responses even in normal subjects (Rabinak et al., 2013). In a small number of clinical trials, the major PTSD symptoms such as nightmares, excessive arousal (e.g., difficulty sleeping, being "on guard," etc.), and return of conditioned fear responses were reported to be improved by THC, nabilone and cannabis (Fraser, 2009; Cameron, Watson, & Robinson, 2014; Greer, Grob, & Halberstadt, 2014). However, the prevailing view among psychiatrists is that there is not yet sufficient evidence to support cannabinoids as suitable treatment for PTSD, because it is a complex illness in which a variety of different mechanisms could be involved (Papini, Sullivan, Hien, Shvil, & Neria, 2015).

Psychosis

As noted earlier, CBD alone does not activate CB_1 receptors and so has no psychoactive effects. CBD partially blocks THC from binding to CB_1 receptors and so tends to decrease the psychoactive effects of THC, including the ability of THC to produce hallucinations and altered thought processes. These actions suggested the possibility that CBD might be useful as a treatment for similar symptoms even in psychosis not caused by cannabis (Schubart et al., 2014; Silva, Balbino, & Weiber, 2015). Support for this idea was provided by a number of case reports describing the improvement of symptoms in patients with psychosis

treated with CBD. So far there is only one double-blind controlled study in which CBD was compared with amisulpride, a new anti-psychotic drug; the study included 42 patients with psychosis over a four-week period. The symptom improvement by the two drugs was comparable, but there were far fewer serious side effects with CBD than with amisulpride (Leweke et al., 2012). This study is an encouraging start, but much more clinical trial research is required, especially longer-term trials, before the value of CBD treatment of psychosis can be assessed.

Substance use disorders

The endocannabinoid system has been found to affect activity in certain brain pathways related to the rewarding effects of opioids and other drugs. Those pathways are believed to play an essential role in the addictiveness of the drugs. Since THC has addictive properties, whereas CBD opposes the psychoactive effects of THC, it was proposed that CBD might have anti-addiction properties. CBD decreased the ability of heroin-related cues to restart heroin self-administration in previously heroin-addicted rats, and in some but not all studies it also decreased the withdrawal symptoms when heroin was stopped (Prud'homme, Cata, & Jutras-Aswad, 2015). A few studies in humans have also shown that CBD reduced the "liking" for cannabis, and eased withdrawal symptoms in patients trying to stop use of cannabis or of tobacco (Prud'homme et al., 2015). These are interesting findings, but their relation to the basic mechanisms of addiction is not clear, and similar findings were not obtained in studies of alcohol or cocaine addiction. Taken together, they do not yet provide sufficient evidence for the use of CBD in the treatment of substance use disorders.

(f) Neuroprotection

Nerve cell degeneration is a process of loss of nerve cell function and structure that can lead to cell death. It can be caused by a variety of factors, including mechanical injury to the brain, insufficient oxygen supply, toxic materials and genetically determined diseases such as Huntington's disease and amyotrophic lateral sclerosis (Lou Gehrig disease). The mechanisms giving rise to degeneration include inflammation, excessive stimulation of brain cells and formation of harmful chemicals inside nerve cells. Brain cells are more vulnerable to damage by these factors when they are active than when they are at rest. Thus, by decreasing the level of nerve cell activity, cannabinoids can protect the cells against these types of damage just as barbiturates and certain other sedatives can. CBD and cannabinoids acting on CB_2 receptors also have more specific actions that directly block the inflammatory and damaging processes (Fagan & Campbell, 2014).

This neuroprotective effect has been studied in animal experiments as a possible emergency treatment for stroke, oxygen deficiency in the newborn, head injury, Parkinson's disease and other types of brain damage. One clinical trial in patients with severe head injury, found that the synthetic cannabinoid dexanabinol rapidly reduced the increased pressure inside the skull, and produced greater recovery of symptoms at three and six months after the injury (Knoller et al., 2002). However, there have not been long-term follow-up studies in stroke or head injury patients to see whether the final outcome is superior with cannabinoid treatment.

Clinical trials of cannabis and of CBD in Parkinson's disease have shown minor benefit in uncontrolled studies (Lotan et al., 2014), but not in a double-blind trial (Chagas et al., 2014). Cannabinoids have given moderate benefit in some symptoms of multiple sclerosis, such as frequency of urination, but not in the major movement disorder (Koppel et al., 2014). Similarly, in Tourette's syndrome there are anecdotal reports that cannabis treatment reduced the frequency of the tics that are characteristic of this disease, but this finding has not been confirmed by properly designed clinical trials (Muller-Vahl, 2013). Numerous laboratory studies have shown that CBD and other cannabinoids can decrease the biochemical changes in the brain that are thought to be responsible for Alzheimer's disease, but a well-designed clinical trial found no evidence of a beneficial effect of THC on the symptoms of patients with Alzheimer's disease (van den Elsen et al., 2015). In general, there is not yet enough good clinical evidence to demonstrate the therapeutic value of the neuroprotective actions of cannabinoids.

(g) Obesity

Since stimulation of CB_1 receptors increases appetite, it seems reasonable that inhibition of those receptors might act as a treatment for obesity by decreasing appetite. Rimonabant®, a CB_1 inverse agonist (i.e., that produces effects opposite to those of THC), was successful in aiding weight loss, but had serious side effects including depression and anxiety, and was withdrawn from use. As an alternative to inverse agonists, a cannabinoid-like compound that attaches to the CB_1 receptor but does not produce any effects of its own reduced food intake in mice and rats without causing signs representing depression (Meye, Trezza, Vanderschuren, Ramakers, & Adan, 2013). However, this effect has not yet been explored clinically. It has also been proposed that higher doses of THC that inhibit rather than stimulate appetite might be explored as a possible treatment for obesity (Le Foll, Trigo, Sharkey, & Le Strat, 2013; see also Section 4, Dosage, below).

(h) Glaucoma

Consistent with the dosing problem noted above in the treatment of cancer, a similar problem is encountered with the claimed use of cannabinoids to treat glaucoma. This disease involves damage to the retina as a result of increased pressure of the fluid in the posterior chamber of the eyeball. To prevent the damage, it is necessary to keep the intraocular pressure continuously low. THC does indeed reduce this pressure, but only for three or four hours after a normal dose. Therefore, to prevent retinal damage, a patient would have to smoke cannabis (or take equivalent oral doses of cannabinoids) every few hours—day and night—and thus be continuously exposed to the psychoactive effects (Green, 1998; Flach, 2002). If a water-soluble derivative of sufficient potency can be developed to make it possible to apply the drug locally as eye-drops without the risk of absorption into the bloodstream, it might make cannabinoid therapy useful for glaucoma, but this does not yet exist. Both the Canadian and American ophthalmological societies do not support cannabis as a practical treatment for glaucoma (Buys & Rafuse, 2010; American Academy of Ophthalmology, 2014).

(i) Other possible uses

As suggested by the widespread actions of the endocannabinoid system, a number of possible therapeutic uses of cannabis and cannabinoids on other tissues have been proposed. These include use of cannabigerol and some other cannabinoids, which do not act on CB_1 receptors and thus do not have psychoactive effects, to treat urinary frequency (Pagano et al., 2015); use of synthetic CB_1 cannabinoids that cannot enter the brain to treat gastroesophageal reflux (Plowright et al., 2013); and use of CBD to relax the smooth muscle walls of blood vessels in the treatment of hypertensive heart disease (Stanley, Hind, & O'Sullivan, 2013). Surprisingly, a new chemical called (-)-MRI1867 that is both a **blocker** of CB_1 receptors outside the brain and an **inhibitor** of an enzyme called nitric oxide synthase has been found to markedly reduce fibrosis of the liver caused by hepatitis virus, by alcohol or by toxic chemicals in mice (Kunos, 2016). These are all interesting possibilities with some scientific rationale, but they have not yet been explored clinically.

