

Cannabinoids and cancer: causation, remediation, and palliation

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This review discusses three different associations between cannabinoids and cancer. First, it assesses evidence that smoking of cannabis preparations may cause cancers of the aerodigestive and respiratory system. There have been case reports of upper-respiratory-tract cancers in young adults who smoke cannabis, but evidence from a few epidemiological cohort studies and case-control studies is inconsistent. Second, there is mixed evidence on the effects of THC and other cannabinoids on cancers: in some *in vitro* and *in vivo* studies THC and some synthetic cannabinoids have had antineoplastic effects, but in other studies THC seems to impair the immune response to cancer. As yet there is no evidence that THC or other cannabinoids have anticancer effects in humans. Third, Δ^9 -tetrahydrocannabinol (THC) may treat the symptoms and side-effects of cancer, and there is evidence that it and other cannabinoids may be useful adjuvant treatments that improve appetite, reduce nausea and vomiting, and alleviate moderate neuropathic pain in patients with cancer. The main challenge for the medical use of cannabinoids is the development of safe and effective methods of use that lead to therapeutic effects but that avoid adverse psychoactive effects. Furthermore, medical, legal, and regulatory obstacles hinder the smoking of cannabis for medical purposes. These very different uses of cannabinoids are in danger of being confused in public debate, especially in the USA where some advocates for the medical use of cannabinoids have argued for smoked cannabis rather than pharmaceutical cannabinoids. We review the available evidence on these three issues and consider their implications for policy.

Illicit drug users obtain cannabis preparations from the *Cannabis sativa* plant, which contains more than 60 cannabinoids.¹ The cannabinoid Δ^9 -tetrahydrocannabinol (THC)^{2,3} causes many of the plant's psychoactive effects and is found in the resin that covers the flowering tops and upper leaves of the female plant (figure 1); by contrast, marijuana is prepared from the dried flowering tops and leaves of the female plant.⁴ The flowering tops have the highest THC concentration, and concentrations are much lower in the leaves, stems, and seeds. Cannabis, which normally grows male and female flowers on separate plants, can be cultivated to maximise its THC content by the sinsemilla method, in which female plants are isolated, causing them to increase production of flowers covered by resin glands containing THC or other cannabinoids.⁴

The concentration of THC (figure 2) in marijuana has been reported to range from 0.5% to 5.0%,⁵ whereas sinsemilla cannabis may contain 7.0–14.0% THC.⁵ Hashish, or hash, consists of dried cannabis resin that contains 2.0–8.0% THC. Hash oil is made by extraction of THC from hash (or marijuana) in oil and contains 15.0–20.0% THC.⁶ Evidence suggests that cannabis in the Netherlands may contain much higher amounts of THC than previously thought.⁷ More accurate data on the THC content of cannabis products is needed, as is research on the health implications of increased THC content.⁷

In this discussion, cannabis refers to products derived from *C sativa* that are assumed to be smoked, unless otherwise specified. Cannabinoids refer to pharmaceutical extracts derived from *C sativa* and to synthetic substances that act on cannabinoid receptors

in the brain. Endocannabinoids refer to endogenous cannabinoids that are found in the human brain and body.

Recreational and medical cannabis use

In 2000 there were an estimated 150 million non-medical cannabis users worldwide—ie, 3.7% of the world's population older than 15 years.⁸ Most users are young adults who seek its euphoric and other psychoactive effects.⁹ Europe generally has lower use than Australia, Canada, and the USA; within Europe,

