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Review

Medicinal cannabis in oncology

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ABSTRACT

In The Netherlands, since September 2003, a legal medicinal cannabis product, constituting the whole range of cannabinoids, is available for clinical research, drug development strategies, and on prescription for patients. To date, this policy, initiated by the Dutch Government, has not yet led to the desired outcome; the amount of initiated clinical research is less than expected and only a minority of patients resorts to the legal product. This review aims to discuss the background for the introduction of legal medicinal cannabis in The Netherlands, the past years of Dutch clinical experience in oncology practice, possible reasons underlying the current outcome, and future perspectives.

1. Introduction

The use of cannabis (marijuana, hashish), whether medical or social, has been an issue of debate for years. In the 1980s and 1990s most interest in cannabis focused on limiting its recreational use.[1] Currently, attention has shifted to its clinical and medical properties, even though cannabis use for medical purposes is not new. Indeed, for the past 4000 years,[2] patients and doctors have resorted to cannabis when conventional treatments were ineffective or lacking. The safety and efficacy of cannabis, however, remain controversial.[3] Despite the fact that the US Food and Drug Administration (FDA) does not support the use of (smoked) marijuana for medical purposes,[4] stating that no sound scientific studies, animal or human data support its safety or efficacy, a growing number of US States have passed legislative actions making (medical) cannabis available upon doctor's recommendation.[5,6] Both users and those who advocate medicinal cannabis claim favourable effects for the treatment of refractory neurological symptoms, pain associated with multiple sclerosis (MS) or spinal cord injury,[7] chronic neuralgic pain, aids-related anorexia,[8] HIV-medication-induced nausea and vomiting, Crohn's disease,[9] and Gilles de la Tourette syndrome. In oncology, beneficial effects have been reported for cancer-associated anorexia,[10] (delayed) chemo- or radiotherapy-induced nausea and vomiting.[11] In addition, palliative effects including insomnia relief,[12] mood elevation,[13] appetite stimulation, and analgesia[7] are claimed. Much of the existing controversy regarding the claimed positive effects is largely due to the lack of well-designed (that is randomised, double-blind, and placebo-controlled) and sufficiently powered clinical trials. In addition, the majority of clinical trials have evaluated a wide range of different (synthetic) cannabis products, varying in dose, cannabinoid content, quality, and route of

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administration, in a heterogeneous patient population, making the available clinical data unsuitable for comparison, thus furthermore disabling one to draw sound scientific conclusions. Only very recently have trials emerged which may – in specific indications – put an end to the debate.[14,15]

Part of the explanation for the paucity of clinical trials evaluating the effects of medicinal cannabis is the fact that, although the current (legal) status of medicinal cannabis differs around the world and even within a nation,[16] in the majority of countries the use of medicinal cannabis is illegal and hence registered, and thus standardised products are limited or not available at all. In the United States, only two FDA-approved medicinal cannabis products are available (Marinol® (Marietta, GA) and Cesamet® (Aliso Viejo, CA); Table 1). The Investigative New Drug Application of a third medicinal cannabis product (Sativex®, GW Pharmaceuticals, Salisbury, United Kingdom), which is available in Canada for seriously ill patients under the Canadian Marihuana Medical Access Regulation, has been accepted in April 2006. Sativex® has been evaluated in a phase III clinical trial in patients ($N = 177$) with advanced cancer and was significantly superior to placebo ($P = 0.014$) in the effect on average daily pain relief.[17] Sativex® contains two cannabinoids, Δ9-tetrahydrocannabinol (THC), the main pharmacologically active cannabinoid, and cannabidiol (CBD), a cannabinoid without psychoactive effects but claimed to have anxiolytic, antipsychotic, and anti-spasmolytic effects.[18] However, many patients claim (subjectively) that the favourable effects of cannabis are more pronounced when a whole or partially purified extract of *Cannabis Sativa L.* is used instead of a single synthetic or isolated cannabinoid, which is currently the focus of most clinical trials, underscoring claims that not only THC, but all or some of the (at least) 60 cannabinoids present in cannabis possess pharmacological activity. Since September 2003, in The Netherlands, a legal medicinal cannabis product, constituting the whole range of cannabinoids and meeting pharmaceutical quality standards, is available for (pre)clinical research, drug formulation development, and on prescription for patients. This review aims to discuss the background for the introduction of this product, the past years of Dutch clinical experience in oncology practice with it, and future perspectives.