3. Treatment of Symptoms versus Treatment of Disease

In most of the medical uses or potential uses described above, cannabis or cannabinoids act mainly to relieve a wide variety of **symptoms** of disease, without affecting the underlying disease process. In a considerably smaller number of instances, cannabinoids might theoretically influence the disease process itself, rather than merely its symptoms. The anti-cancer effect discussed previously is one possible example. Another possible example is the ability of THC and CB_2-specific cannabinoids to inhibit the viral enzyme that enables the HIV-1 virus to reproduce itself inside the immune system cells of patients with AIDS (Ramirez et al., 2013; Williams et al., 2014). Further development of this type of possible curative action will most likely involve synthetic cannabinoids or partial modification of the known natural cannabinoids.

4. Dosage

The dosage of cannabis preparations used in most clinical studies has been between less than one gram and not more than five grams per day of a preparation with about 10% THC (Hazekamp & Heerdink, 2013; Health Canada, 2013a; Kahan et al., 2014; Ware et al., 2010). However, the appearance of a wide range of products from licensed producers under the ACMPR, with THC contents ranging from 1% or less to 25% or more, and with similarly varying concentrations of CBD, make it virtually impossible to state a precise dosage for a given patient and a given illness to be treated. The recommended procedure is to start with a low dose and gradually increase it until the required effect is reached, or until the onset of adverse effects prevents any further increase (Carter, Weydt, Kyashna-Tocha, & Abrams, 2004; Health Canada, 2013).

It is also important to remember that the concentration-effect curves for a number of the actions of endocannabinoids and THC-like cannabinoids have an upside down U shape: as the concentration is increased the effect also increases until a maximum effect is reached, but with further increases of concentration the effect starts to decrease until it might be eventually replaced by an opposite effect due to desensitization of the receptors (see Table 1). This phenomenon has been called "endocannabinoid overload" (Lichtman, Blankman, & Cravatt, 2010) and might account for some of the high-dose toxic effects of THC (Kalant, 2014).

Table 1. Examples of high-dose reversal of effects of endocannabinoids and THC-like cannabinoids

Brief or low-concentration effect	Chronic or high-concentration effect
anti-nauseant, anti-emetic	cannabinoid hyperemesis syndrome
neuroprotective actions	neurotoxicity
neural stem cell proliferation	prevention of synapse formation
facilitate extinction learning	prevent extinction learning
relief of anxiety	production of anxiety and panic
stimulation of tumor cell growth	stimulation of tumor cell death
anti-seizure action	production of seizures

5. Contraindications: Who should not be treated with cannabis?

Five types of patients are generally felt by physicians to be unsuited for medication with cannabis or with pure cannabinoids that act through CB_1 or CB_2 receptors:

- Pregnant women: If cannabis is smoked during pregnancy or pure cannabinoids are taken by mouth, whether for medical or non-medical reasons, they cross the placenta and can produce harmful effects on the fetus (Porath-Waller, 2015). If the mother uses cannabis after delivery, cannabis is secreted in the breast milk and can harm the newborn (Behnke & Smith, 2013; Metz & Stickrath, 2015)
- Children and adolescents: Cannabis can have serious adverse effects on various aspects of mental and emotional development, depending on the age at start of use and the duration and intensity of use (George & Vaccarino, 2015). An exception might have to be made for children with certain forms of severe childhood epilepsy who fail to respond to conventional anti-seizure drugs, but do respond to CBD.
- Those with a history of problematic substance use or a substance use disorder, whether of alcohol, prescription drugs or illicit drugs.
- Those with a personal or family history of psychosis: They are at greater risk of developing an acute psychosis through use of cannabis or THC-like cannabinoids.
- Those with pre-existing disease of the heart and coronary arteries (see below under Adverse Effects).

Evidence of Comparative Clinical Efficacy

There is sound evidence from animal experiments and well-designed clinical trials involving humans that cannabis and cannabinoids are effective for the relief of nausea, vomiting and certain types of pain, as well as for the stimulation of appetite. However, the evidence to date does not indicate that they should be the primary or first-line option for these purposes. Many studies have shown, for example, that for treating nausea and vomiting, cannabinoids are more effective than older medications such as phenothiazines (e.g., Stemetil®) or antihistaminics (e.g., Dramamine®), but less effective than newer anti-nauseants such as ondansetron and similar drugs (Machado Rocha, Stefano, De Cassia Haiek, Rosa Oliveira, & Da Silveira, 2008; Soderpalm, Schuster, & de Wit, 2001).

Similarly, the pain-relieving activity of cannabinoids has been demonstrated (Karst, Wippermann, & Ahrens, 2010) and in individual cases it might sometimes be highly effective (Reynolds & Osborn, 2013), but generally it is less effective against some types of pain than morphine or other strong opioids (Sofia, Vassar, & Knobloch, 1975; Raft, Gregg, Ghia, & Harris, 1977). In a study of patients with cancer, relief of chronic pain by oral doses of 10 and 20 mg of THC was found to be equivalent in degree and duration to that given by 60 and 120 mg of codeine. However, the higher dose (20 mg) of THC produced severe adverse psychoactive and emotional effects, which impaired its therapeutic usefulness (Noyes, Brunk, Avery, & Canter, 1975). Later studies have similarly failed to find a beneficial effect of cannabinoids on acute pain, but did find a beneficial effect against chronic pain (Karst et al., 2010). Although the relief of chronic pain is clear, it must be weighed against the adverse effects in determining the overall benefit (Martin-Sanchez, Furukawa, Taylor, & Martin, 2009).

It has been suggested that cannabinoids could be usefully combined with other anti-nauseants or pain relievers in doses that produce superior therapeutic effects while reducing the risks of adverse effects of both medicines. Such claimed benefits of combined therapy have been reported both in animal studies (Karst & Wippermann, 2009; Kwiatkowska, Parker, Burton, & Mechoulam, 2004) and in research involving human patients (Elikkottil, Gupta, & Gupta, 2009; Narang et al., 2008). A study of over 1,500 patients being treated with opioids for chronic non-cancer

pain found that about one in six patients had also used cannabis for pain relief. They were principally younger patients with more severe pain and were not responding well to high-dose opioids alone. Most of them reported that adding cannabis improved their pain relief significantly. However, most of those patients had previously used cannabis non-medically, and it was not clear whether the improvement on adding cannabis to the opioid treatment was really due to better pain relief or to improved emotional outlook (Degenhardt et al., 2015).

Adverse Effects

Very little research has been conducted on the risks associated with the medical use of cannabis, making it challenging for physicians to discuss this concern with their patients. A systematic review of 23 randomized controlled trials and eight observational studies of cannabinoids and cannabis extracts for various medical purposes noted that the short-term use of these substances appeared to modestly increase the risk of less serious adverse medical events such as dizziness (Wang, Collet, Shapiro, & Ware, 2008). This review, however, did not provide information on the long-term use of cannabinoids for chronic disorders (e.g., multiple sclerosis) because the available trials were of relatively short duration (i.e., eight hours to 12 months). Moreover, this review did not assess the adverse effects on the bronchi and lungs associated with the smoking of cannabis.

