

# Clearing the Smoke on Cannabis

## Medical Use of Cannabis and Cannabinoids

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### Background

Cannabis is the most widely used illicit drug in Canada. According to the 2010 Canadian Alcohol and Drug Use Monitoring Survey, 10.7 percent of Canadians aged 15 years and older reported using cannabis in the past year (Health Canada, 2011). A growing body of evidence suggests that using cannabis may negatively impact several aspects of people's lives, including mental and physical health, cognitive functioning, the ability to drive a motor vehicle, and pre- and postnatal development among offspring. However, cannabis and some of its derivatives also have a long history of use as a medicine in many parts of the world. A very thorough and extensively referenced monograph on this subject, suitable for medically or scientifically trained readers, has been published by Health Canada (Health Canada, 2010).

Two general population surveys have asked Canadians about their self-reported use of cannabis for medical purposes. The results from a 1998 survey in Ontario revealed that in the year preceding the survey, 1.9 percent of adults aged 18 years and older reported using cannabis for a medical reason, compared to 6.8 percent reporting non-medical use (Ogborne et al., 2000). According to results from the 2004 Canadian Addiction Survey, of the 14 percent of Canadians aged 15 years and older who reported using cannabis in the past year, 29 percent indicated that they used cannabis, marijuana or hashish to treat pain, nausea, glaucoma, multiple sclerosis, depression or another medical condition in the previous 12 months (Adlaf et al., 2005).

This report—the fifth in a series reviewing the effects of cannabis use on various aspects of human functioning and development (Beirness & Porath-Waller, 2009; Diplock & Plecas, 2009; Porath-Waller, 2009a,b)—examines the research on the medical use of cannabis and cannabinoids.



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*This is the fifth in a series of reports that reviews the effects of cannabis use on various aspects of human functioning and development. In this report, the medical use of cannabis and cannabinoids are presented. 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.*



## History of 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 (1839) 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 due to its unreliability resulting from the variable composition of the extracts and their limited shelf life. As a result, 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 anticonvulsants. When cannabis was made illegal in many countries, this move provoked relatively little opposition because the drug had largely fallen out of use years earlier.

The revival of interest in cannabis in Western countries in the 1970s was related principally to its nonmedical use by young people to produce euphoria and facilitate social interaction. However, as scientific interest revived, the exploration of its potential therapeutic uses was renewed.

## Cannabinoids

The major pharmacologically active elements of cannabis (called 'cannabinoids') had been isolated, chemically identified and synthesized by the 1960s. Since the early 1990s there has been a rapid advance in knowledge of how and where in the body these cannabinoids have an effect. 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 more than 460 known chemicals, more than 60 of which are grouped under the name cannabinoids (Ben Amar, 2006). Cannabinoids are a group of compounds that share a common chemical structure that was first found in the cannabis plant. Some cannabinoids are natural, such as those found in the cannabis plant. One example of a natural cannabinoid is  $\Delta^9$ -tetrahydrocannabinol (THC), which is the primary psychoactive component of the cannabis

plant responsible for the high from smoking cannabis. Another natural cannabinoid is cannabidiol, which has some of the physiological actions of THC but does not produce the high that comes from smoking. Other cannabinoids are synthetic (i.e., made in a laboratory); these are functionally similar to THC. Some of these (e.g., Spice, K2) have been used recreationally and other synthetic cannabinoids, including dronabinol (Marinol®) and nabilone (Cesamet®), are used therapeutically.

Cannabis, also referred to as marihuana or marijuana, is a tobacco-like 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. More than 60 chemicals, called cannabinoids, have been identified as specific to the cannabis plant. A few of these cannabinoids account for most of the known pharmacological actions of cannabis. Cannabis produces euphoria and relaxation, 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 the acts of growing, possessing, distributing and/or selling cannabis are illegal except for those who have received ministerial permission to grow or possess it for their own medical use.