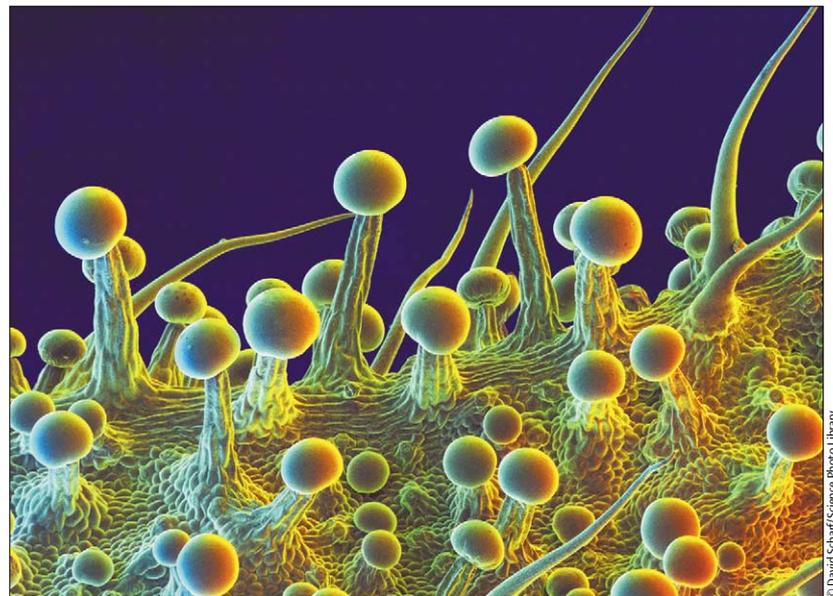


Figure 1: Scanning electron micrograph of *Cannabis sativa* leaf. Trichomes in the foreground secrete a resin that contains THC.

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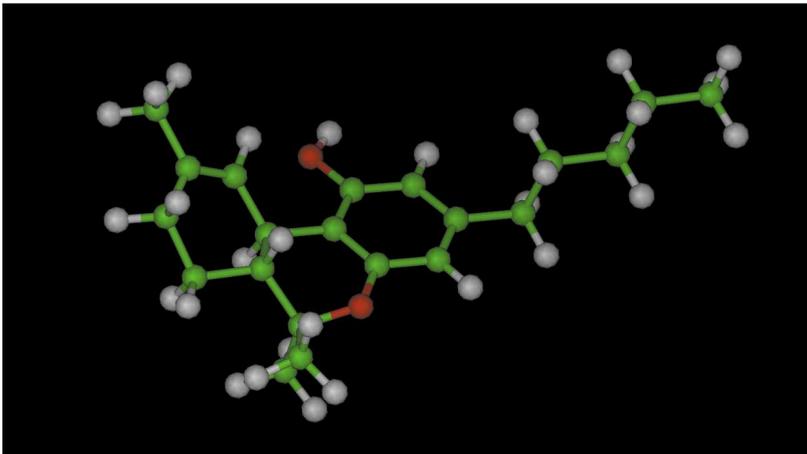


Figure 2: Chemical structure of THC
Green=carbon. Red=oxygen. Grey=hydrogen.

the highest rates are in the UK, Denmark, and France.⁹ The limited data from developing countries suggest that, with some exceptions such as Jamaica and South Africa, cannabis use is lower than that of Europe and English-speaking countries.⁹

Cannabis use in the USA typically begins in the mid-to-late teenage years and peaks in people in their early 20s, before declining in the mid-to-late 20s. Only a few young adults continue to use cannabis into their 30s.¹⁰

Medical use of cannabis products is less common than their recreational use (2% vs 7% in a survey done in Canada in 1998).¹¹ Most people who reported medical use of cannabis in this survey were mainly recreational users who used it for symptom relief during illness. Estimates of medical cannabis users in the USA are much lower, but patients may be deterred from doing so because of the illegality of cannabis use under US federal law.¹²

Methods of cannabinoid use

Marijuana is typically smoked in a hand-rolled cigarette (a so-called joint) or in a water pipe (a so-called bong). Hash can be mixed with tobacco and smoked as a joint or smoked in a pipe with tobacco. Hash oil may be applied to a cigarette or joint, or heated and the vapours inhaled. Smokers typically inhale deeply and hold their breath to ensure maximum absorption of THC. The main advantage of smoking cannabis is the rapid onset and consistent cannabinoid effects.¹³ Hash and marijuana can also be cooked in foods and eaten.

In therapeutic settings, THC is commonly dissolved in sesame oil and swallowed in gelatine capsules. Cannabis extracts have been developed for medical use as a sublingual or oropharyngeal spray¹⁴ and several non-pyrolising vaporisers have also been developed, but their properties and risks have yet to be assessed fully.¹⁵ Use of aerolised THC in animals suggests that, in the future, inhalation may be possible.¹⁶

