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Medical use of cannabis products

Lessons to be learned from Israel and Canada

Introduction

In Germany, the only manufactured drug containing cannabinoids is a nabiximol-containing oromucosal spray which is approved for the management of severe spasticity in multiple sclerosis refractory to conventional treatment. In addition, dronabinol and nabilone can be provided off-label by physicians with a narcotic prescription on a single patient basis, for palliative care and chronic pain [1]. In principle, reimbursement of costs is possible by health statutory institutions if conventional treatments have failed. In most cases, German health statutory institutions refuse the cost transfer of between 300 and 600 €/month. In addition, patients can receive extracts or flowers of cannabis by a pharmacy after receiving an exceptional permission according to §3 Absatz 2 of the German Narcotics Act (Betäubungsmittelgesetz) by the Federal Institute of Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)) [3]. The costs of up to 1500 €/month are not covered by the health insurance companies. On July 22, 2014 the administrative court in Köln ruled that three severely ill patients could grow marijuana for medicinal purposes. The court determined that growing cannabis plants is allowed if conventional treatments have failed, if there is no therapeutic alternative to cannabis, and if the pharmaceutical cannabinoid preparation is prohibitively expensive for the patient [31]. All patients suffered from chronic pain and had received permission from the Federal Opium Agency to use cannabis flowers [3]. In 2014, the medical use of cannabis was approved for only 109 patients [5].

The German government has lodged an appeal on points of law against the decision of the court in Köln and has announced a legislative project. According to the federal drug representative Marlene Mortler and the federal minister of health Hermann Gröhe the barriers for the medical use of cannabis as medication should be reduced. The costs should be covered by the health insurance companies [4].

The Drug Commission of the German Medical Association (Arzneimittelkommission der Deutschen Ärzteschaft) currently does not recommend the use of medical cannabis because the concentrations of cannabinoids can vary widely and contaminations, for example, pesticides can harm the patient [1]. The German Pain Society has recommended the use of synthetic cannabinoids for specific indications after established treatment options have failed, and when potential contraindications, comorbidities, and patient preferences have been taken into account [6].

While discussing potential indications for cannabis and changes of the regulatory framework it might be useful to consider the experiences of countries with a previous and often more liberal prescription practice of cannabinoids. Although medicinal cannabis has been available in various states in the USA over the years, each with unique health-care regulations, we will confine this review to the experience of two countries that have overreaching health-care policies applicable throughout the country and likely more applicable to the German context. Therefore, we will examine this issue from the Canadian and Israeli perspective. Canadian and Israeli physicians who were charged by their jurisdictions with a medical expertise on medical cannabis in pain medicine and rheumatology will outline their viewpoint with regard to the following points in their countries:

- The historical background
- The legislative framework
- The indications and contraindications of natural and synthetic cannabinoids
- The problems associated with medical cannabis

They discuss which lessons could be learned by German physicians and the German government from the Canadian and Israeli experience.

The Israeli perspective

Historical background

Israel carries somewhat of a leading place in the field of studying the canna-

binoid system and its effects on the central nervous system (and otherwise) due to the groundbreaking work of Professor Mechoulam from the Hebrew University in Jerusalem, who was the first to identify tetrahydrocannabinol (THC), the active component of cannabis in the 1960s [20]. It is interesting to speculate whether this breakthrough was achieved in Israel as a result of a less restrictive legal attitude towards the whole cannabis issue, compared with the USA and Europe. One way or another, this breakthrough has led to an ever expanding world of research into the field of studying the endocannabinoid system in health and disease [21].

Regulatory framework: Israeli medical cannabis plan

Cannabis is defined by Israeli law as a "dangerous drug" in accordance with the Dangerous Drugs Ordinance [New Version] 1973 and the Regulations made under this Ordinance, as well as the provisions of the Single Convention on Narcotic Drugs 1961, including the amendments of 1972. This ordinance specifies a punishment of up to 20 years imprisonment for anyone who illicitly grows, produces, or extracts such a drug.

The provisions of this Ordinance continue to be the legal basis under which the Israeli government acts in order to regularize medicinal use of cannabis. By government resolution it was determined that the Ministry of Health shall maintain a "government agency" pursuant to the provisions of the said Convention. This agency is currently termed the "Medical Cannabis Unit" and is a unit within the Ministry of Health [28]. This unit is charged with the regulation of the field of cannabis for medical and research use. The Medical Cannabis Unit is the authorized body in the Ministry of Health to issue patients with permits to use cannabis for medical purposes. The unit operates hand-in-hand with the physicians recommending medical cannabis, the cannabis growers and suppliers, the other relevant government bodies (Ministry of Agriculture, Ministry of Public Security, Ministry of Justice, Ministry of Finance, Israeli police, etc.), and the individuals being treated with medical cannabis. The unit is also committed to working with the Israeli Medical Association, professional medical associations in the relevant fields, the pharmacists' association, etc.

As part of its work, the medical cannabis unit has an *Indications Committee*, which works on broadening (or narrowing) the range of indications and clinical recommendations. The unit also includes a "Growing Committee," responsible for issues of growing, distinction between varieties, quality, pests, etc. A *security committee* is responsible for security standards of growing and transportation, and an *R&D committee* is responsible for advancement of research.

