

MARIJUANA AS MEDICINE

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HEALTH CANADA'S POLICIES ON MARIJUANA PUT PATIENTS AT RISK

Health Canada is making marijuana available to an increasing number of ailing Canadians through a new regulatory agenda. Unfortunately, both of the main components of the new agenda — the research plan and the exemption plan — fail to either draw or adhere to appropriate boundaries.

This lack of boundaries is due in part to a lack of thorough knowledge about the drug — while claims and testimonials about the benefits of marijuana abound, crucial information about its active chemical components and their specific benefits remain unknown. At this point in time, we know more about the harm caused by marijuana smoke than we do about the benefits.

Numerous studies have found that marijuana smoke produces pulmonary damage similar to that produced by tobacco smoke, only more severe. Major health agencies, including Health Canada, the American National Institutes of Health, and the Institutes of Medicine, have all recognized the severity of these risks in their informational reviews.

Despite their written recognition of the health risks associated with smoking marijuana, however, Health Canada is funding clinical trials of smoked marijuana under its medical mari-

juana research plan. In fact, the plan's call for proposals explicitly states that studies of smoked marijuana will be given funding priority over studies of non-smoked cannabinoids.

Because of the health risks entailed in such research, Health Canada does stipulate that studies and trials should be restricted to, "short-term, self-limiting symptomatic conditions" (that is, conditions which should clear up relatively quickly by themselves,

participants will be warned adequately about the risks they are assuming by smoking the drug.

The lack of appropriate boundaries in the medical marijuana research plan is mirrored in the medical marijuana exemption plan. Under this plan, any patient for whom conventional treatments have failed or been deemed inappropriate can apply for an exemption to the Controlled Drug and Substances Act's prohibition on marijuana. In order for an application to be successful, the applicant's treating physician must prescribe a daily dosage and state that in the applicant's case the benefits of treatment with marijuana outweigh the risks.

This presents a number of problems for physicians. First, since marijuana has not been thoroughly tested as a medicine, most physicians are familiar neither with its potential benefits (if any), nor with the dosage required to achieve those benefits. Second, when a patient is requesting smoked marijuana, the risks associated with smoking, coupled with the lack of clinical knowledge about specific benefits, make any accurate approximation of the risk to benefit ratio of treatment impossible.

Until the contradictions and ambiguities written into Health Canada's new policies on marijuana are addressed, patients, trial participants, and physicians will all be at risk.

At this point in time, we know more about the harm caused by marijuana smoke than we do about the benefits.

such as common colds). Nonetheless, currently funded studies include trials for conditions which are neither short-term nor self-limiting. At McGill University, for example, researchers are studying the effects of smoked marijuana on patients with chronic neuropathic pain.

This is especially worrisome since the terms in which Health Canada's research plan is laid out do not guarantee that par-

MARIJUANA'S THERAPEUTIC POTENTIAL

Advocates of the medical use of marijuana and cannabinoids claim that the drugs offer significant potential in the symptomatic treatment of a wide range of conditions, including AIDS wasting syndrome, arthritis, chronic pain, epilepsy, glaucoma, multiple sclerosis, muscle spasticity, asthma, anorexia nervosa, intractable hiccoughs, and the nausea and vomiting induced by chemotherapy. Of these possible applications, the potential for marijuana and cannabinoids to provide pain relief, to control nausea and vomiting, and to stimulate the appetite, are best supported by available scientific data (TPP 2000; IOM 1999).

AIDS WASTING SYNDROME

One of the first medical applications of marijuana was appetite stimulation in AIDS patients. It has since been used for the same purpose in Cancer patients. Patients claim that smoking marijuana increases their appetite and their enjoyment of food. Dronabinol (a THC capsule) has been studied in patients with AIDS (Gorter 1994) and in patients with cancer (Nelson 1994; Plasse 1994). Both groups showed increased appetite and weight gain. Some doctors have pointed out, however, that the induced weight gain consists primarily of water and fat rather than lean body mass, and so is not as valuable to health as some might believe. They have also pointed out that the weight gain has not been shown to change mortality risk. Some patients, however, have responded by saying that the increased appetite and weight gain are helpful psychologically, if not physically (NIH 1997).