Pharmacology and biology of cannabinoids

When cannabis is smoked, THC is absorbed into the bloodstream in several minutes via the lungs;¹³ by contrast, when taken orally it takes 1–3 h to enter the bloodstream.³ After smoking, THC is metabolised first in the lungs and then in the liver.¹⁷ The metabolite 9-carboxy-THC, which is not psychoactive, is detectable in blood several minutes after smoking cannabis. Slightly more potent than THC, 11-hydroxy-THC is a metabolite that crosses the blood–brain barrier more rapidly, and which is found in very low concentrations in the blood after smoking and at higher concentrations after oral use.¹⁸ THC and its metabolites account for most of the psychoactive effects of cannabis.^{13,17}

Peak blood concentrations of THC occur within 10 min of smoking and decline to 5–10% of their initial concentration within 1 h as THC is converted to its metabolites.³ THC and its metabolites are highly fat soluble and concentrate in lipid-rich tissues where they may remain for substantial periods.¹⁷

Research during the 1990s identified sites of cannabinoid receptors in the brain and the endogenous cannabinoid ligands—endocannabinoids—that act on these receptor sites.¹⁹ Cannabinoid receptors respond to THC and to endocannabinoids such as anandamide and 2-arachidonyl-glycerol.¹⁹

Two types of cannabinoid receptors, CB1 and CB2, have been identified to date.^{20–22} CB1, which is found mainly in the brain, causes the psychological effects of THC because drugs that block the receptor inhibit many of its effects in humans;²³ CB2 is found in the immune system.²¹ CB1 and CB2 are G-protein-coupled receptors found in membranes of nerve cells and are involved in chemical signalling between cells.

The distribution of CB1 and CB2 in the brain, immune system, and reproductive tissues is consistent with many therapeutic and recreational effects of cannabis.²⁴ CB1 is mostly concentrated in brain systems involved in mood control, motor function, memory, food intake, pain, immune function, and reproductive functions.²² A high density of CB1 in the basal ganglia and cerebellum explains why cannabinoids interfere with coordinated movement.³ The absence of cannabinoid receptors in the lower brainstem explains why high doses of THC are rarely lethal.²

Mutagenicity and carcinogenicity

THC and other cannabinoids can change cell metabolism, DNA synthesis, and cell division in vitro, but these events stop cell division rather than lead to cancer.²⁵ There is no evidence that THC and other cannabinoids are mutagenic in standard microbial assays of mutagenicity such as the Ames test,²⁵ and THC is not carcinogenic in skin tests on mice.²⁶

Cannabis smoke is mutagenic in vitro,^{27,28} in the Ames test,²⁹ and in skin tests done on mice.²⁹ Carcinogens found in cannabis smoke are similar to those in tobacco

smoke; however, cannabis smoke contains cannabinoids whereas tobacco smoke contains nicotine.²⁷

Anticancer effects of cannabinoids

Evidence suggests that THC, other naturally occurring cannabinoids (eg, cannabidiol, and cannabinol), synthetic cannabinoid agonists, and endocannabinoids have antineoplastic effects *in vitro*^{30,31} against lung carcinomas, gliomas, thyroid epithelioma, lymphomas, skin carcinomas, uterine carcinoma, breast cancer, prostate carcinoma, and neuroblastoma.³⁰ *In vivo* studies^{30,31} have found that naturally occurring and synthetic cannabinoids have antineoplastic effects in mice given xenografts of lung carcinomas, gliomas, thyroid epitheliomas, lymphomas, and skin carcinomas. The mechanisms of these antineoplastic effects are not well understood, but the role of cannabinoid receptors in their mediation is suggested by expression studies and by the inhibitory action of cannabinoid antagonists.³⁰ Cannabinoids may also induce apoptosis in some cancer-cell lines and inhibit angiogenesis.³⁰

There is conflicting data in animals and *in vitro* on the antitumour effects of THC. Some studies indicate that THC promotes the growth of tumours in mice with lung cancer by modulation of immune-system responses to the tumour,³² and some *in vitro* studies suggest that THC (and marijuana smoke) inhibit apoptosis in the transformed pulmonary-cell line A549.³³

To date, there are no published studies of antineoplastic effects of cannabinoids in humans, although at least one such study is under way.³⁰ More studies are clearly needed in light of previous attempts to translate anticancer effects *in vitro* and *in vivo* into substantial anticancer effects in humans³⁰ and given the conflicting findings on the effects of THC on tumour growth and apoptosis.

