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The intersection between cannabis and cancer in the United States

Daniel W. Bowles[a,b,c,*], Cindy L. O'Bryant[a,d], D. Ross Camidge[a], Antonio Jimeno[a,b]

[a] *Developmental Therapeutics Program, University of Colorado Cancer Center, Aurora, CO 80045, United States*
[b] *Head and Neck Cancer Program, University of Colorado Cancer Center, Aurora, CO 80045, United States*
[c] *Medical Marijuana Advisory Committee, Colorado Department of Public Health and Environment, Denver, CO 80246, United States*
[d] *University of Colorado School of Pharmacy, Aurora, CO 80045, United States*

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Abstract

In the last 15 years there has been a major shift in the laws governing medical use of cannabis in the United States. Corresponding with this change there has been escalating interest in the role that cannabis, commonly referred to as marijuana, and cannabinoids play in the care of patients with cancer. This review will examine cannabis' and cannabinoids' current and potential roles in cancer care. Specifically, we will examine five areas of cannabis medicine: (1) pharmacologic properties of cannabis; (2) its potential role in the development of human cancers, particularly smoking-related malignancies; (3) cannabinoids' potential as anti-cancer therapies; (4) cannabis and cannabinoids in the palliation of common cancer-associated symptoms; (5) current legal status of cannabis for medical purposes in the United States.

Keywords: Cancer; Cannabinoids; Cannabis; Medical marijuana; Tetrahydrocannabinol

1. Introduction

Cannabis, commonly known as marijuana, is a natural product derived from the *Cannabis sativa* plant. The psychoactive properties of its active ingredients, cannabinoids,

* Corresponding author at: Developmental Therapeutics and Head and Neck Oncology Programs, University of Colorado Cancer Center, MS 8117, 12801 E. 17th Avenue, Aurora, CO 80045, United States.
Tel.: +1 303 724 3847; fax: +1 303 724 3889.
E-mail address: daniel.bowles@ucdenver.edu (D.W. Bowles).

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have led to its use for religious and medicinal purposes for thousands of years. Increasingly, cancer care professionals are expected to answer questions from patients and other health care providers on the role of cannabis and cannabinoids in clinical practice, often with little more information than the National Cancer Institute's PDQ® on cannabis and cannabinoids [1]. This review will explore the intersection of cannabis, synthetic cannabinoids, and cancer in the United States (US). We will examine the pharmacologic properties of cannabis and cannabinoids, the role that cannabis may play in cancer development and symptom palliation, as well as its potential as an anti-cancer therapy. Finally we will review the current legal status of medical cannabis in the United States. The epidemiology and non-cancer related effects of cannabis use have recently been reviewed elsewhere and will not be addressed here [2].

2. Pharmacology of cannabinoids

Cannabinoids are divided into phytocannabinoids, endogenous endocannabinoids, and synthetic cannabinoids. More than 60 phytocannabinoids have been identified within the cannabis plant [3]. The primary phytocannabinoid responsible for cannabis' psychoactive and physiological effects is Δ^9-tetrahydrocannabinol (THC) [3]. Cannabinoids mediate their actions through cannabinoids receptor type 1 (CB_1) and CB_2, two G-coupled receptors in the endocannabinoid signaling system. Activation of either receptor leads to the inhibition of adenylate cyclase, decreased production of cyclic adenosine monophosphate (cAMP), and activation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways [3,4]. CB_1 receptors are found predominantly in the central and peripheral nervous systems and suppress neuronal excitability and transmitter release, leading to hypothermia, sedation, euphoria, and altered mental status [5]. CB_2 receptors are found in higher concentrations in immune tissues and may modulate the immune system via cytokine release. They are not related to psychoactive effects [3]. CB_1 and CB_2 are reviewed extensively elsewhere [6,7]. Cannabidiol (CBD), another phytocannabinoid, can also exert anti-inflammatory effects by activation of transient receptor potential vanillin (TRPV) channel proteins and inhibiting cyclooxygenase enzymes 1 and 2 (COX-1/2) [8,9].

Inhalation and oral ingestion are the most common routes of administration for natural and synthetic cannabis products but rectal, sublingual, transdermal, ophthalmic, intrathecal, and intravenous routes have also been developed. Concentrations of THC in natural cannabis preparations can vary significantly based on a number of factors including the plant variety, type of preparation (hash oil > hash > sinsemilla [seedless plant] > smoked or ingested leaves and flowers) and cultivation technique. There is evidence that cannabis' potency has doubled in the US and abroad since the 1980s [10,11]. Dronabinol (Marinol™), a synthetic THC, and nabilone (Cesamet™), a synthetic THC-mimetic, are FDA-approved cannabinoids. Nabiximols (Sativex™) is an oromucosal spray containing THC and cannabidiol extract approved in Canada and the United Kingdom that is currently undergoing clinical testing in the US and Europe.

Table 1
Pharmacokinetic properties of inhaled and orally ingested cannabinoids.

	Inhaled	Orally ingested
Peak blood levels (min)	3–10	60–120
Bioavailability (%)	10–40	<15
Time to peak psychoactive activity (min)	20	120–240
Maximal duration (min)	Dose dependant	240-360

THC's pharmacologic parameters vary based upon the delivery form (Table 1). THC is highly protein bound in the blood but the steady state volume of distribution is large (approximately 10 L/kg) due to its lipophilicity [4]. THC's half-life ($t_{1/2}$) is variable based on the route of administration and dose but can be generally characterized by an initial $t_{1/2}$ of 3–4 h, followed by a terminal $t_{1/2}$ of 25–36 h with low levels of drug being eliminated over a longer period of time due to its large volume of distribution [4]. Vaporized cannabis has a similar pharmacokinetic profile to smoked cannabis but with less carbon monoxide exposure [12]. THC is primarily metabolized in the liver by the CYP2C subfamily and is eliminated predominantly in the feces and less in the urine. 11-OH-THC is the principle metabolite formed when THC is ingested by mouth [13]. Detectable levels of THC can be found in the urine for up to 12 days after use due to extensive enterohepatic recirculation of metabolites; however, this period could be longer for regular users [4].