NAUSEA & VOMITING

Many patients claim that marijuana can help to control nausea and vomiting, particularly that caused by chemotherapy. Several studies

have tested this hypothesis. One study of dronabinol found the drug to be superior to placebo in controlling chemotherapy-induced nausea and vomiting (Sallan 1975) another, which compared dronabinol and smoked marijuana, found dronabinol to be more popular with patients (Levitt 1984); and another, which studied smoked marijuana, found it to be moderately effective, but with a high incidence of side effects (Vinciguerra 1998). Based on these studies, marijuana does seem to have the potential to relieve nausea and vomiting in some patients. However, its high rate of side effects may limit its usefulness, especially in light of the high rate of efficacy and low rate of side effects of other currently available treatments (IGAR 1995; Kris 1996).

PAIN

Patients claim that marijuana can relieve several types of pain. This claim is backed up by some scientific belief: since cannabinoids are thought to work by a different mechanism than opioids or nonsteroidal anti-inflammatory drugs (NSAIDs), they have the potential to relieve pain that is resistant to other available treatments. To date, studies have explored marijuana's potential in relieving pain caused by cancer, pain caused by paraplegia, pain caused by muscle spasticity, and neurologic pain. Some studies and several surveys have reported at least moderate success (Noyes 1975; Consroe 1997; Dunn 1974; Staquet 1978). In all cases, however, marijuana's side effects have proven problematic. Sedation, mental clouding, mental impairment, and anxiety are all side effects that are frequently reported to be debilitating. Further, these side effects may be essential to relief: some experimental subjects have reported that while their level of pain remains the same with marijuana treatment, it simply bothers them less.

NEUROLOGICAL & MOVEMENT DISORDERS

Patients claim that marijuana has antispasticity, analgesic, anti-tremor, and anti-ataxia effects. In particular, patients have reported that the spasticity and nocturnal spasms produced by MS and partial spinal cord injury can be relieved to some extent by smoked marijuana and oral THC (NIH 1997; IOM 1999). No large-scale controlled studies have yet been performed to compare marijuana or its constituents with other available therapies for these conditions (NIH 1997; IOM 1999). Animal experiments, however, have shown some promise. The convulsions associated with various models of epilepsy, for example, have been controlled in animals by marijuana. There is also evidence that cannabidiol (CBD), a naturally occurring cannabinoid without psychoactive properties, is particularly effective in controlling epileptic seizures (Consroe 1986). In 1980, a double-blind study was conducted to test the effects of CBD on human epileptic patients. The study found the drug to be considerably effective when used in combination with conventional anti-epileptic drugs (Cunha 1980). Despite this, there has been no further study of CBD for this application.

GLAUCOMA

Some patients claim that marijuana can cure glaucoma. Indeed, it has been shown to reduce intraocular pressure. However, in order to keep pressure down, a patient must take marijuana every two to four hours. Furthermore, there is no evidence that it can reduce intraocular pressure enough to prevent optic nerve damage. These considerations, along with the fact that the other available treatments work well with minimal side effects, have led glaucoma researchers to largely abandon hope for effective treatment of glaucoma with marijuana (AAO 1992; Hepler 1971).

MARIJUANA & SMOKE

Numerous studies have been performed since the 1970s to assess the effects of marijuana smoke on the lungs. They have consistently found that marijuana smoke produces pulmonary damage similar to that produced by tobacco smoke, only more severe (Wu *et al* 1988; Tashkin *et al* 1976; Fehr 1983; IOM 1999; Kalant 1999). This is attributed in part to marijuana's constitution and content:

- marijuana produces 50% more tar than the same weight of strong tobacco (Wu *et al* 1988; Fehr 1980; Rickert 1982)
- marijuana smoke contains 70% more benzopyrene than tobacco smoke from American cigarettes (Novotny *et al* 1976; Fehr 1983);

and in part to the way in which marijuana is smoked compared to the way in which tobacco is smoked:

- marijuana tends to be smoked with a two-thirds larger puff volume, a one-third greater depth of inhalation, and a fourfold longer breath-holding time than tobacco (Wu *et al* 1988).