- The cannabis plant produces marijuana (cannabis herb) and hashish (cannabis resin).
- Cannabinoids are chemicals found in the cannabis plant. A few account for most of the known actions of cannabis on mental and bodily functions.
- $\Delta^9$ -tetrahydrocannabinol (THC) is thought to be the most active cannabinoid.

## 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 are the best drugs to use 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 appear to be less effective than newer anti-nauseants such as ondansetron and similar drugs (Machado Rocha et al., 2008; Soderpalm et al., 2001).

Similarly, the pain-relieving activity of cannabinoids has been demonstrated (Karst et al., 2010), though there is some evidence that it may be less effective against some types of pain than stronger opioids (Sofia et al., 1975; Raft et al., 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 psychic and emotional effects, which impaired its therapeutic usefulness (Noyes et al., 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 et al., 2009). The side effects of cannabinoids, however, are less severe than those of the stronger opioids.

It has been suggested that cannabinoids may 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 et al., 2004) and in research involving human patients (Elikottil et al., 2009; Narang et al., 2008).

## Current and Approved Uses of Cannabis and Cannabinoids as Medicine

In Canada, cannabis for medical purposes is legally accessed through the *Marihuana Medical Access Regulations* (MMARs)<sup>1</sup> (Government of Canada, 2010). Because the cannabis accessed through this program is monitored and standardized, it is less risky to use than cannabis that is obtained illegally, which may be contaminated with unknown substances. In addition, there are currently four other cannabinoid products available for medical use in Canada—more than in any other country worldwide. The forms of cannabinoids that are used or tested as medicines by physicians are mainly the following:

- Dronabinol: Synthetic THC in pill form that is marketed as Marinol®;
- Nabilone: A synthetic derivative of THC in pill form that is marketed as Cesamet®;
- Cannabidiol: Although not used medically by itself, it is a constituent of an oral spray containing equal proportions of THC and cannabidiol that is marketed as Sativex®; and
- Plant-derived THC: The primary psychoactive cannabinoid component of the cannabis plant that produces the high.

There are only a few approved therapeutic uses for these aforementioned cannabinoid products. In many countries, including Canada, they are approved to relieve and prevent nausea and vomiting caused by anticancer chemotherapy, and to stimulate appetite in AIDS patients with a severe loss of body weight. In Canada, Sativex® is also approved for the relief of 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. In addition to these cannabinoid products, levonantradol, which can be given by injection or orally, is a very potent cannabinoid that exhibits anti-nausea and pain-relieving effects. Although levonantradol is available in some countries, it is not currently approved in Canada, the United States or Western Europe.

<sup>1</sup> The term *marihuana*, rather than *cannabis*, is used in Health Canada's *Marihuana Medical Access Regulations*. The term *marijuana* is the common way of spelling this drug for non-medical use.



## Adverse Effects

There is a lack of research documenting the risks associated with the medical use of cannabis, making it challenging for physicians to comply with the provision in the MMARs requiring them to discuss the risks associated with this therapy with their patients (Government of Canada, 2010). 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 et al., 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 associated with the smoking of cannabis such as respiratory effects.

A recent cross-sectional study examining the effects of inhaled or ingested cannabis on cognitive functioning in patients with multiple sclerosis revealed that cannabis users performed significantly poorer than nonusers on measures of information-processing speed, working memory, executive functioning and visuospatial perception (Honarmand et al., 2011). Thus, subjective benefits from smoking cannabis reported by patients need to be weighed against the associated adverse effect of cognitive impairment.

Studies of recreational cannabis users provide some indication of the health risks that may result from smoking cannabis over the long term, including neurocognitive deficits (Crean et al., 2011; Porath-Waller, 2009a), psychosis (Large et al., 2011; Porath-Waller, 2009a), various respiratory ailments and possibly cancer (Diplock & Plecas, 2009; Reid et al., 2010). There remains a need for follow-up studies examining the long-term health effects of the medical use of cannabinoids and smoked cannabis.