3. Cannabinoids and cancer development

One of the principle concerns over the medical use of cannabinoids, particularly inhaled cannabis, is their carcinogenic potential. There is little direct evidence that THC or other cannabinoids are carcinogenic. THC is not carcinogenic in skin tests on rodents [14] and THC and other cannabinoids are not mutagenic according to the Ames test [15]. By contrast, cannabis smoke is carcinogenic in rodents [16] and mutagenic in the Ames test [17]. Cannabis smoke contains several of the same carcinogens as tobacco smoke [18] at up to 50% higher concentrations [19,20] and with three times the tar per cigarette [21]. Respiratory mucosa exposed to chronic cannabis smoke shows pre-neoplastic histological and molecular changes [22,23]. Despite this *in vitro* and *in vivo* evidence, however, it has been difficult to strongly correlate cannabis use and the development of human cancers.

For instance, the epidemiologic data correlating head and neck squamous cell carcinoma (HNSCC) risk and cannabis are inconsistent. Three studies have found a statistically significant increased risk of HNSCC in cannabis users. In a

hospital-based case–control study, ever users of cannabis had a 2.6-fold (95% CI 1.1–6.6) increased risk of HNSCC compared with blood-bank controls when adjusted for cannabis dose, duration of use, and confounding variables such as alcohol or tobacco use [24]. Similarly, heavy cannabis smokers in Northern Africa had an odds ratio of 2.62 (95% CI 1–6.86) for nasopharyngeal carcinomas despite attempts to control for tobacco use, though this may be confounded by the fact that cannabis may have been mixed with tobacco in this population [25]. A recent study found that human papilloma virus (HPV)-16 positive HNSCC was associated with increased cannabis smoking intensity (joints per month, $p = 0.007$), duration (in years, $p = 0.01$), and cumulative joint-years (one joint year equals one joint per day per year, $p = 0.003$) when adjusted for alcohol and tobacco use [26]. The authors hypothesized that this correlation may be due to cannabis-induced immune suppression through CB_2 [26]. Cannabis use was not associated with HPV-16 negative HNSCC. In contrast, seven studies have found no association between cannabis use and HNSCC development. Two small, population-based case–control studies of oral cavity and oropharyngeal cancers in England did not find an association between cannabis use and HNSCC in patients 45-years-old or younger, though the exact pattern of cannabis use was not specified [27,28]. Another small case–control study from New Zealand found no association between cannabis use and HNSCC once adjusted for tobacco and alcohol intake [29]. The INHANCE Consortium has provided three large, population-based case–control studies including over 4000 HNSCC patients and 5000 controls from around the world [30–32]. In each study no link between cannabis use and HNSCC was found when controlled for alcohol and tobacco use. Intriguingly, a case–control study from Boston with over 400 HNSCC subjects recently found that, after adjusting for confounders, 10–20 years of cannabis use was actually associated with a significantly reduced risk of HNSCC (OR 0.38, 95% CI 0.22–0.67) [33]. Subjects using 0.5–1.5 doses per week had lower risk than those using less than 0.5 doses per week (OR 0.52, 95% CI 0.32–0.85). At this point the majority of studies do not support the hypothesis that smoked cannabis is strongly associated with an increased risk of HNSCC once tobacco and alcohol intake are controlled, though smoked cannabis may raise the risk of HPV-16-associated HNSCC.

The data correlating lung cancer and cannabis smoking are equally heterogeneous. A systematic review evaluating 19 studies from 1966 to 2006 found no significant tobacco-adjusted association between cannabis smoking and lung cancer development despite evidence of precancerous histopathologic changes of the respiratory mucosa [34]. This conclusion was supported by an INHANCE Consortium study with over 1200 lung cancer cases where no correlation between lung cancer and cannabis use could be found [31]. However, a pooled analysis of three studies of male cannabis smokers in North Africa found that the odds ratio for developing lung cancer was 2.4 (95% CI, 1.6–3.8) for ever cannabis smokers [35]. A case control study of patients with lung cancer under 55 years of age in New Zealand found an 8% (95% CI, 2–15) increased risk for each joint-year (one joint/day/year) of cannabis use [36]. This effect persisted only in the highest tertile of cannabis use (>10.5 joint-years of exposure) when adjusted for tobacco use (RR 5.7, 95% CI 1.5–21.6) [36].

The development of other cancers has been inconsistently associated with cannabis use. A study of 65,855 members of a US health management organization (HMO) that classified member as experimenters (six or fewer lifetime usages), former users, or current users found no increased risk of HNSCC, lung, colorectal, melanoma, or breast cancers in current or former cannabis smokers versus never smokers or experimenters when controlled for tobacco use, alcohol intake, and socioeconomic status [37]. There was a trend towards increased prostate (RR 3.1, 95% CI 1–9.5) and cervical cancer (RR 1.4, 95% CI 1–2.1). Another US study of 105,005 HMO members, however, found an increased risk of malignant primary gliomas (RR 2.8, 95% CI 1.3–6.2) in people who smoked cannabis once per month or more [38]. Smaller studies have implicated cannabis use in the development of bladder cancer [39] and testicular germ cell tumors [40]. The reasons for the great heterogeneity in epidemiologic studies correlating cannabis use and cancer may have to do with difficulties in quantifying cannabis use, unmeasured confounders in the cases or controls, and variable expression of cannabinoids receptors in target tissues.