A later cross-sectional study examining the effects of inhaled or ingested cannabis on cognitive functioning in patients with multiple sclerosis revealed that individuals who used cannabis performed significantly poorer than those who did not on measures of information-processing speed, working memory, executive functioning, and visual and spatial perception (Honarmand, Tierney, O'Connor, & Feinstein, 2011). Therefore subjective benefits from smoking cannabis reported by patients need to be weighed against the associated adverse effect of cognitive impairment.

Studies of recreational cannabis use provide some indication of the health risks that might result from smoking cannabis over the long term, including neurocognitive deficits (Crean, Crane, & Mason, 2011; McInnis &Porath-Waller, 2016), psychosis (Large, Sharma, S., Compton, Slade, & Nielssen, 2011; McInnis &Porath-Waller, 2016), various respiratory ailments and possibly cancer (Reid, Macleod, & Robertson, 2010; McInnis & Plecas, 2016). Psychosis has usually been seen in individuals who used cannabis non-medically and who took unusually large doses, or who took edible forms, became impatient at the slow onset of effects, and took additional doses (Hudak Severn, & Nordstrom, 2015). However, psychosis has also been observed in healthy experimental subjects who were given a moderate dose by mouth (Favrat et al, 2005). The advent of edible preparations for medical use in American states has led to an increase in emergency room visits, as a number of children have mistaken them for ordinary sweets (Ingold, 2014). A small but growing number of cases have been reported of heart attacks (myocardial infarction) produced in men, even young men, who smoked cannabis for non-medical purposes (Franz & Frishman, 2016). No such cases have been reported so far in persons using it at lower doses for medical reasons, but caution should be shown in those with already impaired coronary blood flow.

A recently observed adverse effect, called cannabinoid hyperemesis syndrome, consists of recurrent episodes of nausea, vomiting and stomach pain, that is relieved by frequent hot showers (Beech, Sterrett, Babiuk, & Fung, 2015; Alaniz, Liss, Metx, & Stickrath, 2015), and disappears on cessation of cannabis use. Another recently observed problem is that a considerable number of young men developed strokes shortly after using cannabis, and these individuals had no recognizable risk factors for stroke other than concurrent heavy use of alcohol and tobacco in about half of the cases (Hackam, 2015). There remains a need for follow-up studies examining the long-term health effects of the medical use of cannabinoids and smoked or ingested ("edible") cannabis, especially in those with long-term use.

No research to date has investigated the risk of development of cannabis use disorder in the context of long-term supervised medical use. However, reviews have suggested there is low abuse potential for the prescription cannabinoids nabilone (Cesamet®) and dronabinol (Marinol®) (Calhoun, Galloway, & Smith, 1998; Ware & St. Arnaud-Trempe, 2010). The evidence on the risk factors for cannabis use disorder comes primarily from studies of individuals who used cannabis recreationally and who began using the substance in adolescence and early adulthood and who use the most potent products. These individuals smoke cannabis with a greater frequency and intensity than older adults, who would presumably use smaller doses for symptom relief (Hall & Swift, 2006). However, a recent study in four American states suggests that those who say they use for both medical and recreational purposes tend to use more frequently and in larger amounts than those who use only for medical purposes (Pacula et al., 2016), and they would presumably be at greater risk of developing cannabis use disorder.

Although both cannabis and cannabinoids have been used for their therapeutic potential, it is important to distinguish smoked cannabis from synthetic cannabinoid products. Patients who smoke cannabis for medical purposes are

not assured a reliable and reproducible dose as compared to synthetic products that are delivered in controlled doses by nontoxic delivery systems (e.g., capsules, oral sprays). Even the preparations made by licensed producers differ widely in composition and strength from one another, and both physician and patient need to be aware of possible risks in changing from one preparation to another. If cannabis is obtained through illegal means, it can lack quality control and standardization or be contaminated with pesticides and microbes or both. In addition, the regular use of cannabis by smoking can cause chronic respiratory irritation (Kalant, 2008; McInnis & Plecas, 2016).

Given the impairing effects of cannabis on driving (Beirness & Porath-Waller, 2015), physicians should also advise their patients to refrain from operating a motor vehicle while under the influence of cannabis.

Access to Medical Cannabis in Canada

The Government of Canada initially created the *Marihuana Medical Access Regulations* (MMARs) in 2001 in response to an Ontario court decision. The MMARs allowed access to cannabis for medical purposes for Canadians meeting certain requirements. Under the MMARs, individuals submitted applications for authorization to Health Canada. These applications required physician support confirming that the individual suffered from one of a list of approved conditions. Individuals had the option to obtain medical cannabis by growing their own or through a designated grower, or by purchase from Health Canada.

In 2013, the Government replaced the MMARs with the *Marihuana for Medical Purposes Regulations* (MMPRs), which came into effect on April 1, 2014. Under the MMPRs, Health Canada no longer issues authorizations. Individuals must receive a medical document from a healthcare practitioner to authorize use. All medical cannabis had to be obtained from a producer licensed by Health Canada, from a healthcare practitioner or from a hospital. Individuals were forbidden to grow their own. As of August 24, 2016, the MMPRs have been replaced by the new *Access to Cannabis for Medical Purposes Regulations*. Under these regulations, Canadians with a medical document can produce a limited amount of cannabis for their own medical purposes or designate someone to produce it for them. Individuals wishing to supply their own cannabis in this way must apply for a registration certificate from Health Canada, and designated growers must also be registered. These changes are a direct result of the Federal Court ruling in the case of *Allard v. Canada* (Health Canada, 2016).

Areas for Future Research

The systematic study of the possible benefits of cannabinoid therapy combined with other drugs might well lead to better methods of clinical use. However, preparations containing THC or other drugs acting on the two known cannabinoid receptors will still lead to the very broad spectrum of action that gives rise to the psychoactive side effects. Therefore, clinically useful cannabinoid therapies will most likely focus on ways to improve the selectivity of the desired effects. One possible improvement is to use cannabinoids that do not act on either of the two known cannabinoid receptors and therefore are devoid of the psychoactivity that is usually unwelcomed by patients who have not previously used cannabis for non-medical purposes. For example, CBD has the sedative, anti-convulsant, anti-inflammatory and neuroprotective effects of THC, but not the psychoactivity and, as noted earlier in this report, it is being explored more fully as a therapeutic agent (Carlini & Cunha, 1981; Scuderi et al., 2009). A number of other cannabinoids found in cannabis could offer similar possibilities (Izzo, Borrelli, Capasso, Di Marzo, & Mechoulam, 2009). Likewise, although most research thus far has indicated that CBD shows some therapeutic benefits, further research is needed to determine whether other cannabinoids might also have therapeutic applications. However, the fact that natural cannabinoids cannot be patented will deter pharmaceutical companies from investing effort in their therapeutic development unless active semisynthetic modifications of those cannabinoids can be produced.

Another way of achieving more selective cannabinoid-like therapeutic action is to produce drugs that either stimulate or inhibit the cell mechanisms for producing and destroying the endocannabinoids, rather than act on the cannabinoid receptors themselves. Such an approach has been tested as a treatment for pain (Lau & Vaughan, 2014). In the scientific exploration of other neurotransmitters (the chemical messengers that transmit information between nerve cells), it has been found that the various molecules involved in their actions differ slightly in different tissues. A particular receptor, for example, might be found in the liver in a slightly different form from that of the same receptor in the heart or brain. It seems quite possible that the constituents of the endocannabinoid systems will also show such variations in different tissues. Such variations would make it possible to synthesize cannabinoid-like drugs that specifically target a particular tissue to produce a desired therapeutic effect while avoiding the brain or other organs in which side effects are produced. Such highly selective cannabinoid derivatives, in forms that can be taken orally or by injection, would permit many more therapeutic uses of this versatile family of drugs.