Cannabis smoking and cancer

Cancers of the aerodigestive tract and lung

Cannabis smoking is most likely to cause cancers in sites that receive heaviest long-term exposure to carcinogens in cannabis smoke—ie, the aerodigestive tract (mouth, tongue, and oesophagus) and lung.²⁵ The same histopathological and mutagenic changes thought to be precursors of lung carcinoma have been found in the lungs of chronic cannabis smokers.^{34,35} Furthermore, case reports have documented cancers of the upper aerodigestive tract in young adults who have been chronic smokers of cannabis.^{36–38}

Epidemiological studies have reported inconsistent associations between cannabis smoking and cancers. Sidney and colleagues³⁸ reported on cancer incidence over an 8.6-year follow-up of 64 855 members of the US Kaiser Permanente Medical Care Program (average age at entry 33 years), in which 38% never used cannabis, 20% were experimenters (ie, used cannabis less than six times), 20% were past users, and 22%

were current users. The study found no overall excess cancer incidence in ever users or current users of cannabis. Tobacco smokers had a higher risk of tobacco-related cancers than did non-tobacco smokers (irrespective of cannabis use), but cannabis smokers were not at increased risk compared with non-smokers of tobacco. However, the study by Sidney and colleagues³⁸ has two limitations that probably decrease the chances of finding an association between cannabis use and cancer. First, the average age of the cohort was only 43 years at follow-up and secondly, only 22% of participants reported regular cannabis use at accrual and most of these would have discontinued use during follow-up.¹⁰

Zhang and co-workers³⁹ compared cannabis use in 173 patients with primary squamous-cell carcinoma of the head and neck with 176 controls. Patients were seen at the Memorial-Sloan Kettering Hospital, New York, NY, USA, 1992–94, and controls were age-matched, sex-matched, and cancer-free blood donors from the same hospital. Patients were more than 2.6 times more likely to have used cannabis than were controls after adjustment for cigarette smoking, alcohol use, and other risk factors. A dose-response relation between frequency and duration of cannabis use was stronger in adults younger than 55 years.

Two studies did not find any association between cannabis use and oral squamous-cell carcinomas. A case-control study by Llewellyn and colleagues⁴⁰ of 116 patients (identified from a cancer register) and 207 age-matched and sex-matched controls (sampled from the same general practices as the patients) did not associate self-reported cannabis use with oral cancers in young adults; however, only 10% of participants were heavy users of cannabis. Rosenblatt and co-workers⁴¹ reported on a larger community-based study of 407 patients and 615 controls aged 18–65 years in WA, USA, and found no relation between risk of oral squamous-cell cancer and the various indices of cannabis use, including ever users versus never users, frequency, and duration of use. They argued that the findings from Zhang and co-workers³⁹ arose from a spuriously low frequency of cannabis use in blood-donor controls. In the study by Rosenblatt and co-workers,⁴¹ the frequency of cannabis use in controls matched that predicted from population surveys of cannabis use in the adult population of the USA.

There is a conspicuous lack of evidence on the association between cannabis smoking and lung cancers; however, this gap should be rectified by the findings from a large US case-control study funded by the US National Institutes of Health. The main uncertainties about the risks of respiratory and oral cancer are whether cannabis smoking increases the risk of rarer forms of these cancers; reduces the age of first diagnosis; or causes cancers to become more aggressive. The interaction of these risks with alcohol

and tobacco, which many cannabis users also use, also needs to be defined. The limitations of self-reporting will need to be addressed, given that cannabis use is still illegal in countries where these studies were done. The ideal cohort study would be much larger than those previously, would ensure the confidentiality of participants, and would follow-up larger numbers of regular users of cannabis for longer periods than those that have been studied to date. Risks may become clearer as baby-boomer birth cohorts (who were the first to smoke cannabis in substantial numbers) enter the age groups in which cancer incidence begins to rise steeply.^{41,25}

Childhood cancers

Three case-control studies have found associations between cannabis use during pregnancy and increased risk of cancer in children. A case-control study of acute non-lymphoblastic leukaemia to assess the role of maternal and paternal exposures to petrochemicals, pesticides, and radiation in cancer investigated maternal drug use, including marijuana use, before and during pregnancy as a possible confounder. The mothers of children with acute non-lymphoblastic leukaemia were 11 times more likely to have used cannabis before and during pregnancy than were mothers of controls. This relation persisted after adjustment for other risk factors. Reporting bias by the mothers of patients was an alternative explanation of the finding because cannabis use in controls was much lower than in case-control studies of other childhood cancers.²⁵

Two case-control studies have reported an increased risk of rhabdomyosarcoma⁴² and astrocytomas⁴³ in children born to women who reported smoking cannabis during pregnancy. Neither study was a planned investigation of the association between these childhood cancers and maternal cannabis use; rather, cannabis use was one of many possible confounding variables measured.