Current status for herbal and synthetic cannabinoids

Herbal cannabis is supplied in Israel in two main forms: as an oil extract for oral or sublingual ingestion and as dried flowers—which can be used for smoking or other forms of inhalation. Neither of these are pure THC but rather contain various concentrations of active ingredients—THC, cannabidiol (CBD), etc.—typically over 12 % THC. Upon first requesting a permit for cannabis the physician is asked to specify whether to supply the oral formula or the dried flowers—based on clinical judgment, patient preference, etc. It is generally assumed that the oral formula is safer, due to its not containing the products of burning such as tar, whereas the administration through inhalational may have a stronger and more rapid effect due to bypassing gastrointestinal absorption and hepatic metabolism [13, 15].

Nabiximole is licensed in Israel for the very limited indication of treating moderate to severe painful spasticity in multiple sclerosis patients as well as adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate-to-severe pain during the highest tolerated dose of strong opioid therapy. Other synthetic cannabinoids (nabilone, etc.) are not available in Israel.

Nabiximole is currently not included in the Israeli health "basket," which means that the health maintenance organizations (HMO) are not committed to subsidizing it for patients. It is however partially subsidized for patients who have extended coverage (which is like a premium insurance offered by the HMOs).

Current status for medical cannabis

In March, 2013, the medical cannabis unit published Procedure 106, updated on July, 2014, regarding the issue of permits to use cannabis for medical purposes.

Procedure 106 states that permits to use medical cannabis will be granted only for a list of recognized indications (see below) and only after fully utilizing (presumably unsuccessfully) all other recognized forms of treatment [28].

The procedure states *contraindications* for the use of cannabis including the following:

- Congestive heart failure,
- psychosis (past or present)
- Anxiety disorder
- First degree relatives suffering from psychiatric disorders (especially in individuals under the age of 30)
- History of drug abuse or addiction

The *indications* listed include the following:

- Oncology—either for treating metastatic cancer or for treating chemotherapy-related symptoms
- Gastroenterology—patients with inflammatory bowel disease after failing immunomodulatory treatment including anti-TNF (and ruling out surgical options)
- Pain—patients suffering from neuropathic pain of "a clear organic source" being treated in a pain clinic for a year or more and after failing on other modes of treatment
- AIDS—for treating severe cachexia
- Neurology—multiple sclerosis-related spasticity, Parkinson's disease-related pain, Tourette disease
- Psychiatry—posttraumatic stress disorder (PTSD)
- The procedure also refers to "terminally ill patients"

Notably, Procedure 106 allows *exceptions* to the specified indications. The procedure states that an expert physician, who is treating a patient suffering from an illness not included in the list of indications, can send a request for exceptional approv-

Abstract · Zusammenfassung

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Medical use of cannabis products. Lessons to be learned from Israel and Canada

Abstract

Introduction. The German government intends to reduce the barriers for the medical use of cannabis products. A discussion on the indications and contraindications of the medical use of cannabis and on the changes of the regulatory framework has already begun in Germany. It is useful to draw from the experiences of other countries with a more liberal medical use of cannabis.

Methods. The Israeli and Canadian experience is outlined by physicians who have been charged with expertise on the medical use of cannabis by their jurisdiction.

Results. In Israel, only the plant-based cannabinoid nabiximol (mixture of tetrahydrocannabinol/cannabidiol) can be prescribed for spasticity/chronic pain in multiple sclerosis and for cancer pain. The costs of nabiximole are reimbursed by some, but not by all health maintenance organizations. The medical use of marijuana is permitted; however, it is strictly regulated by the government. Selected companies are allowed to produce marijuana for medical use, and only certain physicians are licensed to prescribe marijuana as a therapeutic drug for specific indications such as chronic neuropathic, and cancer pain, inflammatory bowel diseases, or posttraumatic stress disorder if conventional treatments have failed. The costs of marijuana are not reimbursed by health insurance companies.

In Canada, synthetic cannabinoids and the plant-based (nabiximol) are licensed for neuropathic and cancer pain, HIV-related anorexia and chemotherapy-associate nausea. The costs of these synthetic cannabinoids are covered by health insurance companies. The medical use of marijuana as a treatment option is allowed for individual patients suffering from any medical condition when authorized by a medical practitioner or nurse. Licensed producers are the only source for patients to newly access medical cannabis, although those with previous permission to grow may continue cultivation at the present time. The costs of marijuana are not reimbursed by health insurance companies.

There are multiple contraindications for the medical use of cannabis products in both countries.

Conclusions. The use of standardized, synthetic, and plant-based cannabis products should be allowed in Germany for defined medical conditions when high-level evidence of efficacy and safety exists. The costs should be reimbursed by the health insurance companies. Contraindications for the medical use of cannabis should be defined. Growing marijuana by patients for their medical use should not be allowed.

Keywords

Cannabinoids · Herbal cannabis · Medical use · Israel–Canada · Regulatory framework

Medizinischer Gebrauch von Cannabisprodukten. Was können wir von Israel und Kanada lernen?

Zusammenfassung

Einleitung. Die Bundesregierung will die Hindernisse für den medizinischen Gebrauch von Cannabisprodukten abbauen. Eine Diskussion über die Indikationen und Kontraindikationen des medizinischen Gebrauchs von Cannabisprodukten und der Änderung der gesetzlichen Rahmenbedingungen hat begonnen. In dieser Situation ist es nützlich, die Erfahrungen von Ländern mit einer liberaleren Gebrauch von Cannabis für medizinische Zwecke zu berücksichtigen.