2. Rationale behind the Dutch policy

The introduction in The Netherlands of a legal medicinal cannabis product meeting pharmaceutical quality standards is the result of a policy that was initiated by the Dutch government in 1998. Unable to definitely exclude a therapeutic effect of medicinal cannabis due to inconclusive data, the Dutch Minister of Public Health continued to advocate the initiation of clinical trials evaluating the safety and efficacy of medicinal cannabis, thus necessitating the availability of a legal product. In 1998, a national (i.e. governmental) agency was established, which holds the monopoly regarding trade, import, and export of cannabis, obligatory according to the United Nations Single Convention on Narcotic Drugs. The Office of Medicinal Cannabis (OMC) was operational as of January 2001. Initially, the prime task of this agency was to organise regulated and well-controlled cultivation and distribution of cannabis that would meet pharmaceutical quality standards and that would be solely intended for clinical research evaluating the efficacy of medicinal cannabis and for drug-formulation development projects to be conducted by pharmaceutical companies. Additionally, the stimulation and initiation of such research and development programmes was also a responsibility delegated to the OMC. However, given the time required to achieve the aforementioned goals, an officially registered drug would not be available for patients in the near future. Consequently, as only a minority of patients resorted to drugs registered outside The Netherlands, mainly due to the high costs and, according to patients' experience, minimal efficacy compared to a whole extract of the *Cannabis Sativa L.* plant, the majority of patients would continue to (be forced to) frequent illegal distributors and so-called 'coffee-shops'. Although coffee-shops are not prosecuted when selling a restricted amount of cannabis under the Dutch soft drug policy, their activities nevertheless remain formally illegal. This was an undesirable situation, most importantly because the pharmaceutical content and quality

Table 1 – Cannabinoid containing drugs available

Cannabinoid	Registered name	Route of administration	Indications	Firm	Legal status
Dronabinol (synthetic THC)	Marinol®	Oral	Anorexia / weight loss (aids patients) Nausea and vomiting (Cancer patients)[a]	Solvay Pharmaceuticals (Marietta, GA, US)	FDA approval April 2003
Nabilone (dronabinol analogue)	Cesamet®	Oral	Nausea and vomiting (Cancer patients)[a]	Valeant Pharmaceuticals (Aliso Viejo, CA, US)	FDA approval May 2006
THC & CBD (isolated from *Cannabis Sativa L.*)	Sativex®	Sublingual	Symptomatic relief of neuropathic pain (MS patients)	GW Pharmaceuticals (Salisbury, UK)	Approval NOC/c policy in Canada[b] Limited availability in Spain and UK

Abbreviations: THC, Δ9-tetrahydrocannabinol; CBD, cannabidiol, FDA, United States Food and Drug Administration; MS, multiple sclerosis; NOC/c, Notice of Compliance with Conditions Policy for its indicated use.

a Who have failed to respond adequately to conventional antiemetics.

b In addition, a regulatory application in Canada to seek approval for treatment of pain in patients with advanced cancer that has not been adequately relieved by opioid medications, has recently been submitted.