The cumulative effect of the content of marijuana and the method by which it is smoked, is that, by volume, smoke from marijuana is more damaging than tobacco smoke:

- smoking two to three marijuana cigarettes a day is widely estimated to have the same effect on the risk of cancers and on the prevalence of acute and chronic respiratory symptoms as smoking 20 or more tobacco cigarettes a day (Wu *et al* 1988; Tashkin 1980; Fehr 1983).

Smoking marijuana is strongly associated with chronic bronchitis, is considered very likely to cause cancers of the respiratory system, and is believed to damage the alveolar macrophages (self-cleansing and self-protecting mechanisms of the lungs), making regular marijuana smokers more prone to bacterial lung and bronchial infections (Wu *et al* 1988; Tashkin *et al* 1976; Fehr 1980;

Fehr 1983; IOM 1982; IOM 1999). One recent study also found that THC promoted tumour growth in mice by impairing the body's anti-tumour immunity system (Zhu 2000).

SAFER METHODS OF DELIVERY

Given the health risks associated with smoking, many people have experimented with alternate methods of delivering the desired effects of marijuana (for both recreational and medicinal purposes). The most popular lay versions of this involve ingesting the plant, either in tea or in baking. Pharmaceutical companies have investigated alternate methods of delivery as well, and to this end are developing products such as transdermal patches, sublingual sprays, smokeless inhalers, and ingestible capsules (Wood 2000; Gieringer 2001; GW 2001). Two ingestible THC capsules, dronabinol and nabilone, are currently available on the Canadian market.

The main criticism of these methods is that they deliver the desired effects slowly and with a significant delay in onset, whereas smoked marijuana delivers effects rapidly (usually within ten minutes). Other criticisms include ineffectiveness, increased side-effects, and difficulty controlling dosage (NIH 1997).

The development of effective means of delivering the desired effects of marijuana without smoke is also hindered by the lack of knowledge of the exact chemical components that produce particular effects. More than 60 different cannabinoids and over 400 active components have been identified in samples of marijuana (BMA 1997; Turner 1980). Although THC is generally considered the most significant of these, it is not clear that THC alone produces the desired effects (TTP 2000; Hubbard 1999). In the case of marijuana's potential to control epileptic seizures, for example, CBD appears to be the primarily effective compound, rather than THC (Kalant 1999).

RECENT EVENTS

December 1997

Supreme Court of Ontario rules that Terrence Parker, a severe epileptic, has the right to cultivate and possess marijuana for medicinal use. The court orders a medical exemption to be read into the Controlled Drugs & Substances Act (CDSA).

May 1999

Health Canada establishes procedures to allow Canadians to apply for exemptions to the CDSA to possess and cultivate marijuana for medical purposes.

June 1999

Health Canada releases a five-year research plan for evaluating the risks and benefits of marijuana for medical purposes.

October 1999

The Ontario Court of Appeal upholds the lower court's ruling in the Terrence Parker case. The court gives Parliament one year in which to either amend the law prohibiting the possession of marijuana, or lose it.

September 2000

Health Canada announces intent to regulate access to marijuana for medical purposes.

December 2000

Health Canada contracts Prairie Plant Systems Inc. of Saskatoon to provide standardized marijuana for medical and research purposes.

April 7, 2001

Draft regulations regarding medical marijuana published in Canada Gazette, Part 1.

HEALTH CANADA'S MEDICAL MARIJUANA RESEARCH PLAN

In 1999, Health Canada's Therapeutic Products Program (TPP), in association with the Canadian Institutes of Health Research (CIHR), announced a research plan for the investigation of marijuana for medical purposes. As the first phase of the plan, the CIHR put out a call for research proposals. The call is primarily for proposals that focus on the use of smoked marijuana, although the call notes that funding might, in certain circumstances, be given to those seeking to investigate other aspects of marijuana and cannabinoids, such as systems of delivery other than smoking (CIHR 1999). The call stipulates that proposals will be accepted for projects lasting between one and three years, and that trials should be restricted to "short-term, self-limiting symptomatic conditions" (TPP 2000).