Methoden. Die israelischen und kanadischen Erfahrungen werden von ÄrztInnen dargestellt, die von ihren jeweiligen Regierungen mit Gutachten zum medizinischen Gebrauch von Cannabis beauftragt wurden.

Ergebnisse. In Israel ist das auf Pflanzenbasis hergestellte Cannabinoid Nabiximol (Mischung Tetrahydrocannabinol/Cannabidiol)zur Behandlung von Spastik/Schmerz bei multipler Sklerose und bei Krebsschmerz zugelassen. Die Kosten werden von einigen, nicht jedoch allen Krankenversicherungen übernommen. Der medizinischen Gebrauch von pflanzlichem Cannabis („Medizinalhanf") ist erlaubt, jedoch streng von der Regierung kontrolliert. Ausgewählte Firmen können Cannabis für medizinische Zwecke anbauen. Nur spezialisierte Ärzte dürfen Medizinalhanf für spezifische Indikationen wie chronische neuropathische oder Tumor-Schmerzen, chronisch entzündliche Darmerkrankungen oder posttraumatische Belastungsstörung verschreiben, wenn konventionelle Behandlungen versagt haben. Die Kosten für Medizinalhanf werden nicht von den Krankenversicherungen übernommen.

In Kanada ist das synthetische Cannabinoid Nabilon und das pflanzlich basierte Nabiximol für einige Indikationen (neuropathischer und Krebsschmerz, HIV- assoziierte Anorexie, chemotherapieinduzierte Übelkeit) zugelassen. Die Kosten werden von den Krankenkassen übernommen. Der Gebrauch von Cannabis („Medizinalhanf") ist Patienten bei allen Krankheitsbildern erlaubt, wenn ein Arzt oder eine Krankenschwester bescheinigen, dass die etablierten Behandlungen fehlgeschlagen sind. Lizensierte Hersteller sind der einzige legale Zugang für Patienten zu Medizinalhanf. Die Kosten für Medizinalhanf werden nicht von den Krankenversicherungen übernommen. Patienten, die vor einigen Jahren die offizielle Erlaubnis erhielten, dürfen Marihuana weitere für eigene medizinische Zwecke anbauen.

In beiden Ländern bestehen umfangreiche Kontraindikationen für den medizinischen Gebrauch von Cannabisprodukten.

Schlussfolgerung. Der Gebrauch von standardisierten pflanzenbasierten und synthetischen Cannabisprodukten bei definierten medizinischen Indikationen, für die ein hoher Evidenzgrad der Wirksamkeit und Sicherheit besteht, sollte in Deutschland erlaubt werden. Die Kosten der Behandlung sollten von den Krankenkassen übernommen werden. Kontraindikationen für den medizinischen Gebrauch von Cannabisprodukten müssen erstellt werden. Der Anbau von Cannabis durch den Patienten für medizinische Zwecke sollte nicht erlaubt werden.

Schlüsselwörter

Cannabinoide · Pflanzliches Cannabis · Medizinischer Gebrauch · Israel · Kanada · Gesetzliche Regelungen

al of medical cannabis, and must explain in detail, with references, why the physician assumes the condition may be improved by the use of cannabis. In such cases the treating physician must also offer parameters for assessing improvement and must be committed to follow up on the patient.

The cost of medical cannabis is not covered at all by the HMOs—the patient pays a flat monthly sum (about 100$)—regardless of the dose.

The Israeli experience

Prevalence of use of medical cannabis

The number of patients being treated with medical cannabis in Israel appears to increase rapidly. Clear data are not, however, available regarding the exact number of patients being currently treated with medical cannabis and for which indications.

A document which was published in the media and which claimed to display Ministry of Health data stated that in the year 2013, 8713 persons were granted a license for medical cannabis. A total of 1518 persons were licensed for malignant indications and 4864 for "chronic pain." This broad category included many different subcategories, including "central pain syndrome" (3284) and "chronic pain syndrome" (246). Only 943 of the patients treated for pain were diagnosed as "neuropathic pain." Fibromyalgia appeared separately (47 patients). Thus, it appears that in real life the official indications have only a general guidance effect regarding the question which patients end up using cannabis, whereas many patients are given relatively nonspecific labels in order to qualify.

Problems with the medical use of cannabis

In the field of rheumatology, medical cannabis is usually used for treating chronic pain, although the anti-inflammatory effects are also of possible value. Rheumatologists are novices in the field of cannabis. Until recently most patients who received the treatment did so through pain clinics. Thus, many rheumatologists in Israel (as in Canada) feel insufficiently informed in the proper use of cannabis [9, 10]. Recently, however, pain specialists in Israel appear to be reluctant to recommend cannabis for patients with rheumatological problems and, thus, rheumatologists are increasingly being faced with this challenge. Many difficulties are faced by the physicians, including

- The lack of unity among various strains of cannabis which are supplied (i.e., different strains—different amounts of active ingredients) and among the different suppliers
- The need for close clinical follow-up after patients treated with cannabis—which is not practical given long waiting lists for seeing a rheumatologist
- Lack of clarity regarding the forms of administration (i.e., smoking, inhalation, oral ingestion, etc.)
- Increasing public pressure to prescribe cannabis.