(e.g. regarding micro-biological purity and absence of heavy metals) of illegal medicinal cannabis was not standardised or subject to any form of safety assessment or control.[19] Furthermore, most patients used cannabis without prior consultation of their physician, thus without adequate medical counselling. Therefore, in October 2001, the Minister of Public Health decided that the OMC would also be responsible for the legal availability of a crude medicinal cannabis product, available upon prescription for *all* patients (thus not only those participating in a clinical trial), to be dispensed by their community pharmacy. Main arguments underlying this decision included the fact (i) that patient groups (notably representing AIDS, cancer, and MS patients) were ardently advocating the rapid and ready availability of a legal medicinal cannabis product; (ii) that there was a certain social and political pressure to listen to these groups; (iii) that the parliament was in favour of rapid availability of cannabis for patients; and (iv) that (at that stage) a health insurance company was willing to reimburse the costs. Based on the available scientific data, the OMC considered that patients suffering from the following indications could potentially benefit from medicinal cannabis and (thus) resort to the legal product: (i) spasticity in combination with pain associated with MS or spinal cord injury, (ii) nausea and vomiting caused by chemotherapy, radiotherapy and treatment with HIV-medication, (iii) chronic neuralgic pain, (iv) Gilles de la Tourette syndrome, and (v) palliative treatment of cancer HIV/AIDS (http://www.cannabisbureau.nl).

3. Legal Dutch medicinal cannabis

Currently the OMC provides three medicinal cannabis products, Cannabis Flos varieties Bedrocan®, Bedrobinol®, and Bediol® which contain a standardised content of THC (18%, 13%, and 5%, respectively) and CBD (0.8%, 0.2%, and 6%, respectively). A single cultivator, selected by the OMC, cultivates the cannabis. The quality of each batch is analysed according to an analytical monograph formulated by the National Institute for Public Health and Environment. Specifications to be complied with, besides THC and CBD content, include the absence of pesticides and heavy metals and adequate microbiological purity. Finally, a pharmacy can only dispense medicinal cannabis to a patient after receipt of a prescription from a physician.

4. Dutch experience in clinical practice

During the exploratory phase of the development of medicinal cannabis, the Ministry of Public Health and the OMC conducted several surveys and consulted different parties including coffee-shop owners and patient representative groups to estimate the number of patients which would potentially use legal medicinal cannabis if available and to sound the willingness of physicians to prescribe it. It was estimated that approximately 10,000 patients would potentially resort to legal medicinal cannabis and that the majority of physicians ($N = 400$ consulted) were willing to prescribe medicinal cannabis if it was legally available and notably, if more clinical data became available regarding its efficacy and safety.[20]

Between September 2003 and January 2004, the PHARMO Institute, an independent scientific research organisation specialised in pharmaco-epidemiological drug studies, performed a prospective follow-up study among community pharmacies to gain insight into the use of medicinal cannabis.[21] The majority of medicinal cannabis users were female (67%), aged between 40–49 years (25%), and had previous experience with medicinal cannabis use (60%), which they used in combination with analgesics (37%) and psycholeptics (35%). Forty-two percent suffered from MS and 8% from cancer. Cannabis was mainly prescribed for chronic pain complaints (73%) and predominantly administered as herbal tea (74%), one to two times daily (55%). In conclusion, after legalisation, less than 1700 patients (instead of the expected estimate of 10,000) obtained medicinal cannabis from a pharmacy, indicating that the majority of patients (>80%) still frequented the illegal circuit.

In September 2006, the PHARMO Institute conducted a new pharmaco-epidemiological study using their database, which includes drug dispensing, and hospitalisation data of more than 2 million residents, representative for The Netherlands. The drug dispensing histories contain data on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens, and the duration of use. From September 2003 to March 2006 all patients who were dispensed medicinal cannabis were selected from the database. Monthly frequencies of patients using medicinal cannabis were determined and extrapolated to the total population in The Netherlands.

Again, the study results show that, in clinical practice, the total number of patients prescribed legal medicinal cannabis is much lower than anticipated and has even declined ever since introduction of the product in September 2003 (Fig. 1). The number of cancer patients which have resorted to legal medicinal cannabis fluctuates over the evaluated period, reaching peak levels (22–23% of the total number of patients) approximately a year after introduction (Fig. 2). After that, there is a trend towards a decreased use to a lowest point of