Alternative modes of delivery are being explored to overcome the adverse effects of smoking cannabis. Sativex® is sprayed onto the oral mucosa and absorbed directly from the mouth into circulation, which has the benefit of avoiding the inhalation of smoke. Clinical studies using delivery systems such as vaporizers that do not involve the combustion of cannabis and hence do not produce smoke might be helpful to overcome the health risks associated with smoking cannabis (McInnis & Plecas, 2016). It seems probable that other developments of this type will be actively pursued.

Conclusions and Implications

Based on the available evidence, the approved therapeutic use of cannabis is mainly limited to the treatment of nausea, vomiting and certain types of pain, and the stimulation of appetite in AIDS patients. Further research is needed to determine its most appropriate use relative to that of other current treatments for nausea and pain. The possible benefits of combining cannabinoid therapy with other drugs might well lead to better methods of clinical use. Much of the more recent research has focused on a broad range of other proposed therapeutic uses for cannabinoids (e.g., multiple sclerosis, cancer, epilepsy, inflammatory conditions) and the results from this work are encouraging, but not yet well-enough supported by properly designed clinical trials to permit their recommendation for those clinical uses.

It appears unlikely that cannabis will realize the full therapeutic potential that has been observed when studying the effects of the endocannabinoid system. Preparations containing THC or other drugs acting on the two known cannabinoid receptors will still suffer from the very broad spectrum of action that gives rise to the side effects. There is promise in further clinical studies of CBD, as well as in designing tailored medications developed from cannabinoids for specific conditions or symptoms with improved risk–benefit profiles. Research is currently underway to develop a new generation of safe and effective cannabinoid medications that avoid the adverse effects associated with smoking or ingesting whole cannabis.

An important distinction needs to be made between the risks associated with smoked cannabis and with cannabinoid products that are delivered in controlled doses by nontoxic delivery systems. Moreover, patients who smoke cannabis for medical purposes are not assured the reliable, standardized and reproducible dose that they would otherwise receive from using other cannabinoid products and could experience chronic respiratory ailments.

There is a need for education for healthcare practitioners to enhance their capacity to support patients who require cannabis for medical purposes. In particular, healthcare practitioners need more information on potential risks, relative safety and precautions for patients who use medical cannabis. As well, knowledge gaps remain on the appropriate dosages and treatment plans that can best serve healthcare practitioners' patients (Ziemianski et al., 2015). The development of resources and tools, such as clinical guidelines (College of Family Physicians of Canada, 2014), are essential to support the capacity of healthcare practitioners.

In summary, research supports the medical use of cannabis to relieve nausea, vomiting and chronic pain, and to stimulate appetite, but the research is still emerging in its application to other disease conditions. Future development is likely to be focused on exploiting CBD and possibly other cannabinoids without psychoactivity, and improving the specificity of synthetic cannabinoids and their delivery by safer methods than smoking.

References

Adams, R., & Baker, B.R. (1940). Structure of cannabidiol. VII. A method of synthesis of a tetrahydrocannabinol which possesses marihuana activity. *Journal of the American Chemical Society, 62*, 2405–2408.

Adlaf, E.M., Begin, P., & Sawka, E. (2005). *Canadian Addiction Survey (CAS): A national survey of Canadians' use of alcohol and other drugs: prevalence of use and related harms*. Ottawa, Ont.: Canadian Centre on Substance Abuse.

Aggarwal, S.K. (2013). Cannabinergic pain medicine: a concise clinical primer and survey of randomized-controlled trial results. *Clinical Journal of Pain, 29*(2), 162–171.

Alaniz, V.I., Liss, J., Metz, T.D., & Stickrath, E. (2015). Cannabinoid hyperemesis syndrome: a cause of refractory nausea and vomiting in pregnancy. *Obstetrics and Gynecology, 125*(6), 1484–1486.

Alexander, A., Smith, P.F., & Rosengren, R.J. (2009). Cannabinoids in the treatment of cancer. *Cancer Letters, 285*(1), 6–12.

American Academy of Ophthalmology. (2014). *Complementary therapy assessment: marijuana in the treatment of glaucoma*. Retrieved from www.aao.org/complimentary-therapy-assessment/marijuana-in-treatment-of-glaucoma-cta--may-2003.

Andries, A., Frystyk, J., Flyvbjerg, A., & Stoving, R.K. (2014). Dronabinol in severe, enduring anorexia nervosa: a randomized controlled trial. *International Journal of Eating Disorders, 47*(1), 18–23.

Beech, R.A., Sterrett, D.R., Babiuk, J., & Fung, H. (2015). Cannabinoid hyperemesis syndrome: a case report and literature review. *Journal of Oral and Maxillofacial Surgery, 73*(10), 1907–1910.

Behnke, M., & Smith, V.C. (2013). Prenatal substance abuse: short- and long-term effects on the exposed fetus. *Pediatrics, 131*(3), e1009–1024.

Beirness, D.J., & Porath-Waller, A.J. (2015). *Clearing the smoke on cannabis: Cannabis use and driving—An update.* Ottawa, Ont.: Canadian Centre on Substance Abuse.

Ben Amar, M. (2006). Cannabinoids in medicine: a review of their therapeutic potential. *Journal of Ethnopharmacology, 105*(1–2), 1–25.

Blair, R.E., Deshpande, L.S., Sombati, S., Elphick, M.R., Martin, B.R., & DeLorenzo, R.J. (2009). Prolonged exposure to WIN55,212-2 causes downregulation of the CB_1 receptor and the development of tolerance to its anticonvulsant effects in the hippocampal neuronal culture model of acquired epilepsy. *Neuropharmacology, 57*(3), 208–218.

Blessing, E.M., Steenkamp, M.M., Manzanares, J., & Marmar, C.R. (2015). Cannabidiol as a potential treatment for anxiety disorders. *Neurotherapeutics, 12*(4), 825–836.

Boychuk, D.G., Goddard, G., Mauro, G., & Orellana, M.F. (2015). The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. *Journal of Oral and Facial Pain and Headache, 29*(1), 7–14.

Burstein, S. (2015). Cannabidiol (CBD) and its analogs: a review of their effects on inflammation. *Bioorganic and Medicinal Chemistry, 23*(7), 1377–1385.

Buys, Y.M., & Rafuse, P. (2010). *Medical use of marijuana for glaucoma.* Ottawa, Ont.: Canadian Ophthalmological Society. Retrieved from www.cos-sco.ca/advocacy-news/position-policy-statements/medical-use-of-marijuana-for-glaucoma/.

Calhoun, S.R., Galloway, G.P., & Smith, D.E. (1998). Abuse potential of dronabinol (Marinol). *Journal of Psychoactive Drugs, 30*(2), 187–196.

Cameron, C., Watson, D., & Robinson, J. (2014). Use of a synthetic cannabinoid in a correctional population for posttraumatic stress disorder-related insomnia and nightmares, chronic pain, harm reduction, and other indications: a retrospective evaluation. *Journal of Clinical Psychopharmacology, 34*(5), 559–564.

Canadian Medical Association. (2016). *Canadian physician resources – 2016 basic facts.* Ottawa, Ont.: Author. Retrieved from www.cma.ca/En/Pages/basic-physician-facts.aspx.

Carlini, E.A., & Cunha, J.M. (1981). Hypnotic and antiepileptic effects of cannabidiol. *Journal of Clinical Pharmacology, 21*(8–9 Suppl), 417s–427s.