Public opinion in Israel has witnessed increasing interest in the issue of medical cannabis, as well as in the issues of legalization and decriminalization of recreational use. This has been expressed politically by the establishment of a pro-legalization party ("Ale Yarok") which has been running (unsuccessfully) in the national elections on a pro-legalization ticket. This party achieved 1.12 % of the national vote in the recent general elections held in Israel on March 17, 2015, failing to enter Parliament. Notably, the party ran a leading pain expert in their list. Politicians from both the left and right wing of the spectrum have expressed support for the use of medical cannabis, a cause which appears to have wide public support as well.

The issue of medical cannabis and driving appears to be unclear. Patients who are given medical cannabis are asked to verify if they know it is forbidden to drive while being treated with cannabis. Since cannabinoids can be identified in urine days and even weeks after the last consumption, it is not clear whether this means these patients are supposed not to drive at all or how long after using cannabis driving is allowed. This issue is particularly important for chronic pain patients, for whom driving may be a crucial aspect of maintaining the ability to function or work.

Similarly, the question of using cannabis while in the military service is an emerging dilemma. Military conscription is mandatory in Israel for a period of 3 years for men and 2 years for women. The Israel Defence Forces have traditionally been very strict in its punitive attitude towards recreational use of cannabis by military personnel. On the other hand, cannabis has been approved for use in patients with PTSD, often of military origin. How the military will deal with soldiers who are being treated with medical cannabis is another challenge.

Personal perspective

As a rheumatologist dealing with both general rheumatology patients and with a special interest in fibromyalgia, I have had in recent years an increasing number of cases in which medical cannabis emerged as a reasonable step to take.

My personal experience with the use of cannabis for treating chronic pain is anecdotal and limited, but generally positive. In some patients suffering from chronic intractable pain, due either to "pure" fibromyalgia or to chronic connective tissue disease, often accompanied by "secondary" fibromyalgia, cannabis appears to make a significant change. Subjective improvement in sleep is often the first effect reported including improvement in falling asleep and more refreshing sleep quality. Some patients report a decrease in pain intensity, whereas others describe the pain as remaining present but being less aversive or disruptive in nature. Improved mood is also sometimes reported and can be particularly striking among chronic pain patients who have been dysphoric or depressed for long periods. Occasional patients report a significant improvement in their capacity to function at work or at home after initiating treatment with cannabis. Patients who failed to respond to a broad spectrum of medical and non-pharmacological treatments do sometimes appear to gain significantly from this treatment. My personal impression is that further research is urgently needed, both into the clinical utilization and standardization of cannabinoids and into the underlying biology of the cannabinoid system. At the same time there is a growing need for medical education at all levels, from medical schools to continued

medical education, in order to make what knowledge we have available and accessible for health-care professionals and in order to demystify medical cannabis and allow a more rational approach to this challenging issue.

Lessons to be learned for German government and physicians

The Israeli Cannabis experience has developed in a somewhat haphazard fashion over recent years and the relatively rapid proliferation of both indications and permits granted has not always seemed to reflect a clear strategy. On the upside, the Israeli system continues to maintain a flexible format in which indications are continuously being re-evaluated and new ones are added as necessary. This pattern seems to be appropriate considering the limited (but growing) state of current knowledge regarding the medical use of cannabis.

Lack of sufficient education among health-care providers regarding the cannabis issue continues to be an obstacle and often has an effect on the standpoint taken up by the professional associations.

Technical difficulties continue to develop. Due to the increasing numbers of patients, time required for processing requests is an issue, and the number of officials in charge of this function (including physicians) must be increased.

In view of this background, the following recommendations might be made for a country such as Germany, while evaluating the prospect of introducing medical cannabis:

Strategic planning would be recommended *before* implementing new legislation, regarding the indications (and contra-indications) for the use of cannabis, and a proactive educational program would be advisable for the medical community, in order to increase confidence and diffuse ungrounded preconceptions regarding this sensitive topic.

Professional medical associations should be involved in the decision-making, although ultimately the strategic decision must be made by policy-makers taking into consideration broad societal considerations, including safety.

Ideally, the medical cannabis topic should be detached from any public discussion regarding recreational legalization; these are quite different topics which deserve separate consideration.

Controlled introduction of synthetic cannabinoids (not available in Israel) would be a sensible alternative and should be seriously considered. This option has obvious advantages as far as issues of safety, reproducibility, and abuse potential are concerned.

Clinical as well as basic research is urgently called for regarding the mechanisms and clinical utility of cannabis in various forms of disease and symptoms. Due to the inherent difficulties in advancing the clinical research of cannabis on an industry basis (since no company can patent a plant), government or academic funding for this type of research would be highly productive.

The Canadian perspective

Historical background

Over the years Canadian clinicians and researchers alike have had an interest in the potential medicinal properties of cannabinoids in general with research funded by the Canadian Institutes of Health Research (CIHR). Court rulings and legislative changes over the past 15 years have however given further impetus to the immediate need to understand the effects of herbal cannabis in particular. The issue of legalizing herbal cannabis (marijuana) for medicinal use in Canada began in 2000. A person with epilepsy and uncontrolled seizures was charged with possession and cultivation of cannabis, thereby contravening the *Controlled Drugs and Substances Act*. In a ruling of the Ontario Court of Appeals, *R.* v. *Parker*, [2000] O.J. No. 2787, it was noted that the charter rights were violated by the blanket prohibition of cannabis for medicinal purposes as the defendant had no other means of obtaining the drug for his medical needs and requirement to maintain health. With this ruling the prohibition of cannabis in the *Controlled Drugs and Substances Act* was deemed unconstitutional and invalid, forcing the government to the drawing board to enable an exemption program for access to medical marijuana within the following 12 months [15].