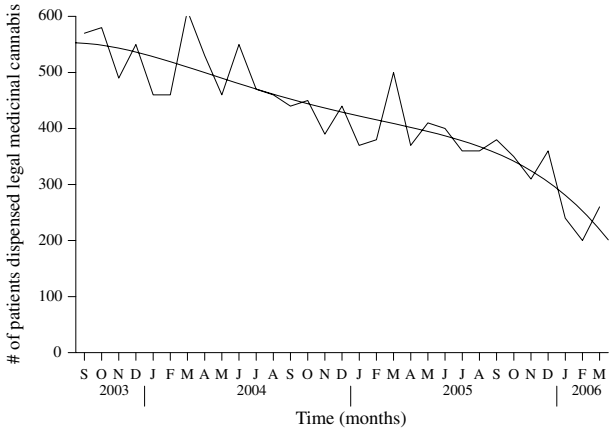

Fig. 1 – Number of patients dispensed legal medicinal cannabis during the evaluated period (September 2003–March 2006) in the PHARMO Record Linkage System (N = 2,000,000) extrapolated to the total population in The Netherlands, including the trend line (polynomial 4).

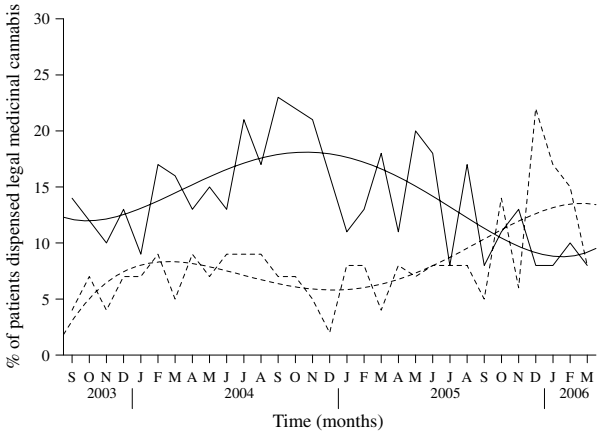

Fig. 2 – Percentage of patients dispensed legal medicinal cannabis diagnosed with cancer (solid line) and multiple sclerosis (dashed line) during the evaluated period (September 2003–March 2006) including the respective trend lines (polynomial 4).

approximately 8% at the end of this period, comparable to the results of the initial study. Legal cannabis use is lower among patients diagnosed with MS, which underscores complaints, notably from this group of users, about the lack of efficacy of Bedrocan® and Bedrobinol® compared with illegal products available from coffee-shops. Accordingly, in February 2007, the OMC has introduced a third variety (Bediol granulate®) with a significantly higher CBD content (claimed to be beneficial for syndromes associated with spasticity) and a lower THC content.

It has been suggested that the use of (legal) medicinal cannabis can lead to a decreased administration of concomitantly used co-medication. The current evaluation shows that morphine use among legal medicinal cannabis users is low, yet relatively stable (Fig. 3). The use of non-opioid analgesics (acetylsalicylic acid/acetaminophen) and NSAIDs (non-steroidal anti-inflammatory drugs) is higher, and seems to fluctuate in the same manner; the same holds for the use of psychotropic drugs (antipsychotics, benzodiazepines, and antidepressants). For none of the categories of co-medication does the introduction of legal medicinal cannabis seem to have led to a decreased use.

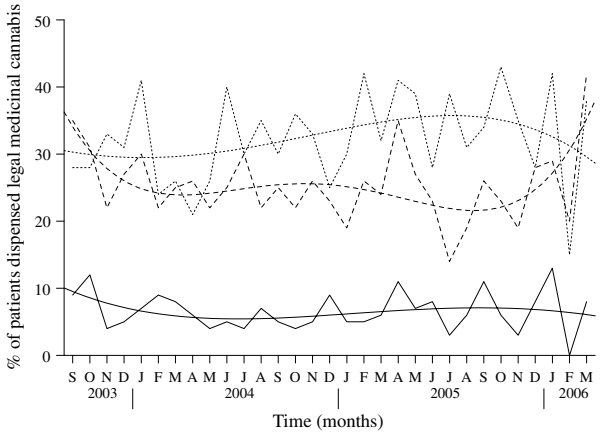

Fig. 3 – Percentage of patients dispensed legal medicinal cannabis, which concomitantly use morphine (solid line), non-opioid analgesics (dashed line) and psychotropic drugs (dotted line) during the evaluated period (September 2003–March 2006), including the respective trend lines (polynomial 4).