Carter, G.T., Weydt, P., Kyashna-Tocha, M., & Abrams, D.I. (2004). Medicinal cannabis: rational guidelines for dosing. *IDrugs, 7*(5), 464–470.

Chagas, M.H., Zuardi, A.W., Tumas, V., Pena-Pereira, M.A., Sobreira, E.T., Bergamaschi, M.M., ... Crippa, J.A. (2014). Effects of cannabidiol in the treatment of patients with Parkinson's disease: an exploratory double-blind trial. *J Psychopharmacol, 28*(11), 1088–1098.

College of Family Physicians of Canada. (2014). *Authorizing dried cannabis for chronic pain or anxiety: preliminary guidance from the College of Family Physicians of Canada.* Mississauga, Ont.: College of Family Physicians of Canada.

Corey-Bloom, J., Wolfson, T., Gamst, A., Jin, S., Marcotte, T.D.,Bentley, H., & Gouaux, B. (2012). Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. *Canadian Medical Association Journal, 184*(10), 1143–1150.

Crean, R.D., Crane, N.A., & Mason, B.J. (2011). An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. *Journal of Addiction Medicine, 5*(1), 1–8.

Dando, I., Donadelli, M., Costanzo, C., Dalla Pozza, E., D'Alessandro, A., Zolla, L., & Palmieri, M. (2013). Cannabinoids inhibit energetic metabolism and induce AMPK-dependent autophagy in pancreatic cancer cells. *Cell Death & Disease, 4*, e664.

De Petrocellis, L., Ligresti, A., Schiano Moriello, A., Iappelli, M., Verde, R., Stott, C.G., ... Di Marzo, V. (2013). Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. *British Journal of Pharmacology, 168*(1), 79–102.

Degenhardt, L., Lintzeris, N., Campbell, G., Bruno, R., Cohen, M., Farrell, M., & Hall, W.D. (2015). Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. *Drug and Alcohol Dependence, 147*, 144–150.

Elikkottil, J., Gupta, P., & Gupta, K. (2009). The analgesic potential of cannabinoids. *Journal of Opioid Management, 5*(6), 341–357.

Esposito, G., Filippis, D.D., Cirillo, C., Iuvone, T., Capoccia, E., Scuderi, C., ... Steardo, L. (2013). Cannabidiol in inflammatory bowel diseases: a brief overview. *Phytotherapy Research, 27*(5), 633–636.

Fagan, S.G., & Campbell, V.A. (2014). The influence of cannabinoids on generic traits of neurodegeneration. *British Journal of Pharmacology, 171*(6), 1347–1360.

Farabi, S.S., Prasad, B., Quinn, L., & Carley, D.W. (2014). Impact of dronabinol on quantitative electroencephalogram (qEEG) measures of sleep in obstructive sleep apnea syndrome. *Journal of Clinical Sleep Medicine, 10*(1), 49–56.

Favrat, B., Menetrey, A., Augsburger, M., Rothuizen, L.E., Appenzeller, M., Buclin, T., ... Giroud, C. (2005). Two cases of "cannabis acute psychosis" following the administration of oral cannabis. *BMC Psychiatry, 5*, 17.

Fine, P.G., & Rosenfeld, M.J. (2014). Cannabinoids for neuropathic pain. *Current Pain and Headache Reports, 18*(10), 451.

Flach, A.J. (2002). Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. *Transactions of the American Ophthalmological Society, 100*, 215–222; discussion 222–214.

Flachenecker, P., Henze, T., & Zettl, U.K. (2014). Long-term effectiveness and safety of nabiximols (tetrahydrocannabinol/cannabidiol oromucosal spray) in clinical practice. *European Neurology, 72*(1–2), 95–102.

Fowler, C.J. (2015). Delta(9)-tetrahydrocannabinol and cannabidiol as potential curative agents for cancer: A critical examination of the preclinical literature. *Clinical Pharmacology and Therapeutics, 97*(6), 587–596.

Franz, C.A., & Frishman, W.H. (2016). Marijuana use and cardiovascular disease. *Cardiology in Review, 24*(4), 158–162.

Fraser, G.A. (2009). The use of a synthetic cannabinoid in the management of treatment-resistant nightmares in posttraumatic stress disorder (PTSD). *CNS Neuroscience & Therapeutics, 15*(1), 84–88.

Freimuth, N., Ramer, R., & Hinz, B. (2010). Antitumorigenic effects of cannabinoids beyond apoptosis. *Journal of Pharmacology and Experimental Therapeutics, 332*(2), 336–344.

Friedman, D., & Devinsky, O. (2015). Cannabinoids in the treatment of epilepsy. *New England Journal of Medicine, 373*(11), 1048–1058.

Fukuda, S., Kohsaka, H., Takayasu, A., Yokoyama, W., Miyabe, C., Miyabe, Y., ... Nanki, T. (2014). Cannabinoid receptor 2 as a potential therapeutic target in rheumatoid arthritis. *BMC Musculoskeletal Disorders, 15*, 275.

Gaoni, Y., & Mechoulam, R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society, 86*(8), 1646–1647.

Geffrey, A.L., Pollack, S.F., Bruno, P.L., & Thiele, E.A. (2015). Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia, 56*(8), 1246–1251.

George, T., & Vaccarino, F. (2015). *The effects of cannabis use during adolescence.* Ottawa, Ont.: Canadian Centre on Substance Abuse.

Government of Canada. (2010). *Marihuana Medical Access Regulations.* Ottawa, Ont.: Author. Retrieved from lois-laws.justice.gc.ca/PDF/SOR-2001-227.pdf.

Government of Canada. (2014). *Marihuana for Medical Purposes Regulations.* Ottawa, Ont.: Author. Retrieved from www.laws-lois.justice.gc.ca/eng/regulations/SOR-2013-119/.

Green, K. (1998). Marijuana smoking vs cannabinoids for glaucoma therapy. *Archives of Ophthalmology, 116*(11), 1433–1437.

Greer, G.R., Grob, C.S., & Halberstadt, A.L. (2014). PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *Journal of Psychoactive Drugs, 46*(1), 73–77.

Guzman, M., Duarte, M.J., Blazquez, C., Ravina, J., Rosa, M.C., Galve-Roperh, I., ... Gonzalez-Feria, L. (2006). A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *British Journal of Cancer, 95*(2), 197–203.

Hackam, D.G. (2015). Cannabis and stroke: systematic appraisal of case reports. *Stroke, 46*(3), 852–856.

Hall, W.D., & Swift, W. (2006). The policy implications of cannabis dependence. In R. A. Roffman & R. S. Stephens (Eds.), *Cannabis dependence: its nature, consequences and treatment* (pp. 315–339). UK: Cambridge University Press.

Harvey, B.S., Sia, T.C., Wattchow, D.A., & Smid, S.D. (2014). Interleukin 17A evoked mucosal damage is attenuated by cannabidiol and anandamide in a human colonic explant model. *Cytokine, 65*(2), 236–244.

Haustein, M., Ramer, R., Linnebacher, M., Manda, K., & Hinz, B. (2014). Cannabinoids increase lung cancer cell lysis by lymphokine-activated killer cells via upregulation of ICAM-1. *Biochemical Pharmacology, 92*(2), 312–325.

Hazekamp, A., & Heerdink, E.R. (2013). The prevalence and incidence of medicinal cannabis on prescription in the Netherlands. *European Journal of Clinical Pharmacology, 69*(8), 1575–1580.

Health Canada. (2013a). *Information for health care professionals: cannabis (marihuana, marijuana) and the cannabinoids dried plant for administration by ingestion or other means psychoactive agent.* Ottawa, Ont.: Author. Retrieved from www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/marihuana/med/infoprof-eng.pdf.