4. Cannabinoids and cancer therapy

There is evidence that cannabinoids may have anti-cancer effects. This was noted in lung adenocarcinoma models in the 1970s [41] and subsequent studies have demonstrated tumor growth inhibition *in vitro* and *in vivo* in glioblastoma multiforme, breast, prostate, thyroid, colon, skin, pancreatic, leukemia and lymphoma models [42]. The exact mechanism by which this anti-tumor effect occurs may involve suppression of proliferative cell signaling pathways, inhibition of angiogenesis and cell migration, stimulation of apoptosis, and/or induction of autophagy [42,43]. In gliomas, the use of THC and WIN 55, 212-2, a synthetic CB_1/CB_2 receptor agonist, induced cell death by down-regulating the PI3K/Akt and MAPK signaling pathways and inducing apoptosis through the activation of the pro-apoptotic Bcl-2-associated death promoter (BAD) protein [44,45]. Colon cancer cells exposed to cannabinoids undergo tumor necrosis factor-α-mediated, ceramide-induced apoptosis *in vivo* and *in vitro* [46]. Additionally decreased expression of vascular endothelial growth factor (VEGF) and other proangiogenic factors has been noted in glioma and skin cancer models treated with JWH-133, a CB_2-selective agonist, and WIN 55,212-2 [47]. It also appears that CB_2 may be more important than CB_1 in mediating cannabinoids' anti-cancer activity. CB_1

and CB_2 mediated apoptosis in prostate cancer cells exposed to anandamide, an endocannabinoid, but proliferation was inhibited exclusively through CB_2 [48]. Methanandamide, an analogue of anandamide, induced apoptosis and inhibited cell growth via CB_2 in prostate cancer cells [49]. Selective activation of CB_2 with JWH-133 induced apoptosis via ceramide synthesis and MAPK activation in an *in vivo* glioblastoma model [50]. In a mouse model of human epithelial growth factor receptor-2 (HER2)-positive breast cancer, THC and JHW-133 decreased tumor size and lung metastasis through Akt inhibition via CB_2 [51]. However, CB_1 and CB_2 activation were both were necessary for cannabinoid-induced anti-tumor activity in another mouse model of breast cancer [52]. On the contrary, breast cancer cells expressing low levels of cannabinoid receptors showed growth enhancement when exposed to cannabinoids, possibly due to altered immune response [53]. Interestingly, the anti-cancer effects of cannabidiol (CBD) may occur completely independently of cannabinoid receptor activation. In bladder cancer cells CBD induced apoptosis via activation of the TRPV2 channel protein [54], whereas it induced apoptosis in breast cancer cells independent of both cannabinoid and vanillin receptors [55].

Cannabinoid receptors have been found in higher concentrations on tumor cells than on the corresponding normal tissue in a variety of cancers. For example, CB_2 is expressed in 91% of HER2-positive breast cancers but only 35–72% of HER2-negative breast cancers and 5% of normal breast tissue [51,52]. B-cell non-Hodgkin's lymphomas typically express higher levels of CB_1 and/or CB_2 mRNA than reactive lymph nodes [56]. Additionally, cannabinoids may act to selectively inhibit the growth of tumor cells while sparing normal tissue [42,44]. For instance, glioma cells exposed to cannabinoids undergo ceramide-induced cell death whereas astrocytes are protected from oxidative stress by the same cannabinoids-mediated manner [44]. The anti-tumor activity of THC on glioma cells is enhanced by cannabidiol [57]. Finally, the expression of CB_1 and/or CB_2 receptors has been associated with prognosis in several tumors. Improved prognosis has been correlated in hepatocellular carcinomas to the overexpression of CB_1 and CB_2 receptors [58] and higher expression of CB_2 receptors was related to higher tumor grade in gliomas [59].

Despite preclinical data for cannabinoid-mediated anti-tumor activity, there has been only one clinical trial published in this area. This phase I study assessed the safety and efficacy of THC in patients with refractory glioblastoma multiforme. A total of nine patients underwent a tumor debulking surgery then had an infusion catheter inserted into the resection cavity. THC was instilled into the cavity daily for 10–64 days for total doses ranging from 0.80 to 3.29 mg. One patient had mild psychotropic effects but it was otherwise well-tolerated. THC decreased tumor growth on MRI and tumor ki-67 immunostaining and angiogenesis on post-treatment biopsies [60]. Further preclinical and clinical studies are required to fully define cannabinoids' potential as anti-cancer agents.

5. Cannabinoids and cancer symptom management

In the 1970s researchers began investigating purified and synthesized cannabinoids' roles in the palliation of cancer symptoms [61]. Numerous trials of cannabinoids have subsequently been performed for several indications. The use of cannabinoids for cancer palliation has now extended to cannabis itself, as cancer is a qualifying condition for cannabis use in every state in the US where cannabis is approved for medical purposes. Acknowledging that symptom palliation may vary based upon the product (e.g. cannabis, cannabis extract, or synthetic cannabinoid) and method of use (e.g. inhaled or ingested), we will discuss the role of cannabinoids in cancer symptom palliation.

5.1. Analgesia

The data supporting cannabinoids for pain relief have been mixed. In experimental models of acute pain, inhaled cannabis resulted in dose-dependent pain relief whereas cannabis extracts had no effect [62,63]. In a series of studies in patients with chronic pain, THC, CBD, or both tended to outperform placebo, particularly in the setting of neuropathic pain [64]. For instance, 46% of patients with HIV neuropathy given inhaled cannabis had at least 30% pain relief compared to 18% given placebo [65]. Several other studies have supported inhaled cannabis [65–68] or pharmaceutical preparations [69,70] as superior to placebo in palliating neuropathic pain of different etiologies. Unfortunately, there are little data regarding inhaled cannabis or cannabis extract in comparison to conventional pain medications for cancer-related or chronic non-neuropathic pain. A systematic review of single dose studies of dronabinol, nabilone, and levonandradol found them to be as effective as 50–120 mg of oral codeine [71]. One study found nabilone to be less effective than modest doses of dihydrocodeine in patients with neuropathic pain and has less desirable side effects [72]. No studies comparing inhaled or ingested cannabis to conventional analgesics could be identified. Therefore, it appears that inhaled cannabis and pharmaceutical cannabinoids are more effective than placebo in treating neuropathic pain, but their effectiveness compared to conventional pain medications is uncertain.

