The intersection between cannabis and cancer in the United States

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Contents
1. Introduction ............................................................................................................ 1
2. Pharmacology of cannabinoids ................................................................................... 2
3. Cannabinoids and cancer development ........................................................................... 2
4. Cannabinoids and cancer therapy .................................................................................. 3
5. Cannabinoids and cancer symptom management ............................................................. 4
5.1. Analgesia ........................................................................................................ 4
5.2. Anorexia ........................................................................................................ 4
5.3. Nausea and vomiting ............................................................................................. 5
6. The legal climate in the United States .............................................................................. 5
6.1. Legal and practical challenges ................................................................................... 6
7. Conclusions ............................................................................................................ 7
Conflicts of interest statement ............................................................................................. 7
Funding ................................................................................................................. 7
Reviewers ............................................................................................................... 7
Acknowledgements ..................................................................................................... 7
References ............................................................................................................. 7
Biography ............................................................................................................ 10

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.

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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,
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 Δ9-tetrahydrocannabinol (THC) [3]. Cannabinoids mediate their actions through cannabinoid receptors type 1 (CB1) and CB2, 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]. CB1 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]. CB2 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]. CB1 and CB2 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.

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 (t1/2) is variable based on the route of administration and dose but can be generally characterized by an initial t1/2 of 3–4 h, followed by a terminal t1/2 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 CB2 [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 CB1/CB2 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 vitro and in vivo [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 CB2-selective agonist, and WIN 55,212-2 [47]. It also appears that CB2 may be more important than CB1 in mediating cannabinoids’ anti-cancer activity. CB1
and CB2 mediated apoptosis in prostate cancer cells exposed to anandamide, an endocannabinoid, but proliferation was inhibited exclusively through CB2 [48]. Methanandamide, an analogue of anandamide, induced apoptosis and inhibited cell growth via CB2 in prostate cancer cells [49]. Selective activation of CB2 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 CB2 [51]. However, CB1 and CB2 activation were both 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, CB2 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 CB1 and/or CB2 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 cannabinoid-mediated manner [44]. The anti-tumor activity of THC on glioma cells is enhanced by cannabidiol [57]. Finally, the expression of CB1 and/or CB2 receptors has been associated with prognosis in several tumors. Improved prognosis has been correlated in hepatocellular carcinomas to the overexpression of CB1 and CB2 receptors [58] and higher expression of CB2 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 psychotrophic 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 levonantradol 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 opiate. 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.

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

\(a\) 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 metoclompramide) 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. In 1996, 56% of voters in California voted in favor of proposition 215 and passed a law eliminating 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”
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 users. The main qualifying condition for medical cannabis in all states where the data are publically available is severe or chronic pain. The main qualifying condition for medical cannabis in all states where the data are publically available is severe or chronic pain (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 data are maintained and shared with the public. This registry, personal communication, April 2011). In Montana, a 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 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].

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 for 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 for 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].

### 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.

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

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

The authors state no conflicts of interest.

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References


Biography

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