Currently funded studies include a clinical trial of smoked marijuana for patients with HIV/AIDS, coordinated by the Community Research Initiative of Toronto and the HIV Trials Network (TPP 2000), and a one-year pilot study of smoked marijuana for chronic neuropathic pain to be conducted at the McGill Pain Centre (McGill 2001).

LOGISTICS

From the outset, Health Canada's medical marijuana research plan has faced several logistical concerns. Most of these have centred on the source of marijuana to be used for clinical trials. In the past, lab experiments have made use of marijuana seized in drug busts, and it was suggested by some that this model could be adopted for clinical trials. This was deemed inappropriate, however, both since it is in contravention with international narcotic conventions, and since seized marijuana could contain unknown and possibly harmful contaminants.

Instead, Health Canada decided to provide the marijuana itself. This way, it could ensure, "a reliable

source of affordable, quality, standardized marijuana" (HC 2001b), that would be free from contaminants. After a competition, the government awarded a five-year exclusive growing contract to Prairie Plant Systems Inc. of Saskatoon Saskatchewan. The contractor has one year in which to establish quality, uniform crops. Once the crops are established, this firm will be responsible for providing all marijuana used for clinical trials and other governmentally-funded marijuana research. Until then, researchers will be able to use marijuana obtained by Health Canada from the US National Institute of Drug Abuse (NIDA), which is a legal and established supplier of marijuana cigarettes.

SAFETY AND MARIJUANA SMOKE

One of the primary goals of the medical marijuana research plan is to assess the safety and efficacy of smoked marijuana and cannabinoids. According to Health Canada, "scientific studies supporting the safety and efficacy of marijuana for therapeutic purposes...are inconclusive" (TPP 1999; CIHR 1999). Despite their repeated claim that available evidence on the safety of smoked marijuana is inconclusive, however, Health Canada's 2000 discussion document on the use of marijuana for medical purposes refers frequently to the health risks associated with smoking marijuana:

- "Smoked marijuana is a crude drug delivery system that... delivers harmful substances" (TPP 2000).
- "Marijuana smoke contains more tars and more carbon dioxide than tobacco. Like tobacco smoke, it is associated with increased risk of respiratory damage, such as bronchitis and possible Chronic Obstructive Pulmonary Disease" (TPP 2000).

- "Studies have suggested that marijuana smoke may be a risk factor in the development of cancers including lung, mouth, and head and neck cancers" (TPP 2000).

Health Canada, then, is funding and promoting the clinical study of smoked marijuana for the symptomatic relief of a wide variety of indications, despite its explicit belief that smoking marijuana is severely harmful to health:

- "Marijuana's potential as a medicine is undermined if patients must inhale harmful smoke... Nevertheless, the investigation of the safety and effectiveness of smoked marijuana is the priority of this program" (CIHR 1999).

GOALS OF THE RESEARCH PROGRAM

The primary reason advanced in defence of this policy is that, "if smoked marijuana is never tested, there will never be an answer as to its potential for the indications for which benefits of smoked marijuana are currently claimed" (TPP 1999a). Given the known health implications of smoked marijuana, the use to which Health Canada intends to put this answer is unclear. Most of the conditions for which marijuana is thought to provide relief are long-term, and Health Canada states that, due to the health risks associated with smoking, marijuana, "is not considered suitable for long-term use" (TPP 2000).

Although the agency does not mention this specifically, it is possible that the smoked marijuana trials currently funded under the medical marijuana research plan are the first step toward developing non-smoked means of cannabinoid delivery. This would be in accordance with the recommendations of both the National Institutes of Health (NIH) and the IOM. In its report on medical marijuana, the

NIH stated that, “the NIH should use its resources and influence to rapidly develop a smoke-free inhaled delivery system for marijuana or THC” (NIH 1997). In its 1999 report, the IOM states that clinical trials of smoked marijuana could be appropriate in certain circumstances, but that, “the goal of clinical trials of smoked marijuana would not be to develop marijuana as a licensed drug, but rather to serve as a first step toward the possible development of non-smoked, rapid-onset cannabinoid delivery systems” (IOM 1999). This may be Health Canada’s intention, though there is little evidence that it is.