There has been no increase in the incidence of non-lymphoblastic leukaemia, rhabdomyosarcoma, and astrocytoma between 1979 and 1995 that could be accounted for by cannabis use during pregnancy.²⁵ The incidence of acute non-lymphoblastic leukaemia⁴⁴ and soft-tissue sarcomas (including rhabdomyosarcomas)⁴⁵ remained steady over this period. However, the incidence of CNS malignant disease (about 52% of which are astrocytomas) did increase between 1979 and 1995,⁴⁶ but was probably a result of improved diagnosis from the wide use of CT and MRI in the USA.⁴⁶

Other cancers

Associations have been found between cannabis use and several other cancers. Sidney and colleagues³⁸ found that males who had ever smoked cannabis (relative risk [RR], 3.1) and males who were current

cannabis smokers (RR, 4.7) had a higher risk of prostate cancer than non-users of cannabis. Eford and colleagues⁴⁷ correlated smoking cannabis at least monthly with malignant primary adult-onset glioma in a managed-care cohort (RR, 2.8 after adjustment for other risk factors), but there was no dose-response relation between cannabis use and this cancer. Moreover, none of these associations emerged from a focused test of an a priori hypothesis; all were reported incidentally because cannabis use was assessed as a potential confounding factor. Therefore, these studies need to be repeated.²⁵

Cannabis and cancer palliation

Until October, 2003, when cannabinoids and cannabis have been advocated for medical use in oncology,³¹ they were used mainly for the relief of symptoms rather than treatment of underlying cancer.¹⁹ Here, we focus on the palliative uses of cannabinoids in cancer treatment.

Antiemetic effects

In the late 1970s and early 1980s, ineffective treatment of chemotherapy-induced nausea prompted oncologists to study the antiemetic properties of cannabinoids.¹⁹ Since these early studies, several clinical trials have compared the effectiveness of THC with placebo or with another antiemetic drug.⁴⁸⁻⁵⁰ Comparisons of oral THC with existing antiemetic agents generally indicated that THC was at least as effective as prochlorperazine.^{48,49,51,52} Although cannabinoids showed some antiemetic efficacy, typically they did not prevent nausea in two-thirds of patients. In a well-controlled study, THC completely controlled emesis in only 13% of patients versus 47% of those who received metoclopramide. THC achieved major control of vomiting (ie, two or fewer episodes) in 27% of patients compared with 73% of the comparator group.¹⁹ Nabilone and levonantradol have also shown greater antiemetic efficacy than THC.¹⁹ Withdrawal rates from these trials also indicated a narrow therapeutic window for cannabinoids, and highlight the need for careful titration of dose.

Since these trials, more effective antiemetic drugs have reduced nausea and vomiting during cancer chemotherapy.¹⁹ Selective antagonists for the 5-hydroxytryptamine 3 receptor and the protachykinin receptor decrease acute emesis, and protachykinin-receptor antagonists delay emesis from highly emetogenic platinum-based chemotherapy.⁵³ To date, clinical trials have not compared the antiemetic effects of cannabinoids with the newer agents; moreover, all studies have involved oral use of cannabinoids, which may be less effective than sublingual or inhaled cannabinoids.

Cannabinoids are unlikely to be used as first-line treatment for nausea and vomiting, but they may prove

to have a limited role as adjunctive antiemetics. Because the mechanisms of cannabinoid-induced antiemesis differ from other agents, they could benefit unresponsive patients, or may be used as adjuvant treatment to enhance the effects of existing antiemetic medications if there prove to be synergistic effects between cannabinoids, 5-hydroxytryptamine-3-receptor antagonists, and dexamethasone similar to those observed between cannabinoids and prochlorperazine.