5. Research with medicinal cannabis

Table 2 lists the research sites which, since the OMC started distribution in September 2003, have initiated (pre)clinical research or drug formulation development research with the medicinal cannabis varieties Bedrocan® or Bedrobinol® or with products that have been derived from these two varieties (e.g. products containing isolated cannabinoids).[20] Most of the research programmes are still ongoing, with several exceptions; however, most of the completed studies did not evaluate the efficacy of cannabis for the treatment of a specific medical condition.[22,23] Furthermore, several preliminary results have been published and presented at the 3rd Conference of the International Association for Cannabis as Medicine (September 2005, Leiden, The Netherlands). Until 2005, the interest of (inter)national pharmaceutical companies to initiate drug-formulation development strategies using the varieties Bedrocan® and Bedrobinol®, was minimal. However, most recently, the Dutch Medicines Evaluation Board has received an application for the marketing authorisation of a new cannabis drug from a consortium of Dutch pharmaceutical firms. This concerns a tablet containing THC (average purity 99.5%) isolated from the crude cannabis extract of the OMC and differs from Marinol®, Sativex®, and Cesamet® in the chosen formulation; Marinol® is a softgel capsule where THC is solubilised in an oil base, thus guaranteeing physico-chemical stability. However, substantial first-pass effect after oral administration results in low and variable bioavailability of THC (5–20%), which largely hinders adequate and reliable therapy. The oromucosal spray Sativex® was designed to circumvent this first-pass effect, as THC and CBD are readily absorbed from the well-perfused buccal cavity. However, in clinical practice, a substantial portion of the administered dose is swallowed, again making it difficult to determine the adequate dose. This disadvantage is 'masked' by those claiming that the oromucosal spray is advantageous as it allows flexible and individualised dosing, i.e. patients can titrate their overall dose and pattern of dosing according to their response to, and tolerance of, the medicine. The new sublingual formulation is based on pure dronabinol (THC) and an encapsulation and formulation process which applies supercritical carbon dioxide resulting in THC coated on a micro-level yielding physico-chemically stable and highly water soluble drug powder, which is then used to produce tablets. In addition, THC inhalation using a Volcano® vapouriser (http://www.storz-bickel.com), which, through the use of hot air, allows for conversion of THC (isolated from *Cannabis Sativa L.* from the OMC) into volatile THC, thus preventing THC loss due to first-pass effects and also avoiding formation of toxic combustion by-products formed during smoking or insufficient conversion of THC acid into THC upon the preparation of medicinal cannabis tea,[24] is also under clinical evaluation.[25]

Specific oncology-orientated research conducted with the crude cannabis variants, that is, Bedrocan®, Bedrobinol®,

Table 2 – Research conducted with medicinal cannabis (Bedrocan® and Bedrobinol®) from the Dutch Office of Medicinal Cannabis