No research to date has investigated the risks of incident cannabis dependence 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 et al., 1998; Ware & St. Arnaud-Trempe, 2010). The

evidence on the risk factors for cannabis dependence comes primarily from studies of recreational cannabis users who began using the substance in adolescence and early adulthood and who use the most potent products. These users smoke cannabis with a greater frequency and intensity than older adults, who would presumably use smaller doses for symptom relief (Hall & Swift, 2006).

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). If cannabis is obtained through illegal means, it can lack quality control and standardization and/or be contaminated with pesticides and microbes. In addition, the regular use of cannabis by smoking can cause chronic respiratory irritation (Kalant, 2008; Diplock & Plecas, 2009).

Given the impairing effects of cannabis on driving (Beirness & Porath-Waller, 2009), physicians should also advise their patients to refrain from operating a motor vehicle while under the influence of cannabis.

## Access to Medical Marijuana in Canada

Created in response to an Ontario court decision, the (MMARs) allow access to marijuana for Canadians suffering from grave or debilitating illnesses when conventional treatments are inappropriate or fail to provide adequate relief. A medical practitioner must support an individual's application to possess marijuana. It is important to note that physicians do not prescribe the use of medical marijuana for their patients; they simply certify that patients have medical complaints that might benefit from the use of marijuana. It is also important to emphasize that the MMARs do not address the issue of legalizing marijuana for general consumption.

According to recent statistics from Health Canada (Bureau of Medical Cannabis, Health Canada; personal communication, December 22, 2011), 12,225 Canadians are authorized under the MMARs to possess dried marijuana, with the majority residing in British Columbia (4,798) and Ontario (4,312). Of the 36,199

family physicians and 33,869 medical and surgical specialists practising medicine in Canada (Canadian Medical Association, January 2011), 4,177 physicians supported patients' applications to possess marijuana for medical purposes (Bureau of Medical Cannabis, Health Canada; personal communication, December 22, 2011).

## Proposed Medical Uses of Cannabinoids in Managing Diseases

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 cannabinoids. In this case, the evidence of efficacy for the latter is much less clear.

### Multiple sclerosis

Numerous claims have been made for a beneficial effect on the symptoms of multiple sclerosis, especially for the relief of pain and spasticity. However, many of these claims are self-reports and are not accompanied by any independent scientific verification (Aggarwal et al., 2009). A number of controlled clinical trials have reported beneficial effects of smoked cannabis and/or cannabinoids in multiple sclerosis, but the findings are inconsistent with respect to the effects on spasticity. In most instances the patients reported subjective relief of the sensations of pain and spasm, but objective measures of spasticity did not reveal any significant improvement (Centonze et al., 2009; Thaera et al., 2009; Lakhan & Rowland, 2009; Zajicek & Apostu, 2011). The reason for this discrepancy of findings is not yet clear, but it is possible that the patients who experience relief of spasm-related pain confuse it with relief of the spasm itself.

### Cancer

Although the anticancer effect of cannabinoids has been intensively studied in cell cultures (test-tube studies) and in animals with tumours, no firm conclusions are yet possible. It has been confirmed repeatedly that various cannabinoids, binding to both of the known types of cannabinoid receptor, can retard or prevent the growth of cancer cells as well as their ability to invade surrounding normal tissues and metastasize (i.e., give rise to colonies of cancer cells at distant sites in many

different tissues). It has also been suggested that some actions of endocannabinoids (substances found naturally in the body that have actions similar to those of THC) may reduce the risk that mutations will give rise to cancer cells (Alexander et al., 2009; Freimuth et al., 2010). 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. (More on endocannabinoids on p. 6.)