In 2001, the Government of Canada adopted the *Marijuana Medical Access Regulations* (MMAR) which recognized herbal cannabis as a treatment option for patients suffering from various medical conditions, when the medical practitioner attested that "conventional treatment(s) have been tried or considered, and had been found to be ineffective or medically inappropriate" [18]. The diagnosis needed to be specified and had to be identified by Health Canada as being an eligible condition for a medical cannabis exemption. The physician then signed a document attesting to this information which the patient submitted to Health Canada to support the application for possession of marijuana for medicinal purposes. Approval for possession or cultivation of a specified amount of herbal cannabis was given by Health Canada officials for a period up to 1 year. This treatment was not reimbursed by either public or private insurers and patients were responsible for carrying the costs of the cannabis. It is notable that this was not a prescription-based model, with physicians functioning more in a gatekeeper's role. Following approval, Health Canada sent the cannabis directly to the patient, or some patients were allowed to grow their own cannabis.

These regulations were challenged in 2008 in the Ontario Superior Court, when a person argued that the MMAR were unconstitutional as he was unable to obtain a physician signed document to submit to Health Canada to access marijuana for medical reasons to treat symptoms of fibromyalgia. The trial judge agreed with his claim stating that the claimant had a constitutional right to access a treatment with marijuana. Following an appeal, the Ontario Court of Appeals tempered the concept of a constitutional right to cannabis in the decision *R.* v. *Mernagh*, 2013 ONCA 67. The Court affirmed that a medical doctor was entitled to exercise professional judgment in deciding whether to provide a medical document to a specific patient for use of medicinal cannabis. Therefore, this judgment dismisses the claim that access to medicinal cannabis is a right according to the Canadian constitution. A request to the Supreme Court of Canada for permission to appeal this decision was dismissed.

Regulatory framework

As of March 31, 2014 the Government of Canada repealed the MMAR of 2001 and replaced these regulations with the "Marijuana for Medical Purposes Regulations" (MMPR) [19]. In effect since April 1, 2014, marijuana is legally available as a therapeutic treatment for patients. The reasons put forward by the Government of Canada for this change in legislation were related to public safety. It was claimed that indoor cultivation of cannabis, purportedly for personal use, but with amounts far in excess of personal needs, was a fire hazard, and there were concerns raised by the police regarding potential theft. Under these new regulations the medical practitioner or nurse practitioner is entirely responsible for providing a document to allow use of marijuana. As marijuana is not a Health Canada-approved medicinal product, the "document" is not a true medical prescription, and marijuana cannot be obtained, as for other prescriptions, from a registered pharmacy. Licensed producers are the only source for patients to access medical cannabis, thereby bypassing the usual medical surveillance provided by pharmacists. By this legislation the government has abrogated responsibility for medical use of herbal cannabis, with the transfer of this responsibility to the medical community. In parallel, the government has created a campaign to warn against the potential harms associated with recreational cannabis use and suggested indications for use. This is therefore a costly program with estimates that marijuana use is increasing rapidly.

Current status for pharmaceutical cannabinoids

In Canada there are three pharmacologic preparations that have received approval and notice of compliance for therapeutic use by Health Canada [3]. Herbal cannabis, although not approved by Health Canada as a therapeutic product, is a legal substance for medicinal use [13]. The pharmacologic preparations are as follows: two oral agents, dronabinol, a ste-

reoisomer of Δ^9-THC; and nabilone, a synthetic analogue of Δ^9-THC; and an oromucosal spray, nabiximols, which is a combination of Δ^9-THC and CBD, as well as other minor cannabinoids, terpenoids, and flavonoids, obtained from a botanical extract from established and well-characterized *Cannabis sativa* strains. Dronabinol, although approved in Canada for the treatment for human immunodeficiency virus-related anorexia associated with weight loss and severe nausea and vomiting associated with cancer chemotherapy, was withdrawn from the Canadian market by the manufacturer, not for safety reasons, in February, 2012.

Nabilone is approved in Canada for severe nausea and vomiting associated with cancer chemotherapy, with any other use deemed as "off-label." Nabiximols is approved in Canada as adjunctive treatment for symptomatic relief of spasticity in adult patients with multiple sclerosis who have not responded adequately to other therapy and who demonstrate meaningful improvement during an initial trial of therapy. There is also marketing authorization "with conditions," as adjunctive treatment for symptomatic relief of neuropathic pain in adult patients with multiple sclerosis and adjunctive analgesic treatment in adult patients with advanced cancer who experience moderate-to-severe pain during the highest tolerated dose of strong opioid therapy for persistent background pain.

The contraindications for nabilone and nabiximols are fairly similar. Both are contraindicated in persons with known hypersensitivity to marijuana or other cannabinoid agents, in those with a history of psychotic reactions, and during pregnancy, in nursing mothers, or pediatric patients. For nabilone there are warnings for use in persons with severe liver disease or a history of nonpsychotic emotional disorder, and it should not be taken with alcohol, sedatives, hypnotics, or other psychomimetic substances. Additional contraindications for nabiximols are allergy to propylene glycol, ethanol or peppermint oil, patients with serious cardiovascular disease, and men intending to start a family.