Health Canada. (2013b). *Canadian Alcohol and Drug Use Monitoring Survey (CADUMS).* Ottawa, Ont.: Author. Retrieved from www.hc-sc.gc.ca/hc-ps/drugs-drogues/stat/_2011/summary-sommaire-eng.php.

Health Canada. (2015). *Statement on Supreme Court of Canada decision in R. v. Smith.* Ottawa, Ont.: Author. Retrieved from www.hc-sc.gc.ca/dhp-mps/marihuana/info/licencedproducer-producteurautorise/decision-r-v-smith-eng.php.

Health Canada. (2016). *Medical Use of Cannabis.* Ottawa, Ont.: Author. Retrieved from www.hc-sc.gc.ca/dhp-mps/marihuana/index-eng.php.

Hernandez, S.L., Sheyner, I., Stover, K.T., & Stewart, J.T. (2015). Dronabinol treatment of refractory nausea and vomiting related to peritoneal carcinomatosis. *American Journal of Hospice and Palliative Care, 32*(1), 5–7.

Hofmann, M.E., & Frazier, C.J. (2013). Marijuana, endocannabinoids, and epilepsy: potential and challenges for improved therapeutic intervention. *Experimental Neurology, 244*, 43–50.

Honarmand, K., Tierney, M.C., O'Connor, P., & Feinstein, A. (2011). Effects of cannabis on cognitive function in patients with multiple sclerosis. *Neurology, 76*(13), 1153–1160.

Hudak, M., Severn, D., & Nordstrom, K. (2015). Edible cannabis-induced psychosis: intoxication and beyond. *American Journal of Psychiatry, 172*(9), 911–912.

Hussain, S.A., Zhou, R., Jacobson, C., Weng, J., Cheng, E., Lay, J., ... Sankar, R. (2015). Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox-Gastaut syndrome. *Epilepsy & Behavior, 47*, 138–141.

Iannotti, F.A., Hill, C.L., Leo, A., Alhusaini, A., Soubrane, C., Mazzarella, E., ... Stephens, G.J. (2014). Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. *ACS Chemical Neuroscience, 5*(11), 1131–1141.

Ingold, J. (2014, May 21). Children's Hospital sees surge in kids accidentally eating marijuana. Denver Post. Retrieved from www.denverpost.com/2014/05/21/childrens-hospital-sees-surge-in-kids-accidentally-eating-marijuana/.

Irving, P., Iqbal, T., Nwokolo, C., Subramanian, S., Bloom, S., Prasad, N., ... Taylor, A. (2015). PTH-056 Trial to assess cannabidiol in the symptomatic treatment of ulcerative colitis. *Gut, 64*(Suppl 1), A430–A430.

Issa, M.A., Narang, S., Jamison, R.N., Michna, E., Edwards, R.R., Penetar, D.M., & Wasan, A.D. (2014). The subjective psychoactive effects of oral dronabinol studied in a randomized, controlled crossover clinical trial for pain. *Clinical Journal of Pain, 30*(6), 472–478.

Izzo, A.A., Borrelli, F., Capasso, R., Di Marzo, V., & Mechoulam, R. (2009). Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. *Trends in Pharmacological Sciences, 30*(10), 515–527.

Jawahar, R., Oh, U., Yang, S., & Lapane, K.L. (2013). A systematic review of pharmacological pain management in multiple sclerosis. *Drugs, 73*(15), 1711–1722.

Johnson, J.R., Lossignol, D., Burnell-Nugent, M., & Fallon, M.T. (2013). An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *Journal of Pain and Symptom Management, 46*(2), 207–218.

Kalant, H. (2001). Medicinal use of cannabis: history and current status. *Pain Research and Management, 6*(2), 80–91.

Kalant, H. (2008). Smoked marijuana as medicine: not much future. *Clinical Pharmacology and Therapeutics, 83*(4), 517–519.

Kalant, H. (2014). Effects of cannabis and cannabinoids in the human nervous system. In B. Madras & M. J. Kuhar (Eds.), *The effects of drug abuse on the human nervous system* (pp. 387–422). Waltham, MA: Academic Press.

Kalant, O.J. (1972). Report of the Indian Hemp Drugs Commission, 1893–94: a critical review. *International Journal of the Addictions, 7*(1), 77–96.

Karst, M., & Wippermann, S. (2009). Cannabinoids against pain. Efficacy and strategies to reduce psychoactivity: a clinical perspective. *Expert Opinion on Investigational Drugs, 18*(2), 125–133.

Karst, M., Wippermann, S., & Ahrens, J. (2010). Role of cannabinoids in the treatment of pain and (painful) spasticity. *Drugs, 70*(18), 2409–2438.

Knoller, N., Levi, L., Shoshan, I., Reichenthal, E., Razon, N., Rappaport, Z.H., & Biegon, A. (2002). Dexanabinol (HU-211) in the treatment of severe closed head injury: a randomized, placebo-controlled, phase II clinical trial. *Critical Care Medicine, 30*(3), 548–554.

Koay, L.C., Rigby, R.J., & Wright, K.L. (2014). Cannabinoid-induced autophagy regulates suppressor of cytokine signaling-3 in intestinal epithelium. *American Journal of Physiology: Gastrointestinal and Liver Physiology, 307*(2), G140–148.

Koehler, J., Feneberg, W., Meier, M., & Pollmann, W. (2014). Clinical experience with THC:CBD oromucosal spray in patients with multiple sclerosis-related spasticity. *International Journal of Neuroscience, 124*(9), 652–656.

Koppel, B.S., Brust, J.C., Fife, T., Bronstein, J., Youssof, S., Gronseth, G., & Gloss, D. (2014). Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology, 82*(17), 1556–1563.

Kunos, G. (2016). *Hybrid inhibitor of peripheral CB_1 receptors and iNOS for the treatment of liver fibrosis. Report to Meeting of the NIAAA Advisory Council.* Retrieved from drive.google.com/file/d/0B-vqvlcdExm3S1NTN3pRTlk2N3c/view?pref=2&pli=1.

Kwiatkowska, M., Parker, L.A., Burton, P., & Mechoulam, R. (2004). A comparative analysis of the potential of cannabinoids and ondansetron to suppress cisplatin-induced emesis in the Suncus murinus (house musk shrew). *Psychopharmacology, 174*(2), 254–259.

Langford, R.M., Mares, J., Novotna, A., Vachova, M., Novakova, I., Notcutt, W., & Ratcliffe, S. (2013). A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. *Journal of Neurology, 260*(4), 984–997.

Large, M., Sharma, S., Compton, M.T., Slade, T., & Nielssen, O. (2011). Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Archives of General Psychiatry, 68*(6), 555–561.

Lau, B.K., & Vaughan, C.W. (2014). Targeting the endogenous cannabinoid system to treat neuropathic pain. *Frontiers in Pharmacology, 5*, 28.

Le Foll, B., Trigo, J.M., Sharkey, K.A., & Le Strat, Y. (2013). Cannabis and delta9-tetrahydrocannabinol (THC) for weight loss? *Medical Hypotheses, 80*(5), 564–567.

Leweke, F.M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C.W., Hoyer, C., ... Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry, 2*, e94.

Lichtman, A.H., Blankman, J.L., & Cravatt, B.F. (2010). Endocannabinoid overload. *Molecular Pharmacology, 78*(6), 993–995.

Liput, D.J., Hammell, D.C., Stinchcomb, A.L., & Nixon, K. (2013). Transdermal delivery of cannabidiol attenuates binge alcohol-induced neurodegeneration in a rodent model of an alcohol use disorder. *Pharmacology, Biochemistry and Behavior, 111*, 120–127.