There are emerging data suggesting that cannabinoids augment opiates. Cancer patients with intractable pain who were treated with an oromucosally administered extract containing TCH and CBD had improvement in pain compared to those on opiates alone, though no change in total opiate usage was seen [73]. We could not identify controlled studies evaluating inhaled cannabis as an adjunctive medication to traditional pain medications for patients with cancer-related pain.

5.2. Anorexia

Dronabinol is approved in the US for appetite stimulation in patients with weight loss from AIDS; however, its efficacy in cancer patients compared with other agents is limited. A

Table 2
Essential elements of medical cannabis laws in different jurisdictions in the United States as of April 2011.

Jurisdiction	Year legalized	Amount allowed per card holder	New application fee ($)	Dispensaries allowed
Alaska [91]	1998	1 oz and 6 plants (no more than 3 mature)	25	No
Arizona [92]	2010	2.5 oz, 0–12 plants	150	Yes
California [93]	1996	8 oz, 18 plants (6 mature, 12 immature)[a]	66[b]	Yes
Colorado [94]	2000	2 oz and 6 plants (no more than 3 mature)	90	Yes
Hawaii [95]	2000	7 plants (3 mature, 4 immature) and 1 usable oz from each mature plant	25	No
Maine [96]	1999	2.5 oz and 6 plants	100	Yes
Michigan [97]	2008	2.5 oz and 12 plants	100	No
Montana [89]	2004	1 oz, 6 plants	25	No
Nevada [98]	2000	1 oz, 7 plants (3 mature, 4 immature)	150[c]	No
New Jersey [99]	2010	2 oz	200	Yes
New Mexico [100]	2007	6 oz, 18 plants (4 mature, 12 seedlings)	0[d]	Yes
Oregon [101]	1998	24 oz 24 plants (6 mature, 18 seedlings)	100	No
Rhode Island [102]	2006	2.5 oz, 12 plants	75	Yes
Vermont [103]	2004	2 oz, 9 plants (2 mature, 7 immature)	50	No
Washington [104]	1998	24 oz and 15 plants	No registration program	No
Washington, DC [105]	2010	2 oz	Not established	No

[a] These limits were set by senate bill 420 in 2004 but were deemed unconstitutional by the California Supreme Court in January 2010.
[b] There are additional county fees of varying amount.
[c] There is an additional $15–$42 in costs.
[d] There is a $15 patient production license.

recent double-blinded, randomized, 46 patient study suggested that cancer patients with altered chemosensory had increased pre-meal appetite and improved taste when given dronabinol (2.5 mg twice daily) compared to placebo [74]. However, large randomized studies have been discouraging. In a randomized trial of patients with cancer-associated anorexia, low dose dronabinol (2.5 mg twice daily) as a single agent or in combination with high dose megestrol (800 mg per day), a synthetic progestin, was less effective at generating weight gain and improving quality of life than megestrol alone [75]. A subsequent randomized, double-blinded trial from Europe for patients with cancer-associated anorexia found no difference in weight gain or quality of life at 6 weeks for patients treated with cannabis extract (THC 2.5 mg daily and CBD 1 mg daily) or THC (2.5 mg daily) compared to patients given placebo [76]. Patients given cannabinoids had increased side effects. The data for cannabinoids in cancer-associated anorexia based on these three randomized studies are weak and the data for inhaled cannabis for cancer-associated cachexia are lacking.

5.3. Nausea and vomiting

One of the earliest recognized indications for cannabinoids was chemotherapy induced nausea and vomiting (CINV). A prospective, open label, pilot study from 1988 found that inhaled cannabis was effective in 78% of 56 patients who had inadequate control of nausea and vomiting with conventional anti-emetics [77]. Little other data for inhaled cannabis exists for CINV. Pharmaceutical cannabinoids have been investigated extensively, however. A high quality systematic review of the published literature as of 2001 evaluated 30 trials and over 1300 patients. It found that cannabinoids (nabilone, dronabinol, and levonantradol) were more effective than conventional anti-emetics at the time (e.g. prochlorperazine, promethazine, and metaclopramide) in controlling acute CINV [78]. In the chronic CINV setting, dronabinol was not found to be more effective than ondansetron following highly emetogenic chemotherapy [79]. Since the CINV systematic review the use of 5-hydroxytryptamine 3 receptor and protachykinin antagonists have been major advances in the treatment of acute and chronic CINV. The current American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines do not recommend cannabinoids as first-line therapies [80,81].

6. The legal climate in the United States

The laws governing the use of "medical cannabis" in the United States are dynamic and varied. In 1970 the Controlled Substances Act (CSA) classified cannabis as a schedule I agent. Since then the Institute of Medicine, American College of Physicians, and American Medical Association have recommended that the federal government re-evaluate its current regulations to enable research into cannabis' medicinal value [82–84]. In response to its federal schedule I status, states began attempting to legalize medical cannabis in the 1990s. In1996, 56% of voters in California voted in favor of proposition 215 and passed a law eliminating criminal penalties for cannabis use for approved medical conditions. Since then 14 other states and the District of Columbia have joined California in abolishing or limiting state criminal penalties for patients and providers who possess, use, or recommend cannabis (Table 2).

The details of each state's laws vary but there are a number of common threads. Each state defines certain "qualifying"

Table 3
Total patients registered for medicinal cannabis in the United States according to qualifying condition in states with publically available data as of April 2011.