Preclinical Research[a]	Clinical Research	Product Development	Other
Cerebricon (Kuopio, Finland)	azM, Academic Hospital Maastricht, Brain & Behaviour Institute (Maastricht)[b]	University of Leiden, Institute of Biology (Leiden)	Bionorica Extracts (Neumarkt/Oberpfalz, Germany)
IUML, Institute Universitaire de Médecine Légale (Lausanne, Switzerland)	CHDR, Centre for Human Drug Research (Leiden)	Farmalyse (Zaandam)	Cedarburg Pharmaceutical (Grafton, WI, US)
University of London, Centre for Pharmacognosy and Phytotherapy, School of Pharmacology (London, UK)	Erasmus MC Rotterdam, Dept. of Medical Oncology (Rotterdam)	FeyeCon D&I (Weesp)	University of Kentucky College of Pharmacy (Lexington, KT, US)
TNO Nutrition and Food Research (Zeist)	LUMC, Leiden University Medical Center, Dept. of Psychiatry (Leiden)	VSM Geneesmiddelen (Alkmaar)	Health Canada, Drug Analysis Service (Canada)
University of Córdoba, Dept. of Cellular Biology, Physiology & Immunology (Córdoba, Spain)	UMC Utrecht, University Medical Center Utrecht, Pharmacy (Utrecht)	EnzyScreen (Leiden)	Pharma Bio-Research (Zuidlaren)
University Medical Center Freiburg (Freiburg, Germany)	UMCG, University Medical Center Groningen (Groningen)	TNO Pharma (Zeist)	Plant Research International (Wageningen)
University del Piemonte Orientale, Dept. of Chemical Sciences, Pharmaceutics & Pharmacology (Novara, Italy)	LUMC, Leiden University Medical Center, Pharmacy (Leiden)	Ajinomoto Omnichem (Mont-St-Guibert, Belgium)	ReseaChem (Burgdorf, Switzerland)
University of Bern, Dept. for Chemistry & Biochemistry (Bern, Switserland)	RIVM, National Institute for Public Health and Environment (Bilthoven)[c]		
VivaCell Biotechnology (Denzlingen, Germany) William Ransom & Son (Hitchin, UK)			

a Cannabis, migraine & rheumatoid arthritis European CRAFT (Co-operative Research) programme.
b If no country is specified then the research is conducted in The Netherlands.
c A double-blind, randomised, placebo-controlled, cross-over study on the pharmacokinetics and effects of cannabis.[21]

and Bediol®, is limited. We recently reported a pharmacokinetic drug-interaction study which evaluated the effects of medicinal cannabis (Bedrocan®) on the pharmacokinetics of irinotecan and docetaxel, both subject to cytochrome P450 3A mediated biotransformation in cancer patients[26]; the data suggest no (significant) pharmacokinetic drug-interaction. Preclinical cytotoxicity investigations with THC, THC-acid, CBD, and cannabinol (CBN) isolated from *Cannabis Sativa L.* obtained from the OMC have shown that THC and CBN express low to moderate cytotoxicity, whereas THC-acid and CBD express moderate to high cytotoxicity in a melanoma cell line and ovarian cancer cell line, respectively.[27] A research programme is in development to assess the therapeutic potential of cannabinoids for the treatment of cancer.

6. Future perspectives

In November 2005 the Dutch Ministry of Public Health, following a discussion in the Parliament, presented an independently conducted evaluation of the Dutch policy concerning the legal availability of medicinal cannabis.[20] The evaluation was performed in order to aid the Ministry of Public Health in her decisions regarding its future policy towards medicinal cannabis. Most important conclusions of this evaluation were that the number of patients which obtained their medicinal cannabis on prescription from the pharmacy was much lower than expected, that the amount of initiated (pre)clinical research was still inadequate, and that (inter)national pharmaceutical companies had shown a lack of interest to further develop medicinal cannabis into a registered drug; hence the chosen policy was not cost-effective (although no cost-effectiveness studies have adequately addressed this issue).

Several factors have been put forward to explain these findings including (i) the potential number of patients was most likely highly overestimated; (ii) the high pharmacy price compared to illegally produced and sold cannabis in 'coffeeshops', combined with the fact that (iii) the Dutch Health Care insurance board concluded that given the insufficient evidence to support efficacy, medicinal cannabis does not fulfil the criteria to be reimbursed, making patients pay for the