The costs of synthetic cannabinoids are reimbursed by health insurance companies.

Current status for medical cannabis

In contrast, herbal cannabis is not an approved product by Health Canada and does not have a notice of compliance for medicinal use but has been ascribed legal status as a therapeutic agent on the basis of a medical "document," signed by a physician or nurse practitioner. The prescription of herbal cannabis may be made for any medical condition, without need to demonstrate failure of conventional treatments. For patients supported by a physician, herbal cannabis is obtained directly from a registered grower, with no conduit via a pharmacist. Other than recommendations provided by various medical associations and regulatory bodies, there are no specific contraindications to preclude the provision of the medical "document" for a patient to access herbal cannabis. Contraindications or warnings issued by various medical associations include statements that herbal cannabis is not appropriate for persons under 25 years age, those with a personal or family history of psychosis, substance abuse disorder, cardiovascular or respiratory disease and in pregnancy or during breast feeding.

New Government of Canada regulations, the *Marihuana for Medical Purposes Regulations* (MMPR) came into effect on April 1, 2014 [19]. The process by which a patient may obtain herbal cannabis for medicinal reasons is as follows: a signed document (not identified as a prescription per se) is obtained from a physician or a registered nurse, which states the amount of dried marijuana to be used on a daily basis and the duration of use for up to 1 year. It is not required that a diagnosis is identified, and there is also no requirement to attest to trials or failures of other treatment options. The maximal amount of herbal cannabis allowed per day is 5 g, obtained from a licensed producer for a period of 30 days. The cost of the cannabis preparation varies depending on the Δ^9-THC and CBD content but is in the order of about Canadian $8.00/gram, which would translate to about Canadian $500.00 per month. Access to marijuana is obtained without any input from a pharmacist. Once a "document" has been issued, the patient in consultation with the "licensed producer" determines the specific strain and concentration of various molecules of Δ^9-THC and CBD that will be served. Similar to the prior situation for access to marijuana, this treatment is currently not reimbursed by either public or private insurers and patients are responsible for carrying the costs. Although most studies have examined effects of low content of THC (up to 3 %), licensed producers in Canada have available cannabis with THC content over 22 %, with intentions to further increase the THC content. As herbal cannabis is not an approved therapeutic product by Health Canada standards, government regulations have superseded the usual process of due diligence accorded by Health Canada to examine the benefits and risks of a therapeutic intervention.

Health Canada recommends that marijuana should not be smoked and is contraindicated in persons who are 25 years of age or younger; who have a current, past, or strong family history of psychosis; who have a current or past cannabis use disorder; who have a current substance use disorder; who have cardiovascular or respiratory disease; or who are pregnant or planning to become pregnant. It should be used with caution in patients who smoke tobacco, who are at increased risk of cardiovascular disease, who have anxiety or mood disorders (level II evidence), or who are taking higher doses of opioids or benzodiazepines [13].

The costs of marijuana are not reimbursed by health insurance companies.

The Canadian experience

Prevalence of use of medical cannabis

Prior to the introduction of the MMPR in 2014 there were 40,000 users in Canada with a population of 35 million, with two third having a diagnostic label of "severe arthritis." With Health Canada estimates that 10.7 % of Canadians had used marijuana in the year 2010, and extrapolating from numbers of persons registered in the MMAP, it is conservatively estimated that 0.14 % of the Canadian population had

used this substance for medicinal purposes [14]. Unfortunately, there has been no requirement to monitor outcome for persons in Canada accessing medicinal marijuana over the preceding decade resulting in absence of information on either benefit or adverse effects. By Health Canada estimates, the new regulations will lead to a tenfold increase in medical cannabis users in the next decade with over 400,000 authorized users by 2024. The acceptance of these new regulations has therefore transferred the gatekeeper role to physicians, a function previously held by government functionaries.

Regulatory body responses

Medical practice in Canada is governed by licensing authorities for each province. Guidance regarding patient management is also provided by various societies. Although each province has issued directives for physicians who may prescribe herbal cannabis, the overall message across the provinces is similar with some nuanced differences. The guidelines and policies issued to date by most colleges consistently state that more information is required on the medical risks and therapeutic benefits of marijuana. Most colleges suggest that physicians should only sign the medical document when they have the necessary clinical knowledge to engage in a meaningful consent discussion with patients. In general, it is required that physicians adhere to good standards for the practice of medicine, taking into account their own competencies, as well as the risks and benefits of the use of marijuana.

A number of bodies, including The Canadian Medical Association, the Federation of Medical Regulatory Authorities of Canada, The College of Family Physicians of Canada, the Canadian Rheumatology Association, and the Canadian Ophthalmological Society have opposed the change in regulations by Health Canada on grounds that evidence is insufficient to allow for safe prescription of herbal cannabis [7–12, 22, 30]. The Canadian Medical Protective Association, the largest medical mutual defense association in Canada, has cautioned physicians to only provide a prescription for herbal cannabis when conventional treatments have failed or are inappropriate and when "they have the necessary clinical knowledge to engage in meaningful consent discussions with patients," and should inform the patient of "the lack of information to date" [22]. Additionally, the risks and benefits of using medicinal herbal cannabis should be discussed and documented in the medical record. Health Canada has published a comprehensive document summarizing current evidence for therapeutic use of medical marijuana, highlighting the evidence for efficacy or risk in various diseases, with the specific cautions against smoking of cannabis and that alertness may be impaired for up to 24 h following consumption [13]. There is clearly a legal quandary, with the laws governing medical practice all indicative of reservation and caution, but government regulations allowing for medicinal use that is the responsibility of the prescribing health-care professional.