State	Total registered patients	Cancer (%)	Severe or chronic pain (%)
Colorado [94]	123,890	2598 (2.1)	116,858 (94.3)
Montana [89]	29,948	926 (3.1)	28,248 (94.3)
Nevada [106]	2898	73 (2.5)	2610 (90.1)
New Mexico [100]	3535	479 (13.6)	936 (26.6)
Oregon [101]	39,774	1671 (4.1)	35,793 (90.0)
Rhode Island [102]	3161	213 (6.7)	1419 (44.9)
Total	203,196	5960 (2.9)	185,864 (91.5)

Patients may have multiple indications for registration (e.g. cancer and pain) so the total qualifying conditions may exceed 100% of registered patients.

conditions for which patients may be recommended cannabis by an approved health care provider. Cancer, HIV/AIDS, severe nausea and vomiting, severe or chronic pain, and seizures are approved qualifying conditions according to all state laws. Other examples of qualifying conditions include arthritis in California, Alzheimer's disease in Michigan, and post-traumatic stress disorder in New Mexico. Interestingly, while cancer is a qualifying condition in all states, cancer patients make up a small minority of medical cannabis patients (Table 3). In total, cancer patients appear to comprise less than 3% of total medical cannabis users in the US. This compares to the 8–23% of legal cannabis users in the Netherlands, though this percentage may not accurately reflect actual usage rates due to the widespread availability of illegal, but unprosecuted, cannabis in The Netherlands [85]. The main qualifying condition for medical cannabis in all states where the data are publically available is severe or chronic pain (Table 3).

State laws all specify how much cannabis a patient may possess, ranging from 2 ounces and no plants in New Jersey to up to 24 ounces and 15 plants in the state of Washington. Most states allow patients to designate a caregiver to cultivate or possess cannabis. Virtually all allow patients and caregivers to grow cannabis, but most do not address how to obtain the agent otherwise. Several states allow patients to obtain cannabis at non-profit or for-profit commercial centers ("dispensaries"). Laws also vary with regard to how patients and caregivers data are maintained and shared with the public. Most the states have a registry that enrolls and tracks patients and caregivers, provides summary data about the program to the public, and issues appropriate identification cards.

6.1. Legal and practical challenges

According to surveys from the 1990s and 2000s, between 30% and 54% of physicians, including internists and oncologists, were interested in having cannabis as a therapeutic option for their patients [86,87]. However, many physicians are concerned about the legality of making medical cannabis recommendations regardless of state laws. In the 2002 the federal appeals court decision *Conant v. Walters* established that physicians have the right to recommend cannabis under physician–patient communication protected by the First Amendment. However, the ruling also stated that physicians violate federal law if they prescribe cannabis using a prescription pad, cultivate or possess cannabis for patient use, or physically assist patients in using cannabis. The Supreme Court, in their 2005 *Gonzales v. Raich* decision, later established that the federal government has the authority to arrest and prosecute patients who grow or possess cannabis or physicians who recommend or dispense cannabis regardless of their state laws. Despite this ruling, in 2009 the Department of Justice stated that they would not prosecute those individuals who were using cannabis in accordance with their state laws, though this is not in statute.

As cannabis has become an available therapy across the US, concerns that state medical cannabis programs may be vulnerable to misuse, fraud and abuse from patients and physicians have arisen. One worry is that recreational cannabis users are accessing medical cannabis programs. There are data suggesting that many applicants for medical cannabis permits in California were cannabis users prior to application, though whether these applicants obtained permits for medical or recreational use is unknown [88]. Another concern is that patients may obtain cannabis permits in order to divert the agent to family or friends, or for financial gain. There are also concerns regarding the accuracy and quality of the physician recommendation process. It is frequently pointed out that a minority of physicians provides the majority of cannabis recommendations. In Colorado, for example, 1100 different physicians have made recommendations for medical cannabis but only 15 physicians account for over 50% of the current recommendations (Bob O'Doherty, Director of the Colorado Medical Marijuana Registry, personal communication, April 2011). In Montana, 360 separate physicians have made active recommendations but 32 have made over 100 recommendations, whereas 228 have made recommendations to 5 or fewer patients [89]. There are a number of potential explanations for this discrepancy. For instance, physicians may advertise their services as "cannabis specialists" or work is a field, such as pain management, where cannabis recommendations are more common. Regarding recommendation quality guidelines, most states do not explicitly require that health care providers discuss the risks and benefits of cannabis with their patients, raising concerns that some physicians making recommendations

might not follow otherwise standard medical practice [90]. Several states have taken measures to more explicitly define patients' and physician's roles to ensure that recommendation of medical cannabis follow their state's laws.

7. Conclusions

Interest in and use of medicinal cannabis and cannabinoids have risen dramatically in the last 30 years as synthetic and purified cannabinoids have entered the market and states have passed laws eliminating criminal penalties for cannabis possession, use, or physician recommendation for approved medical purposes. Medical cannabis remains a paradox in many ways. Cannabis smoke may be carcinogenic but it has been difficult to conclusively link cannabis use and cancer development epidemiologically, and cannabinoids have shown some promise as anti-cancer therapies. Cannabinoids can palliate some cancer symptoms but it is unclear how effective they are compared to or combined with conventional therapies, or even whether cannabis, purified cannabinoids, or synthetic cannabinoids are more effective. Moreover, while 15 states and the District of Columbia have eliminated criminal penalties for medical cannabis, it remains illegal on the federal level. New research into cannabinoids and cancer is needed, particularly with respect to cannabinoids' effects on the standard oncology outcomes of tumor growth and patient survival. The future interplay between cannabis and cancer in the US is uncertain and will be influenced by public sentiment and political persuasion, but the hope is that scientific inquiry will help guide the discussion by providing further insight into the potential risks and benefits of cannabis and cannabinoids in cancer development, treatment, and palliation.

Conflicts of interest statement

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Reviewers

Mark Ware, M.D., Assistant Professor in Family Medicine & Anesthesia, McGill University, Centre for Medical Education, Lady House, 1110 Pine Avenue West, Montreal, Quebec H3A 1A3, Canada.