Appetite stimulation

CB1 agonists stimulate appetite⁵⁴ and dronabinol (THC) has been registered for use in the USA as an antiemetic and appetite stimulant in patients with AIDS-related wasting disease¹⁹ on the basis of evidence from clinical trials.^{55,56} High doses of megestrol, a synthetic progesterone derivative, also stimulates appetite and leads to weight gain in patients with HIV/AIDS. Low doses of dronabinol did not seem to add to the effects of megestrol in the stimulation of appetite, nor was it as effective in generating weight gain.⁵⁷ Some patients are not suited to dronabinol because of its psychoactive side-effects, difficulty in dose titration to optimise benefit and minimise side-effects, delay in onset of action, and long-term effects when taken orally.¹⁹ Some advocates for patients with AIDS have argued that smoked cannabis is better for titrating doses of THC to achieve optimum symptom control.¹⁹ Sublingual or inhaled cannabinoids may allow better titration of THC compounds without ingestion of the carcinogens in cannabis smoke.

Analgesia

Animal studies suggest that cannabinoids may be useful as analgesics for neuropathic pain. CB1 acts on pathways that partly overlap with those affected by opioids such as morphine, and also acts through pharmacologically distinct mechanisms. CB1 is widely distributed throughout the CNS and peripheral nervous system; concentrations are very high in periaqueductal grey matter.⁵⁴ Cannabinoids and opioids may have additive or synergistic analgesic effects because of similarities in the physical distribution of their receptors.

Studies in humans of analgesia with experimentally induced pain have shown mixed results;¹⁹ however, like assessment of the analgesic effects of opioids,⁵⁸ better analgesic effects have been observed in clinical studies of cannabinoids in patients with severe, persistent cancer pain that was resistant to traditional analgesics.⁵⁹⁻⁶¹ These double-blind placebo-controlled trials showed that cannabinoids had analgesic effects equal to those of codeine, and also improved mood, wellbeing, and appetite. In the setting of chronic pain a series of well-designed n=1 studies⁶² using THC, cannabidiol, both, or placebo are good evidence of the efficacy of cannabinoids and suggest that cannabinoids

may have a role in management of neuropathic pain, but have lesser efficacy in treatment of nociceptive pain.⁶³

A study of a cannabinoid analogue in a few patients suggests a substantial analgesic effect in chronic pain, with fewer psychotropic effects.⁶⁴ In this 7-day placebo-controlled trial, the cannabinoid analogue significantly reduced pain 3 h after use and the benefit lasted 6 h. Water-soluble cannabinoids such as Δ^8 -THC-11-oic acid have a wider range of medication formulations and drug-delivery methods than THC but need to be studied in adequately powered clinical studies to assess their analgesic and other therapeutic effects.⁵⁸

Risks of therapeutic cannabinoid use

Patients may discontinue therapeutic use of cannabinoids because of acute psychoactive effects, especially dizziness, dysphoria, depression, hallucinations, and paranoia. The most serious adverse acute effect of cannabis use is impaired psychomotor function,⁹ which makes it prudent for patients under the influence of cannabis or THC to operate equipment that might endanger the user or others (eg, driving a car or operating equipment).¹⁹ There are also potential synergistic effects between cannabinoids and other psychotropic agents, including alcohol. Short-term immunosuppressive effects are not well established and, if they exist, are probably not substantial enough to preclude short-term medical use. According to the 1999 US Institute of Medicine report,¹⁹ the acute adverse effects of cannabinoids are "within the risks tolerated for many medications", and patients may develop tolerance to some acute, adverse psychotropic effects with continued use.

The effects of chronic cannabinoid use are of potentially greater concern for long-term medical use.⁹ Evidence of long-term adverse effects from cannabinoid use mainly derives from studies of non-medical cannabis smokers that assessed the effects of chronic smoking or the risk of developing dependence on cannabis or THC. Cannabis smoke is a probable risk factor for cancer and lung damage,⁶⁵ thus smoking is an unsafe form of medication for any chronic medical condition.¹⁹ This risk is avoided if, as is most likely, oral, sublingual, or inhalation methods of cannabinoid administration are used medically. There is still a risk of developing dependence on THC, but is highest in adolescents (especially those with conduct disorders) and in people with psychiatric disorders or problems with substance abuse.¹⁹ These high-risk groups are unlikely to be therapeutic users of cannabinoids. Patients with chronic illness may regard cannabinoid dependence as an acceptable risk for gain of therapeutic effects.⁶⁶ Experience with therapeutic use of opioids suggests that older patients who develop physical tolerance to the effects of THC are unlikely to engage in the type of drug-seeking behaviour seen in young recreational cannabis smokers.