Problems with the medical use of cannabis

Over the past two decades, there has been a steady increase in the number of persons driving after recent consumption of illicit drugs and marijuana in particular [17, 25]. Although drug-impaired driving has been a criminal offence in Canada since 1925, enforcement of this law was problematic as the police were not given sufficient directives to allow for charges to be laid, leading to limited convictions over the years [17]. There is mounting evidence that recent marijuana use is associated with road traffic accidents. Recent cannabis use is associated with five times increased risk of death in a motor vehicle accident, with this risk increasing to 40 times when cannabis was combined with alcohol [2].

The medical ethics of prescribing cannabis has become a contentious issue in Canada, highlighted by distress expressed by the health-care community and the variable directives issued by the various provincial licensing authorities. Contrary to the prescription for any other therapeutic product, there is no pharmacy involvement in the prescription of herbal cannabis. Although the cannabis production business is already proving to be extremely lucrative, there has been little incentive for the Canadian growers to support scientific study. Some healthcare providers are even tapping into this industry by providing prescription documents via the Internet or for a fee, although against the law in many provinces.

There is therefore an evident disconnect between physicians perceptions of responsible patient care, Canadian government regulations, and patient advocacy. Legalization to provide access to medicinal cannabis has moved forward in the absence of sound evidence for efficacy and safety, driven by public advocacy and a political agenda. This represents a prescription model like no other in Canada. Over three quarters of rheumatologists polled in Canada have expressed lack of confidence in their competence of knowledge of cannabinoids, and 70 % believed there was not a role for herbal cannabis in rheumatology practice [9].

Issues of liability are bound to arise in the coming years. A tort of negligence, or failure to provide a standard of care required by law, may be alleged in a malpractice suit if it can be shown that a patient was harmed.

Personal experience

If marijuana can truly provide relief for those extreme situations related to end-of-life suffering or where no single treatment is effective, physicians will mostly agree to prescribe. However, it is currently known that the vast majority of users in Canada are persons with musculoskeletal conditions for which other treatment options are available. Importantly, maintained function as well as symptom relief should be the goal of any treatment option for most patients. There is a concern that a diagnosis of "arthritis" may on many occasions be a diagnosis of convenience that is used to justify access to medicinal herbal cannabis. With the knowledge that most users of cannabis for medical reasons were previous recreational users, there is a concern that the distinction between recreational and medicinal use is blurred. It is also notable that these persons are likely functioning in the community which commonly involves driving motor vehicles.

Gleaning from the experience of working in a multidisciplinary pain clinic in the

era of medical legalization of herbal cannabis, we can attest to the anecdotal positive therapeutic effect noted particularly for patients with severe neuropathic pain conditions. In most cases a small amount of herbal cannabis, often less than 0.5 g/day, but with a broad range of THC and CBD content, was sufficient to provide therapeutic effect. We have, however, observed considerable numbers of persons with lesser medical complaints, such as mechanical back pain, who were often previous or current recreational users, requesting medical access to herbal cannabis. When there were concerns regarding motive for use, consultation within the team was always a useful avenue, and on many occasions the patient was informed of a team decision to recommend either for or against use. Another scenario of concern that we have observed is the belief by some patients that herbal cannabis could be used as an agent to treat a potentially serious disease, such as inflammatory arthritis or cancer. With poor adherence to standard medical recommendations, it is also important that all treating health-care professionals be kept "in the treatment loop" to ensure that clinical care is coordinated and that there is a consistent message relayed to the patient.

Lessons to be learned for German government and physicians

Reflecting on the Canadian experience surrounding the legalization of medical marijuana, the following advice could be offered to countries considering legalization of cannabis for medicinal purposes. The legislation in Canada to allow access to medicinal cannabis was driven by court challenges and public advocacy, with a lag in formulation of medical recommendations. With the responsibility for prescribing cannabis now recently placed on the medical community, there was a hasty cobbling together of medical advice by various medical bodies in a process more akin to "damage control" rather than rational medical recommendation. The burgeoning concern for risks both to the individual and society has been overshadowed by enthusiastic public advocacy, with the immediate problem of impaired driving not adequately addressed or publicized. In view of the widespread advocacy for medicinal use, it may be anticipated that recreational use may become even more prevalent, with the perception that cannabis is a relatively harmless agent, with both therapeutic and pleasurable effects. We therefore recommend that very clear guidelines be established for prescribing medicinal cannabis and that breach of these directives should result in penalties for both the prescriber and the person accessing medicinal cannabis.

Any government legislating access to medicinal cannabis should support research to better understand patient characteristics that could benefit from cannabinoids, dosing, method of administration, and benefits and risks. The establishment of a formal registry for all persons receiving herbal cannabis will provide real-world information and should be in place prior to any legalization. In parallel with medical legalization there should be legislation in place concerning driving or operating machinery to foster safety of the individual and society, with recommendation that cannabis should be treated similarly to alcohol regarding driving restrictions.