Donald I. Abrams, M.D., Professor, Clinical Medicine, UCSF, University of California, San Francisco, Divisions of Hematology & Oncology, Box 0874, UCSF, San Fransisco, CA 94143-0874, United States.

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References

[1] Abrams DI. Cannabis and cannabinoids. http://www.cancer.gov/cancertopics/pdq/cam/cannabis/healthprofessional (August 1, 2011, date last accessed).
[2] Hall W, Degenhardt L. Adverse health effects of non-medical cannabis use. Lancet 2009;374:1383–91.
[3] Turcotte D, Le Dorze JA, Esfahani F, Frost E, Gomori A, Namaka M. Examining the roles of cannabinoids in pain and other therapeutic indications: a review. Expert Opin Pharmacother 2010;11:17–31.
[4] Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet 2003;42:327–60.
[5] Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics 2009;6:713–37.
[6] Turu G, Hunyady L. Signal transduction of the CB1 cannabinoid receptor. J Mol Endocrinol 2010;44:75–85.
[7] Atwood BK, Mackie K. CB2: a cannabinoid receptor with an identity crisis. Br J Pharmacol 2010;160:467–79.
[8] Hegde VL, Nagarkatti PS, Nagarkatti M. Role of myeloid-derived suppressor cells in amelioration of experimental autoimmune hepatitis following activation of TRPV1 receptors by cannabidiol. PLoS One 2011;6:e18281.
[9] Ruhaak LR, Felth J, Karlsson PC, Rafter JJ, Verpoorte R, Bohlin L. Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from *Cannabis sativa*. Biol Pharm Bull 2011;34:774–8.
[10] McLaren J, Swift W, Dillon P, Allsop S. Cannabis potency and contamination: a review of the literature. Addiction 2008;103:1100–9.
[11] Pijlman FT, Rigter SM, Hoek J, Goldschmidt HM, Niesink RJ. Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. Addict Biol 2005;10:171–80.
[12] Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther 2007;82:572–8.
[13] Lemberger L, Martz R, Rodda B, Forney R, Rowe H. Comparative pharmacology of Delta9-tetrahydrocannabinol and its metabolite, 11-OH-Delta9-tetrahydrocannabinol. J Clin Invest 1973;52:2411–7.
[14] Chan PC, Sills RC, Braun AG, Haseman JK, Bucher JR. Toxicity and carcinogenicity of delta 9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice. Fundam Appl Toxicol 1996;30:109–17.
[15] Hall W, MacPhee D. Cannabis use and cancer. Addiction 2002;97:243–7.
[16] MacPhee D. Effects of marijuana on cell nuclei. A review of the literature relating to the genotoxicity of cannabis. In: Kalant H, Corrigal W, Hall WD, Smart R, editors. The health effects of cannabis. Toronto: Centre for Addiction and Mental Health; 1999. p. 425–58.
[17] Marselos M, Karamanakos P. Mutagenicity, developmental toxicity and carcinogenicity of cannabis. Addict Biol 1999;4:5–12.
[18] Novotny M, Lee ML, Bartle KD. A possible chemical basis for the higher mutagenicity of marijuana smoke as compared to tobacco smoke. Experientia 1976;32:280–2.
[19] Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. Chem Res Toxicol 2008;21:494–502.
[20] Singh R, Sandhu J, Kaur B, et al. Evaluation of the DNA damaging potential of cannabis cigarette smoke by the determination of acetaldehyde derived N2-ethyl-2′-deoxyguanosine adducts. Chem Res Toxicol 2009;22:1181–8.