Lorente Fernandez, L., Monte Boquet, E., Perez-Miralles, F., Gil Gomez, I., Escutia Roig, M., Bosca Blasco, I., ... Casanova-Estruch, B. (2014). Clinical experiences with cannabinoids in spasticity management in multiple sclerosis. *Neurologia, 29*(5), 257–260.

Lynch, M.E., & Campbell, F. (2011). Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. *British Journal of Clinical Pharmacology, 72*(5), 735–744.

Machado Rocha, F.C., Stefano, S.C., De Cassia Haiek, R., Rosa Oliveira, L.M., & Da Silveira, D.X. (2008). Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. *European Journal of Cancer Care (English Language Edition), 17*(5), 431–443.

Macpherson, T., Armstrong, J.A., Criddle, D.N., & Wright, K.L. (2014). Physiological intestinal oxygen modulates the Caco-2 cell model and increases sensitivity to the phytocannabinoid cannabidiol. *In Vitro Cellular and Developmental Biology: Animal, 50*(5), 417–426.

Madras, B.K. (2015). *Update of cannabis and its medical use*. Paper presented at the 37th meeting of the Expert Committee on Drug Dependence. Retrieved from www.who.int/medicines/access/controlled-substances/6_2_cannabis_update.pdf.

Martin-Sanchez, E., Furukawa, T.A., Taylor, J., & Martin, J.L. (2009). Systematic review and meta-analysis of cannabis treatment for chronic pain. *Pain Medicine, 10*(8), 1353–1368.

Massi, P., Solinas, M., Cinquina, V., & Parolaro, D. (2013). Cannabidiol as potential anticancer drug. *British Journal of Clinical Pharmacology, 75*(2), 303–312.

McGeeney, B.E. (2013). Cannabinoids and hallucinogens for headache. *Headache, 53*(3), 447–458.

McInnis, O.A., & Plecas, D. (2016). *Clearing the smoke on cannabis: Respiratory effects of cannabis smoking—An update.* Ottawa, Ont.: Canadian Centre on Substance Abuse.

McInnis, O.A., & Porath-Waller, A.J. (2016). *Clearing the smoke on cannabis: Chronic use and cognitive functioning and mental health—An Update.* Ottawa, Ont.: Canadian Centre on Substance Abuse.

Mechoulam, R., & Parker, L.A. (2013). The endocannabinoid system and the brain. *Annual Review of Psychology, 64*, 21–47.

Metz, T.D., & Stickrath, E.H. (2015). Marijuana use in pregnancy and lactation: a review of the evidence. *American Journal of Obstetrics and Gynecology, 213*(6), 761–778.

Meye, F.J., Trezza, V., Vanderschuren, L.J., Ramakers, G.M., & Adan, R.A. (2013). Neutral antagonism at the cannabinoid 1 receptor: a safer treatment for obesity. *Molecular Psychiatry, 18*(12), 1294–1301.

Micale, V., Di Marzo, V., Sulcova, A., Wotjak, C.T., & Drago, F. (2013). Endocannabinoid system and mood disorders: priming a target for new therapies. *Pharmacology and Therapeutics, 138*(1), 18–37.

Muller-Vahl, K.R. (2013). Treatment of Tourette syndrome with cannabinoids. *Behavioural Neurology, 27*(1), 119–124.

Naftali, T., Bar-Lev Schleider, L., Dotan, I., Lansky, E.P., Sklerovsky Benjaminov, F., & Konikoff, F.M. (2013). Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clinical Gastroenterology and Hepatology, 11*(10), 1276–1280.e1.

Narang, S., Gibson, D., Wasan, A.D., Ross, E.L., Michna, E., Nedeljkovic, S.S., & Jamison, R.N. (2008). Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *Journal of Pain, 9*(3), 254–264.

Noyes, R., Jr., Brunk, S.F., Avery, D.A., & Canter, A.C. (1975). The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics, 18*(1), 84–89.

O'Shaughnessy, W. (1843). On the preparations of the Indian hemp, or gunjah: Cannabis indica their effects on the animal system in health, and their utility in the treatment of tetanus and other convulsive diseases. *Provincial Medical Journal and Retrospect of the Medical Sciences, 5*(123), 363–369.

Ogborne, A.C., Smart, R.G., & Adlaf, E.M. (2000). Self-reported medical use of marijuana: a survey of the general population. *Canadian Medical Association Journal, 162*(12), 1685–1686.

Olah, A., Toth, B.I., Borbiro, I., Sugawara, K., Szollosi, A.G., Czifra, G., ... Biro, T. (2014). Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. *Journal of Clinical Investigation, 124*(9), 3713–3724.

Pacher, P., Batkai, S., & Kunos, G. (2006). The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacological Reviews, 58*(3), 389–462.

Pacula, R.L., Jacobson, M., & Maksabedian, E.J. (2016). In the weeds: a baseline view of cannabis use among legalizing states and their neighbours. *Addiction, 111*(6), 973–980.

Pagano, E., Montanaro, V., Di Girolamo, A., Pistone, A., Altieri, V., Zjawiony, J.K., ... Capasso, R. (2015). Effect of non-psychotropic plant-derived cannabinoids on bladder contractility: focus on cannabigerol. *Natural Product Communications, 10*(6), 1009–1012.

Papini, S., Sullivan, G.M., Hien, D.A., Shvil, E., & Neria, Y. (2015). Toward a translational approach to targeting the endocannabinoid system in posttraumatic stress disorder: a critical review of preclinical research. *Biological Psychology, 104*, 8–18.

Pertwee, R.G., Howlett, A.C., Abood, M.E., Alexander, S.P., Di Marzo, V., Elphick, M.R., ... Ross, R.A. (2010). International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid receptors and their ligands: beyond CB(1) and CB(2). *Pharmacological Reviews, 62*(4), 588–631.

Plowright, A.T., Nilsson, K., Antonsson, M., Amin, K., Broddefalk, J., Jensen, J., ... Ulander, J. (2013). Discovery of agonists of cannabinoid receptor 1 with restricted central nervous system penetration aimed for treatment of gastroesophageal reflux disease. *Journal of Medicinal Chemistry, 56*(1), 220–240.

Porath-Waller, A.J. (2015). *Clearing the smoke on cannabis: Maternal cannabis use during pregnancy—An update.* Ottawa, Ont.: Canadian Centre on Substance Abuse.

Porter, B.E., & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy & Behavior, 29*(3), 574–577.

Press, C.A., Knupp, K.G., & Chapman, K.E. (2015). Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. *Epilepsy & Behavior, 45*, 49–52.

Prud'homme, M., Cata, R., & Jutras-Aswad, D. (2015). Cannabidiol as an intervention for addictive behaviors: a systematic review of the evidence. *Substance Abuse, 9*, 33–38.

Rabinak, C.A., Angstadt, M., Sripada, C.S., Abelson, J.L., Liberzon, I., Milad, M.R., & Phan, K.L. (2013). Cannabinoid facilitation of fear extinction memory recall in humans. *Neuropharmacology, 64*, 396–402.

Raft, D., Gregg, J., Ghia, J., & Harris, L. (1977). Effects of intravenous tetrahydrocannabinol on experimental and surgical pain. Psychological correlates of the analgesic response. *Clinical Pharmacology and Therapeutics, 21*(1), 26–33.

Ramer, R., & Hinz, B. (2015). New insights into antimetastatic and antiangiogenic effects of cannabinoids. *International Review of Cell and Molecular Biology, 314*, 43–116.