A prescription for any cannabinoid product must be treated similarly to that for other prescribed medications, and with similar precautions required as for a narcotic prescription. A prescription should not be provided by a physician who does not have a longitudinal knowledge of the patient of at least 1 year, and no prescriptions should be obtained by telemedicine. There should be no financial incentive for physicians to provide a prescription, and patients must not pay any additional fee for the prescription. A prescription should only be provided by the physician who is responsible for the care of the condition for which cannabis is recommended, that is, neurologist, rheumatologist, palliative care physician, and only in exceptional circumstances by a primary care physician. Clearly defined medical conditions should be identified as reasons for use of cannabis. Conditions that may benefit from cannabis could include severe neuropathic pain from conditions such as spinal cord injury or tumor-related movement disorders, uncontrolled epilepsy or other well-documented severe chronic pain conditions among others. Caution should be exercised in allowing use for any "pain condition" which could allow legal use with an easy diagnosis of convenience.

The access to cannabis must be through a registered pharmacy and not by any direct contact with the producer or via non-pharmacy vendors.

There should be explicit directives for the physician issuing a prescription for cannabis. The physician must fully document all previous treatment trials to demonstrate justification for a trial of cannabis. Prior to providing a prescription of the herbal product, a treatment trial of a cannabinoid pharmaceutical preparation should be undertaken. The prescription for the herbal product should state the molecular content of THC and CBD, with recommendation to begin with low THC content, and with THC content not exceeding 3 % until further study can help inform ideal molecular content. The initial prescription should be for a treatment trial for 1 month only, with reevaluation prior to any continued prescription. A prescription should not be made for longer than for a 3-month period, with requirement for a health-care encounter for each additional prescription. All patients should be registered in a drug surveillance program to track real-world experience with use including concomitant medication use, health-care utilization, and current functional status, including work history.

Patients should be informed of the current compelling evidence for risks. In particular, cannabis should not be prescribed for any young person below the age of 25 years, unless there are exceptional circumstances and following consultation with a second health-care professional in the same speciality, or a pain medicine or addiction medicine specialist. An addiction risk must be assessed prior to a cannabis prescription, with documentation of risk retained in the medical chart. This will include documentation of previous or current substance use and/or abuse, concomitant drugs with psychoactive effects, and any known criminal record. In the event of a positive response to addiction risk, the opinion of a second physi-

cian with expertise in addiction medicine must be obtained prior to providing a prescription, and the patient should be monitored more rigorously with face-to-face health-care encounters every 2 months.

Herbal cannabis must not be smoked as a rolled joint. Oral use or via a vaporizer are the preferred routes of administration. The vaporizer should be an approved and tested product. Driving restrictions must be in place and need to be regulated by law. Any use of herbal cannabis should preclude the privilege to drive in view of the increased evidence of risk to road safety with psychomotor effects known to outlast measurable serum levels.

Conclusions for clinical practice and healthy policy

If cannabis products should be approved for medical purposes in Germany, the approval process should not be different from that used for other medications. Evidence justifying cannabis products use for various medical conditions will require the conduct of adequately powered, double-blind, randomized, placebo/active-controlled clinical trials to test its short- and long-term efficacy and safety [7, 26]. In addition, studies comparing herbal cannabis with THC or THC/CBD combination in defined medical diseases should be conducted.

Systematic reviews on the evidence available for the efficacy and safety of cannabis products in pain medicine [26], internal medicine [10, 29, 32], neurology [16], and palliative care [24] can help to define indications of the medical use of cannabinoids. Contraindications too should be defined based on a systematic review of the literature and the consensus of medical scientific societies.

The public discussion in Germany led by different political parties, medical societies, and patient representatives has suggested that cannabinoids are broadly effective analgesic drugs that are withheld from chronic pain patients. According to current literature, however, only in distinct individual patients can cannabinoids offer some advantage over current therapy. For example, patients suffering from pain with a spastic component, for example, patients with multiple sclerosis, HIV, paraplegia, or nerve injury, may benefit from the therapeutic use of cannabinoids [16, 26].

If cannabis products are prescribed for defined medical conditions and the costs are reimbursed by health insurance companies, permission for patients to grow cannabis plants for medical use is no longer required. The use of herbal cannabis is associated with risks (no defined dosages of cannabinoids, contamination).

The German Pain Society as the biggest European Chapter of the International Association for the Study of Pain (IASP) supports the initiative of the German Ministry of Health to facilitate the medical use of cannabis products and its reimbursement. Until the legislative project on the medical use of cannabis products is completed, the German Pain Society recommends a differentiated approach for the medical use of cannabis products. A prescription for any cannabinoid product should be treated similarly to that for other prescribed medications, and with similar precautions required as for a narcotic prescription. Individual patients who will benefit from the medical use of cannabis should be identified by a thorough evaluation, should have a defined diagnosis, and there should be a substantiated decision regarding indication and therapeutic value. The medical use of cannabis should be accompanied by detailed documentation and a quality assurance program. Therefore, the German Pain Society supports an individual therapeutic trial in selected patients whose pain is not satisfactorily treated by commonly used analgesics. In addition, and importantly, pharmacotherapy should not be isolated but should be embedded in a multicomponent therapeutic concept [6].

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Compliance with ethical guidelines

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