[21] Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 1988;318:347–51.
[22] Fligiel SE, Roth MD, Kleerup EC, Barsky SH, Simmons MS, Tashkin DP. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. Chest 1997;112:319–26.
[23] Barsky SH, Roth MD, Kleerup EC, Simmons M, Tashkin DP. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. J Natl Cancer Inst 1998;90:1198–205.
[24] Zhang ZF, Morgenstern H, Spitz MR, et al. Marijuana use and increased risk of squamous cell carcinoma of the head and neck. Cancer Epidemiol Biomarkers Prev 1999;8:1071–8.
[25] Feng BJ, Khyatti M, Ben-Ayoub W, et al. Cannabis, tobacco and domestic fumes intake are associated with nasopharyngeal carcinoma in North Africa. Br J Cancer 2009;101:1207–12.
[26] Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. JNCI J Natl Cancer Inst 2008;100:407–20.
[27] Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for oral cancer in newly diagnosed patients aged 45 years and younger: a case–control study in Southern England. J Oral Pathol Med 2004;33:525–32.
[28] Llewellyn CD, Linklater K, Bell J, Johnson NW, Warnakulasuriya S. An analysis of risk factors for oral cancer in young people: a case–control study. Oral Oncol 2004;40:304–13.
[29] Aldington S, Harwood M, Cox B, et al. Cannabis use and cancer of the head and neck: case–control study. Otolaryngol Head Neck Surg 2008;138:374–80.
[30] Rosenblatt KA, Daling JR, Chen C, Sherman KJ, Schwartz SM. Marijuana use and risk of oral squamous cell carcinoma. Cancer Res 2004;64:4049–54.
[31] Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case–control study. Cancer Epidemiol Biomarkers Prev 2006;15:1829–34.
[32] Berthiller J, Lee YC, Boffetta P, et al. Marijuana smoking and the risk of head and neck cancer: pooled analysis in the INHANCE Consortium. Cancer Epidemiol Biomarkers Prev 2009;18:1544–51.
[33] Liang C, McClean MD, Marsit C, et al. A population-based case–control study of marijuana use and head and neck squamous cell carcinoma. Cancer Prev Res 2009;2:759–68.
[34] Mehra R, Moore BA, Crothers K, Tetrault J, Fiellin DA. The association between marijuana smoking and lung cancer: a systematic review. Arch Intern Med 2006;166:1359–67.
[35] Berthiller J, Straif K, Boniol M, et al. Cannabis smoking and risk of lung cancer in men: a pooled analysis of three studies in Maghreb. J Thorac Oncol 2008;3:1398–403.
[36] Aldington S, Harwood M, Cox B, et al. Cannabis use and risk of lung cancer: a case–control study. Eur Respir J 2008;31:280–6.
[37] Sidney S, Beck JE, Tekawa IS, Quesenberry CP, Friedman GD. Marijuana use and mortality. Am J Public Health 1997;87:585–90.
[38] Efird JT, Friedman GD, Sidney S, et al. The risk for malignant primary adult-onset glioma in a large, multiethnic, managed-care cohort: cigarette smoking and other lifestyle behaviors. J Neurooncol 2004;68:57–69.
[39] Chacko JA, Heiner JG, Siu W, Macy M, Terris MK. Association between marijuana use and transitional cell carcinoma. Urology 2006;67:100–4.
[40] Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA. Marijuana use and testicular germ cell tumors. Cancer 2011;117:848–53.
[41] Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA. Antineoplastic activity of cannabinoids. J Natl Cancer Inst 1975;55:597–602.
[42] Pisanti S, Malfitano AM, Grimaldi C, et al. Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. Best Pract Res Clin Endocrinol Metab 2009;23:117–31.
[43] Salazar M, Carracedo A, Salanueva IJ, et al. Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. J Clin Invest 2009;119:1359–72.
[44] Flygare J, Sander B. The endocannabinoid system in cancer-potential therapeutic target? Semin Cancer Biol 2008;18:176–89.
[45] Sarfaraz S, Adhami VM, Syed DN, Afaq F, Mukhtar H. Cannabinoids for cancer treatment: progress and promise. Cancer Res 2008;68:339–42.
[46] Cianchi F, Papucci L, Schiavone N, et al. Cannabinoid receptor activation induces apoptosis through tumor necrosis factor alpha-mediated ceramide de novo synthesis in colon cancer cells. Clin Cancer Res 2008;14:7691–700.
[47] Blazquez C, Casanova ML, Planas A, et al. Inhibition of tumor angiogenesis by cannabinoids. FASEB J 2003;17:529–31.
[48] Mimeault M, Pommery N, Wattez N, Bailly C, Henichart JP. Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production. Prostate 2003;56:1–12.
[49] Olea-Herrero N, Vara D, Malagarie-Cazenave S, Diaz-Laviada I. Inhibition of human tumour prostate PC-3 cell growth by cannabinoids R(+)-Methanandamide and JWH-015: involvement of CB2. Br J Cancer 2009;101:940–50.
[50] Sanchez C, de Ceballos ML, Gomez del Pulgar T, et al. Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor. Cancer Res 2001;61:5784–9.
[51] Caffarel MM, Andradas C, Mira E, et al. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. Mol Cancer 2010;9:196.
[52] Qamri Z, Preet A, Nasser MW, et al. Synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer. Mol Cancer Ther 2009;8:3117–29.
[53] McKallip RJ, Nagarkatti M, Nagarkatti PS. Delta-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. J Immunol 2005;174:3281–9.
[54] Yamada T, Ueda T, Shibata Y, et al. TRPV2 activation induces apoptotic cell death in human T24 bladder cancer cells: a potential therapeutic target for bladder cancer. Urology 2010;76, 509 e1-7.
[55] Shrivastava A, Kuzontkoski PM, Groopman JE, Prasad A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. Mol Cancer Ther 2011;10:1161–72.
[56] Gustafsson K, Wang X, Severa D, et al. Expression of cannabinoid receptors type 1 and type 2 in non-Hodgkin lymphoma: growth inhibition by receptor activation. Int J Cancer 2008;123:1025–33.
[57] Marcu JP, Christian RT, Lau D, et al. Cannabidiol enhances the inhibitory effects of delta9-tetrahydrocannabinol on human glioblastoma cell proliferation and survival. Mol Cancer Ther 2010;9:180–9.
[58] Xu X, Liu Y, Huang S, et al. Overexpression of cannabinoid receptors CB1 and CB2 correlates with improved prognosis of patients with hepatocellular carcinoma. Cancer Genet Cytogenet 2006;171:31–8.
[59] Ellert-Miklaszewska A, Grajkowska W, Gabrusiewicz K, Kaminska B, Konarska L. Distinctive pattern of cannabinoid receptor type II (CB2) expression in adult and pediatric brain tumors. Brain Res 2007;1137:161–9.
[60] Guzman M, Duarte MJ, Blazquez C, et al. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br J Cancer 2006;95:197–203.
[61] Sallan SE, Zinberg NE, Frei 3rd E. Antiemetic effect of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med 1975;293:795–7.