ETHICS, DISCLOSURE, AND RISK

Even if the clinical trials are simply the first step toward the goal of developing non-smoked treatments, the ethics of clinical trials involving smoked marijuana must be considered. In its guidelines, the IOM states that, given the ethical implications of exposing trial participants to health risks, trials should only be performed in the case that “patients are fully informed of their status as experimental subjects using a harmful drug delivery system, and [that] their condition is closely monitored and documented under medical supervision, thereby increasing the knowledge base of the risks and benefits of marijuana use under such conditions” (IOM 1999).

Health Canada does not make any such strong statements about alerting patients to the risk that they are taking by participating in smoked marijuana trials. Its documents make little mention of alerting patients and trial participants about the health risks associated with smoking marijuana, and what statements they do make about the risks associated with marijuana generally imply that the level and type of risks associated with marijuana are unknown (TPP 2001; TPP 1999).

Its statement that the TPP reviews all proposed research projects, “to ensure that the design of the study is appropriate to test the hypothesis and that participants are not exposed to undue risk (TPP 1999), also suggests that warnings of the kind suggested by the IOM may not be made, as it implies that the studies are considered safe. It is not clear how the risks associated with smoking marijuana figure into trial safety assessments.

QUESTIONS FOR HEALTH CANADA

- *In what sense is the claim that available information on the safety of smoked marijuana is inconclusive, consistent with the various claims that smoked marijuana has adverse effects on health?*
- *How are the health risks associated with smoking marijuana factored into risk assessments for clinical trials using smoked marijuana?*
- *What information and/or warnings are patients enrolled in trials given about the health effects of smoking marijuana?*
- *How does McGill’s study of the effects of smoked marijuana on chronic neuropathic pain fit within the parameters laid out for funded studies, which state that trials should be restricted to “short-term, self-limiting symptomatic conditions”?*
- *What are the long-term goals of the impending clinical trials of smoked marijuana? (i.e. Are these trials the first stage in the progress toward developing non-smoked means of delivering the effects of marijuana, should they be found desirable? Or are the trials intended to establish the efficacy of smoking marijuana for its own sake?)*
- *Why is the study of smoked marijuana privileged over the study of alternate methods of delivery under current funding guidelines?*
- *If smoked marijuana is found to be effective in relieving the symptoms of chronic conditions, will it be considered for long-term therapeutic use as a smoked substance?*

RECOMMENDATIONS FOR HEALTH CANADA

- **Funding for studies of marijuana and cannabinoids should be directed at the development and testing of non-smoked means of delivery of specific pharmacologically active compounds.**
- **Any trials of smoked marijuana should be conducted according to the guidelines set out by the Institute of Medicine (IOM)’s 1999 report. In particular, trials involving non-terminal patients should be conducted only as the first phase of a strategy to develop non-smoked means of delivery; and patients should be warned explicitly about their status as experimental subjects in the trial of a harmful substance.**

THE EXEMPTION LAW AND PHYSICIANS IN PRACTICE

Under section 56 of the Controlled Drugs and Substances Act (CDSA), individuals who believe that they require marijuana for medical purposes can apply to the Minister of Health for exemptions to the Act, which ordinarily prohibits the cultivation and possession of marijuana (TPP 2000).

CONDITIONS OF EXEMPTION

Exemptions may be granted to applicants who fall under one of the three following categories:

- those who suffer from symptoms associated either with medical conditions for which the prognosis is death within twelve months, or with the treatment of those conditions;
- those who suffer from symptoms such as severe pain, persistent muscle spasms, cachexia, anorexia, weight loss, nausea, or seizures related to the following medical conditions or their treatment: multiple sclerosis, spinal cord injury or disease, cancer, AIDS/HIV, severe arthritis, epilepsy;
- those who suffer from symptoms associated with medical conditions or their treatment

other than those described above, and for which all conventional treatments have failed or have otherwise been deemed medically inappropriate (HC 2001a).

If a request is granted, the applicant receives a letter of exemption from the Director General of the TPP. This letter contains "a general warning about possible health risks which will be assumed entirely by the patient," as well as a statement to the effect that since marijuana has not been approved in Canada, its "potential benefits and risks cannot be predicted"(TPP 2000).