Commercial obstacles to therapeutic use

Pharmaceutical companies face substantial disincentives to develop and market new cannabinoids.¹⁹ Research and development of cannabinoids are similar to other neuropharmaceuticals, which are costly to develop and register. Only synthetic cannabinoids can be patented and the markets for the symptoms that cannabinoids will probably be used to treat are modest and effective drugs are available for many of these symptoms. Moreover, in the USA, strict regulatory requirements must be met to register a drug derived from, or chemically related to, a prohibited substance.

New formulations of cannabis are under development and in trials in the UK,¹⁴ including standardised THC content in a smokable form to minimise variation in THC availability. There is renewed interest in development of synthetic therapeutic cannabinoids and so-called cannabinergics,^{67,68} however, until these drugs and new formulations have been marketed, the only choice for patients is to use oral THC. If patients are unable to use oral cannabinoids, they may want to smoke cannabis. However, the smoking of cannabis poses major problems for patients, especially in the USA, where this option has been legislatively allowed in only some states (figure 3).⁶⁹

Legal and regulatory obstacles to medical use

In the USA, marijuana is classified under the Controlled Substances Act 1970 as a drug that has no medical use.¹⁹ Various different ways have been suggested to permit the medical use of marijuana, each of which have practical and legal problems. Provision of marijuana in clinical or in other research trials only provides legal access to a few patients, thus excluding legal access to patients who do not wish to participate in trials.¹²

Search strategy and selection criteria

Data for this review were identified by searches of PubMed using the terms “medical marijuana”, “medical use and illicit drugs”, “phytotherapy”, “cannabinoids”, “therapeutic use”, “antineoplastic”, “palliative”, “adverse effects”, “risks”, and “carcinogens”. A few papers published before 1990 were included; only papers published in English between February, 1975, and June, 2004, were included. Major policy and research reports of governments and international organisations were also selected for inclusion. Additional papers were identified from leading edited works on this subject.

Laws that allow physicians to prescribe cannabis in some US states and in Canada face two problems. First, in the USA, state prescription laws conflict with federal law, which exposes physicians and patients to the risk of federal criminal prosecution. Second, in Canada, the federal government permits medical use of marijuana, but physicians have been reluctant to prescribe cannabis because of uncertainty about the indications for its use and because of fears of legal liability for any harm caused by chronic cannabis smoking.¹²

The securing of a legal supply of cannabis is a problem for patients unless it is supplied by the government (like in Canada) or unless patients are allowed to grow their own (as proposed in Australia and allowed in Canada).¹² Supporters of cannabis prohibition have criticised the granting of exemptions from criminal prosecution for patients as back-door legalisation. Governments may find it hard to reassure the public about the risks of diversion to the black market, even if it is likely to be trivial by comparison with the illicit market for recreational cannabis users.⁷⁰

Conclusion

Cannabis smoke is carcinogenic and mutagenic; however, THC alone does not seem to be carcinogenic or mutagenic. Indeed, evidence suggests that THC and other naturally occurring and synthetic cannabinoids may have anticancer effects.

Cannabis smoke is carcinogenic in vitro and in vivo, and is a possible cause of respiratory cancers in regular cannabis smokers. However, epidemiological studies to date have produced conflicting results and larger, better-controlled studies are needed. Suggestive associations between maternal cannabis use and several childhood cancers are not supported by increased incidence of any of these cancers. Other associations between cannabis smoking and tumours of the prostate and brain need to be reassessed in larger and better-controlled epidemiological studies.

THC and other cannabinoids are potentially useful adjuvant treatments in palliative care of people with



Figure 3: People in favour of Ballot Measure 2 on Nov 2, 2004, in Anchorage, AK, USA
The proposition would have legalised use and sale of marijuana, but was rejected by Alaskan voters.

cancer. These cannabinoids improve appetite, reduce nausea and vomiting, and alleviate moderate neuropathic pain, but whether they are more effective than existing drug treatments for these symptoms remains to be seen. A major challenge for palliative use of cannabinoids and cannabis extracts is to develop safer, non-smoked methods of delivery that allow users to titrate doses and achieve desired therapeutic effects while avoiding adverse psychoactive effects. There are substantial medical, legal, and regulatory obstacles to the use of smoked cannabis for medical purposes, whereas non-medical cannabis use continues to be prohibited by law.

Conflict of interest

We declare no conflicts of interest.

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