Ramirez, S.H., Reichenbach, N.L., Fan, S., Rom, S., Merkel, S.F., Wang, X., ... Persidsky, Y. (2013). Attenuation of HIV-1 replication in macrophages by cannabinoid receptor 2 agonists. *Journal of Leukocyte Biology, 93*(5), 801–810.

Reid, P.T., Macleod, J., & Robertson, J.R. (2010). Cannabis and the lung. *Journal of the Royal College of Physicians of Edinburgh, 40*(4), 328–323; quiz 333–324.

Reynolds, T.D., & Osborn, H.L. (2013). The use of cannabinoids in chronic pain. *British Medical Journal Case Reports, 2013*.

Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, open-label, pilot study of add-on oral delta9-tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical Drug Investigation, 34*(8), 587–591.

Saade, D., & Joshi, C. (2015). Pure cannabidiol in the treatment of malignant migrating partial seizures in infancy: a case report. *Pediatric Neurology, 52*(5), 544–547.

Sarfaraz, S., Afaq, F., Adhami, V.M., & Mukhtar, H. (2005). Cannabinoid receptor as a novel target for the treatment of prostate cancer. *Cancer Research, 65*(5), 1635–1641.

Saxon, A.J., & Browne, K.W. (2014). Marijuana not ready for prime time as an analgesic. *General Hospital Psychiatry, 36*(1), 4–6.

Schubart, C.D., Sommer, I.E., Fusar-Poli, P., de Witte, L., Kahn, R.S., & Boks, M.P. (2014). Cannabidiol as a potential treatment for psychosis. *European Neuropsychopharmacology, 24*(1), 51–64.

Scuderi, C., Filippis, D.D., Iuvone, T., Blasio, A., Steardo, A., & Esposito, G. (2009). Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders. *Phytotherapy Research, 23*(5), 597–602.

Serpell, M., Ratcliffe, S., Hovorka, J., Schofield, M., Taylor, L., Lauder, H., & Ehler, E. (2014). A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *European Journal of Pain, 18*(7), 999–1012.

Serpell, M.G., Notcutt, W., & Collin, C. (2013). Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. *Journal of Neurology, 260*(1), 285–295.

Sharkey, K.A., Darmani, N.A., & Parker, L.A. (2014). Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. *European Journal of Pharmacology, 722*, 134–146.

Silva, T.B., Balbino, C.Q., & Weiber, A.F. (2015). The relationship between cannabidiol and psychosis: a review. *Annals of Clinical Psychiatry, 27*(2), 134–141.

Soderpalm, A.H., Schuster, A., & de Wit, H. (2001). Antiemetic efficacy of smoked marijuana: subjective and behavioral effects on nausea induced by syrup of ipecac. *Pharmacology, Biochemistry and Behavior, 69*(3–4), 343–350.

Sofia, R.D., Vassar, H.B., & Knobloch, L.C. (1975). Comparative analgesic activity of various naturally occurring cannabinoids in mice and rats. *Psychopharmacologia, 40*(4), 285–295.

Solowij, N., Broyd, S.J., van Hell, H.H., & Hazekamp, A. (2014). A protocol for the delivery of cannabidiol (CBD) and combined CBD and 9-tetrahydrocannabinol (THC) by vaporisation. *BMC Pharmacology and Toxicology, 15*, 58.

Stanley, C.P., Hind, W.H., & O'Sullivan, S.E. (2013). Is the cardiovascular system a therapeutic target for cannabidiol? *British Journal of Clinical Pharmacology, 75*(2), 313–322.

Statistics Canada. (2015). *Canadian Tobacco, Alcohol and Drugs Survey: Summary of results for 2013.* Ottawa, Ont.: Author.

Stinchcomb, A.L., Valiveti, S., Hammell, D.C., & Ramsey, D.R. (2004). Human skin permeation of delta8-tetrahydrocannabinol, cannabidiol and cannabinol. *Journal of Pharmacy and Pharmacology, 56*(3), 291–297.

Stott, C.G., White, L., Wright, S., Wilbraham, D., & Guy, G.W. (2013). A phase I study to assess the effect of food on the single dose bioavailability of the THC/CBD oromucosal spray. *European Journal of Clinical Pharmacology, 69*(4), 825–834.

Vemuri, V.K., & Makriyannis, A. (2015). Medicinal chemistry of cannabinoids. *Clinical Pharmacology and Therapeutics, 97*(6), 553–558.

Wallace, M.S., Marcotte, T.D., Umlauf, A., Gouaux, B., & Atkinson, J.H. (2015). Efficacy of inhaled cannabis on painful diabetic neuropathy. *Journal of Pain, 16*(7), 616–627.

Wang, T., Collet, J.P., Shapiro, S., & Ware, M.A. (2008). Adverse effects of medical cannabinoids: a systematic review. *Canadian Medical Association Journal, 178*(13), 1669–1678.

Ware, M.A., & St. Arnaud-Trempe, E. (2010). The abuse potential of the synthetic cannabinoid nabilone. *Addiction, 105*(3), 494–503.

Ware, M.A., Wang, T., Shapiro, S., & Collet, J.P. (2015). Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS). *Journal of Pain, 16*(12), 1233–1242.

Ware, M.A., Wang, T., Shapiro, S., Robinson, A., Ducruet, T., Huynh, T., ... Collet, J.P. (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *Canadian Medical Association Journal, 182*(14), E694–E701.

Wilhelmsen, K., Khakpour, S., Tran, A., Sheehan, K., Schumacher, M., Xu, F., & Hellman, J. (2014). The endocannabinoid/endovanilloid N-arachidonoyl dopamine (NADA) and synthetic cannabinoid WIN55, 212-2 abate the inflammatory activation of human endothelial cells. *Journal of Biological Chemistry, 289*(19), 13079–13100.

Williams, J.C., Appelberg, S., Goldberger, B.A., Klein, T.W., Sleasman, J.W., & Goodenow, M.M. (2014). Delta(9)-tetrahydrocannabinol treatment during human monocyte differentiation reduces macrophage susceptibility to HIV-1 infection. *Journal of Neuroimmune Pharmacology, 9*(3), 369–379.

Wilsey, B., Marcotte, T., Deutsch, R., Gouaux, B., Sakai, S., & Donaghe, H. (2013). Low-dose vaporized cannabis significantly improves neuropathic pain. *Journal of Pain, 14*(2), 136–148.

Zajicek, J., Ball, S., Wright, D., Vickery, J., Nunn, A., Miller, D., ... Hobart, J. (2013). Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial. *Lancet Neurology, 12*(9), 857–865.

Zajicek, J.P., & Apostu, V.I. (2011). Role of cannabinoids in multiple sclerosis. *CNS Drugs, 25*(3), 187–201.

Ziemianski, D., Capler, R., Tekanoff, R., Lacasse, A., Luconi, F., & Ware, M.A. (2015). Cannabis in medicine: a national educational needs assessment among Canadian physicians. *BMC Medical Education, 15*, 52.

Zogopoulos, P., Korkolopoulou, P., Patsouris, E., & Theocharis, S. (2015). The antitumor action of cannabinoids on glioma tumorigenesis. *Histology and Histopathology, 30*(6), 629–645.

Acknowledgements

Chad Dubeau provided valuable assistance in gathering literature for this review. The authors wish to acknowledge the reviewers for helpful comments on this version, as well as an earlier version, of this report. Production of this document has been made possible through a financial contribution from Health Canada. The views expressed herein do not necessarily represent the views of Health Canada.

ISBN 978-1-77178-363-7