LOGISTICS

Once granted an exemption to use marijuana for medical purposes, a patient can choose between a number of means by which to obtain the drug. She can buy it from whomever she likes, or she can either apply for a license to grow it herself, or apply for a license for a designated grower – a third party who would be allowed to cultivate a certain amount of marijuana for the patient's treatment. Patients will also have the option of buying marijuana cigarettes from Prairie Plant Systems Inc., the government's supplier, once crops are established.

PHYSICIANS' IMPLICATION IN THE EXEMPTION PROCESS

In order to obtain an exemption, a patient must submit a written application to the TPP. As part of this application she must submit several medical forms, completed by her treating physician. These forms include:

- details of the proposed treatment, including the prescribed daily dosage of dried marijuana in grams;
- detailed medical and drug therapy histories;
- a medical declaration statement, which includes the statement that, "the benefits to the applicant from the recommended use of marijuana would outweigh any risks associated with that use, including risks associated with the long-term use of marijuana"(HC 2001).

The content of these forms raise a number of issues for treating physicians. First, a great many variables make the accurate prescription of a daily dosage very difficult. The concentration of THC in a batch of marijuana can range from 0.5 to 14 percent. A typical joint contains between 0.5 and 1.0g of marijuana,

RECOMMENDATIONS FOR PHYSICIANS

- **Unless and until better data are available concerning the safety and efficacy of marijuana for the treatment of specific medical conditions, physicians should feel comfortable refusing to support patients' applications for CDSA exemption.**
- **When a patient requests a prescription for smoked marijuana, her treating physician should refuse the request, and should advance the health risks associated with smoking as a primary reason for rejecting the request.**
- **Physicians should warn all patients who request prescriptions for medical marijuana of the health risks associated with smoking the substance (regardless of whether they intend to provide the prescription or not).**

which may vary in THC content between 5 and 140 mg (i.e. between 1 and 14 percent). The actual amount of THC delivered in marijuana smoke has been estimated to be between 20 and 70 percent, the rest being lost through combustion or side-stream smoke. The amount of THC from marijuana that reaches the bloodstream (its bioavailability) through smoking has been reported to range between 5 and 24 percent. All of these factors mean that the actual dose of THC absorbed when an individual smokes marijuana is difficult to establish (Martin 1999). Further, the patient's level of drug tolerance and the depth with which she inhales each vary greatly and

impact significantly on the amount of marijuana needed to obtain the desired results (Rickert 1982).

Second, given the lack of scientific knowledge about the benefits of smoked marijuana and the significant body of knowledge concerning the risks, the assessment that the benefits outweigh the risks is impossible for a physician to make, except in the case of terminally ill patients. This led president of the Canadian Medical Association (CMA) to state in an open letter that, "the lack of information on the indications, risks and benefits of medicinal marijuana hinders [physicians'] ability to properly inform patients" (Barrett 2001). In

light of these and other issues, the CMA has officially opposed the CDSA exemption regulation.

CONCLUSIONS

Based on Health Canada's literature and the independent evidence available linking marijuana smoke to acute and chronic health problems, the following conclusions can be drawn:

- **Health Canada's concurrent assertion that knowledge about the safety of marijuana is indeterminate, and acknowledgement that marijuana is widely considered unsafe, are contradictory.**
 - **Health Canada's emphasis on the lack of determinate evidence about the safety of marijuana is at best misleading, at worse unethical.**
 - **There is reason to believe that patients enrolled in clinical trials of smoked marijuana and patients using marijuana through CDSA exemption are not being sufficiently informed about the health risks involved in smoking marijuana.**
 - **There is reason to believe that the available evidence on the health risks associated with smoking marijuana has not been factored in appropriately to risk assessments for clinical trials.**
 - **Given the lack of substantial scientific data regarding the benefits of specific chemical compounds contained in marijuana, marijuana cannot be considered a medicine in the conventional sense.**
 - **When considering applications for CDSA exemption, physicians cannot in good faith testify that the benefits of treatment with marijuana outweigh the risks.**
 - **The health risks associated with smoking marijuana are an appropriate reason for physicians to deny patients access to marijuana for medical purposes.**
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