[62] Kraft B, Frickey NA, Kaufmann RM, et al. Lack of analgesia by oral standardized cannabis extract on acute inflammatory pain and hyperalgesia in volunteers. Anesthesiology 2008;109:101–10.
[63] Wallace M, Schulteis G, Atkinson JH, et al. Dose-dependent effects of smoked cannabis on capsaicin-induced pain and hyperalgesia in healthy volunteers. Anesthesiology 2007;107:785–96.
[64] Notcutt W, Price M, Miller R, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia 2004;59:440–52.
[65] Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology 2009;34:672–80.
[66] Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008;9:506–21.
[67] Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology 2007;68:515–21.
[68] Ware MA, Wang T, Shapiro S, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010;182:E694–701.
[69] Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA 2003;290: 1757–62.
[70] Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812–9.
[71] Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 2001;323:13–6.
[72] Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 2008;336:199–201.
[73] Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010;39: 167–79.
[74] Brisbois TD, de Kock IH, Watanabe SM, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol 2011.
[75] Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. J Clin Oncol 2002;20:567–73.
[76] Strasser F. Comparison of orally administered cannabis extract and Delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia–cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-In-Cachexia-Study-Group. J Clin Oncol 2006;24:3394–400.
[77] Vinciguerra V, Moore T, Brennan E. Inhalation marijuana as an antiemetic for cancer chemotherapy. N Y State J Med 1988;88: 525–7.
[78] Tramer MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 2001;323:16–21.
[79] Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin 2007;23:533–43.
[80] Kris MG, Hesketh PJ, Somerfield MR, et al. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006. J Clin Oncol 2006;24:2932–47.
[81] Roila F, Herrstedt J, Aapro M, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Ann Oncol 2010;21(Suppl. 5):v232–43.
[82] Mack A, Joy JE. Marijuana as medicine? The science beyond the controversy. Washington, DC: National Academy Press; 2001.
[83] American College of Physicians. Supporting research into the therapeutic role of marijuana. Philadelphia: American College of Physicians; 2008.
[84] American Medical Association. Report 3 of the Council on Science and Public Health (I-09). Use of cannabis for medicinal purposes (resolutions 910, I-08; 921, I-08; and 229, A-09). In: AMA interim meeting. 2009.
[85] Engels FK, de Jong FA, Mathijssen RH, Erkens JA, Herings RM, Verweij J. Medicinal cannabis in oncology. Eur J Cancer 2007;43:2638–44.
[86] Doblin RE, Kleiman MA. Marijuana as antiemetic medicine: a survey of oncologists' experiences and attitudes. J Clin Oncol 1991;9:1314–9.
[87] Charuvastra A, Friedmann PD, Stein MD. Physician attitudes regarding the prescription of medical marijuana. J Addict Dis 2005;24:87–93.
[88] O'Connell TJ, Bou-Matar CB. Long term marijuana users seeking medical cannabis in California (2001–2007): demographics, social characteristics, patterns of cannabis and other drug use of 4117 applicants. Harm Reduct J 2007;4:16.
[89] Montana Department of Health and Human Services. Montana Medical Marijuana Program. http://www.dphhs.mt.gov/medicalmarijuana/ (June 19, 2011, date last accessed).
[90] Degenhardt L, Hall WD. The adverse effects of cannabinoids: implications for use of medical marijuana. CMAJ 2008;178: 1685–6.
[91] Alaska Bureau of Vital Statistics. Marijuana Registry. http://www.hss.state.ak.us/dph/bvs/marijuana.htm (April 19, 2011, date last accessed).
[92] Arizona Department of Health Services. Medical Marijuana Program. http://www.azdhs.gov/prop203/ (April 19, 2011, date last accessed).
[93] California Department of Public Health. Medical Marijuana Program. http://www.cdph.ca.gov/programs/mmp/Pages/Medical%20Marijuana%20Program.aspx (April 19, 2011, date last accessed).
[94] Colorado Department of Public Health and Environment. The Colorado Medical Marijuana Registry. http://www.cdphe.state.co.us/hs/medicalmarijuana/ (April 19, 2011, date last accessed).
[95] State of Hawaii Department of Public Safety. Narcotics Enforcement Division. http://hawaii.gov/psd/law-enforcement/narcotics-enforcement (April 19, 2011, date last accessed).
[96] Maine Department of Health and Human Services. Maine Medical use of Marijuana. http://www.maine.gov/dhhs/dlrs/mmm/index.shtml (April 19, 2011, date last accessed).
[97] Michigan Department of Community Health. Michigan Medical Marihuana Program. http://www.michigan.gov/mdch/0,1607,7-132-27417_51869—,00.html (April 19, 2011, date last accessed).
[98] Nevada Department of Health and Human Services. Medical Marijuana. http://health.nv.gov/MedicalMarijuana.htm (April 19, 2011, date last accessed).
[99] State of New Jersey Department of Health and Senior Services. Medicinal Marijuana Program. http://www.state.nj.us/health/med_marijuana.shtml (April 19, 2011, date last accessed).
[100] New Mexico Department of Health. Medical Cannabis Program. http://www.health.state.nm.us/idb/medical_cannabis.shtml (April 19, 2011, date last accessed).
[101] Oregon Department of Human Services. Oregon Medical Marijuana Program. http://public.health.oregon.gov/PHD/OCHHP/OMMP/Pages/index.aspx (April 19, 2011, date last accessed).

[102] Rhode Island Department of Health. Medical Marijuana. http://www.health.ri.gov/healthcare/medicalmarijuana/index.php (April 19, 2011, date last accessed).
[103] Vermont Criminal Information Center. Vermont Marijuana Registry. http://www.dps.state.vt.us/cjs/marijuana.htm (April 19, 2011, date last accessed).
[104] Washington State Department of Health. Medical Marijuana. http://www.doh.wa.gov/hsqa/medical-marijuana/default.htm (April 19, 2011, date last accessed).
[105] Sun LH. DC council approves medical marijuana, posing challenges for doctors. http://www.washingtonpost.com/wp-dyn/content/article/2010/05/04/AR2010050405305.html (April 19, 2011, date last accessed).
[106] Nevada Department of Health and Human Services. Medical Marijuana Program. http://health.nv.gov/BudgetDocuments/2012-2013/MMPWHITEPAPR_FY11.pdf (April 19, 2011, date last accessed).

Biography

Dr. Bowles is a fellow in hematology and medical oncology at the University of Colorado. His clinical and research interests are in head and neck cancer, developmental therapeutics, and cannabinoids and malignancies. He serves as the oncology representative on the State of Colorado's Marijuana Advisory Committee.*Dr. O'Bryant* is an Associate Professor of Pharmacy at the University of Colorado Cancer Center (UCCC).*Dr. Camidge* is an Associate Professor of Medical Oncology at the UCCC specializing in lung cancer and drug development.*Dr. Jimeno* is an Associate Professor of Medical Oncology at the UCCC specializing in head and neck cancers and drug development.