Only one small, uncontrolled clinical trial has been carried out in humans, where THC was injected directly into the cancers of nine patients when recurrent brain cancers were first detected. Although there was an initial relief of symptoms, the THC treatment was not able to cure the cancer or slow the rate of 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 may relate to the doses or concentrations of cannabinoid used in the studies. For example, in one study with prostate cancer cell cultures (Sarfaraz et al., 2005), a 50 percent 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.

### Glaucoma

Consistent with the dosing challenge noted above in treating 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 continuously reduce the intraocular pressure. 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 unwanted psychoactive effects (Green, 1998; Flach, 2002).

### Treatment of Symptoms Versus Treatment of Disease

In the past two decades there has been a rapid advance in the knowledge of the endocannabinoid systems. Endocannabinoids are cannabinoid-like substances produced by the body and act on the brain and nervous system and many other tissues by binding to specific cell sites called receptors. Endocannabinoids decrease a wide variety of symptoms caused by overactivity of different parts of the nervous system, including anxiety, agitation, convulsive activity, hypertension and nausea. They play a similar role in the immune system, where they suppress inflammatory and immune responses. Plant cannabinoids (such as THC) bind to the same receptors and thus mimic the actions of the endocannabinoids. Thus, cannabinoids have the potential for alleviating a wide range of different symptoms of disease; many of these possible therapeutic effects are currently being studied in the laboratory.

In a considerably smaller number of instances, cannabinoids might theoretically influence the disease process itself, rather than merely its symptoms. The anticancer effect discussed previously is one possible example. Another is the so-called ‘neuroprotective’ effect. Nerve cells are more vulnerable to damage caused by lack of oxygen or by the action of certain toxic substances 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. This neuroprotective effect is being studied in animal experiments as a possible emergency treatment for strokes and other types of brain damage. The broad range of effects of cannabinoids in so many different organ systems means that any desired

- Endocannabinoids normally exist in our bodies and bind to cannabinoid receptors and activate them.
- Plant cannabinoids also bind to these same receptors and mimic the actions of endocannabinoids.

therapeutic effect has a very high probability of being accompanied by undesired side effects. Therefore, clinically useful cannabinoid therapies will most likely focus on ways to improve the selectivity of the desired effects.

### Areas for Future Research

The systematic study of the possible benefits of cannabinoid therapy combined with other drugs may well lead to better methods of clinical use. However, 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 unwanted side 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, cannabidiol has the sedative, anticonvulsant, anti-inflammatory and neuroprotective effects of THC—but not the psychoactivity—and will probably be explored more fully as a therapeutic agent (Carlini & Cunha, 1981; Scuderi et al., 2009). A number of other cannabinoids found in cannabis may offer similar possibilities (Izzo et al., 2009). 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. In the scientific exploration of other neurotransmitters (i.e., 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, may 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 unwanted 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. The recently introduced pharmaceutical preparation Sativex® is sprayed onto the oral mucosa and absorbed directly from the mouth into the 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) may be helpful to overcome the health risks associated with smoking cannabis. It seems probable that other developments of this type will be actively pursued.

## Conclusions and Implications

Based on the current available evidence, the therapeutic effectiveness of cannabis is mainly limited to the treatment of nausea/vomiting and certain types of pain. 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 may well lead to better methods of clinical use. Much of the research conducted to date has focused on other proposed therapeutic uses for cannabinoids (e.g., multiple sclerosis, cancer, glaucoma) and the results from this work are much less clear or conclusive.

It appears unlikely that cannabis will realize the full therapeutic potential implied by the endocannabinoid systems. 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 unwanted side effects. The promise lies instead 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 smoked cannabis.

An important distinction needs to be made between the risks associated with smoked cannabis and cannabinoid products that are delivered in controlled doses by nontoxic delivery systems. 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 may experience respiratory ailments.

In summary, research supports the medical use of cannabis to relieve nausea, vomiting and chronic pain, but the research is still emerging in its application to disease conditions. Future development is likely to be focused on improving the specificity of synthetic cannabinoids and their delivery by safer methods than smoking.

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