medicinal cannabis themselves, and any reimbursement policy is up to each individual patient's health insurance company, (iv) the unwillingness/hesitation of physicians to prescribe medicinal cannabis (due to the lack of convincing medical evidence) and/or of patients to demand a prescription, (v) negative publicity in the lay press, (giving) the impression that the Ministry of Public Health is not fully supportive of its own product, (vi) complaints of decreased effectiveness and the fact that only two varieties of comparable THC and CBD content were available at that time, and (vii) the fact that no marketing strategy was implemented upon introduction of the product. Based on this evaluation the Minister of Public Health decided to continue the distribution and availability of legal medicinal cannabis at least until the end of 2006. In October 2006, it was decided to further extend availability until the end of 2007 (and possibly an extra 5 years thereafter),[28] given the fact that the above-mentioned plans of a consortium of Dutch pharmaceutical firms to register a drug formulation based on crude medicinal cannabis are in an advanced stage and show sufficient potential for success, thus assuring a steady source of income for the OMC. In addition, in 2006, several international pharmaceutical parties have ordered increasing quantities of the crude medicinal cannabis varieties for drug development research and the Canadian, German, and Italian governments have shown interest in the Dutch products to dispense to patients. Consequently, these developments will also help to increase the cost-effectiveness of the chosen policy.

7. Conclusion

Summarising, one can conclude that the introduction in 2003 in The Netherlands of two varieties of legal medicinal cannabis, an initiative supported by the Dutch government, in order to stimulate (pre)clinical efficacy and safety research, while at the same time providing patients access to a legal, standardised product meeting pharmaceutical quality requirements, has not (yet) led to the desired outcome. In contrast to the expectations, only a minority of patients resorts to physician prescribed cannabis dispensed by their community pharmacy. (Pre)clinical research with the crude cannabis varieties or with derived isolated cannabinoids is ongoing, yet is far less than expected. Only recently, the first results of well designed trials have become available and more data are anticipated. At present (only) one drug formulation based on THC derived from the cannabis varieties supplied by the OMC is awaiting a decision regarding regulatory approval in The Netherlands. Despite its limited use, both as crude product and as material for other drugs, the Dutch Minister of Public Health, responsible for the initiated policy, decided to guarantee continued distribution and availability of legal medicinal cannabis until the end of 2007, after which a renewed decision, which is likely to depend on the registration of the above-mentioned drug, will be taken.

Based on a pharmaco-epidemiological study, the percentage of cancer patients (in relation to the total number of patients resorting to legal medicinal cannabis) which use legal cannabis has fluctuated between 8% and 23% in the past years. At this moment, cancer-associated use seems to be at a very low level. It is assumed that the majority of patients still acquire their medicinal cannabis through illegal distributors, 'coffee-shops', or by growing it at home. However, there are no data available which give insight into exact numbers, (possibly also because medical use of cannabis is still more or less a taboo); cancer patient representative groups do not record such data, nor do coffee-shop owners.

Several reasons have been put forward to explain the lack of success of the Dutch policy and include the high price in pharmacies, varying reimbursement policies of health insurance companies, claims of a lack of effectiveness, and/or the hesitation of physicians to prescribe medicinal cannabis. The latter may be explained for by the (still) existing lack of well designed clinical trials evaluating the efficacy of medicinal cannabis, which are necessary to support evidence-based use. Only recently, the first results of such trials have become available and more data are anticipated. However, it should be noted that the lack of clinical trials is partly due to the limited amount of registered cannabinoid containing drugs. It seems that a vicious situation regarding medicinal cannabis exists; the controversy regarding the safety and efficacy of medicinal cannabis is likely to remain as long as there are insufficient preclinical data and/or well designed clinical trials with approved drugs; at the same time this situation provides insufficient incentive for pharmaceutical companies to initiate drug formulation development programmes. Drug development is extremely costly and most pharmaceutical companies will only undertake such a project if they are confident (based on exploratory *in vitro* and *in vivo* research) that a drug compound is safe, effective and that there is a sufficiently large population which will resort to the drug and benefit from it.

In conclusion, despite 4 years of clinical experience with legal, standardised medicinal cannabis in The Netherlands, the gap between medicinal cannabis 'believers' and 'non-believers' still exists. It is our opinion that, in the interest of patients, all involved parties (i.e. government, physicians, pharmaceutical drug development firms, patient representative groups) put aside their individual viewpoints and strive together to put an end to this situation. Only sound scientific evidence can put an end to the current ongoing controversy.

Conflict of interest statement

None declared.

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