Cannabis in Cancer Care

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Cannabis has been used in medicine for thousands of years prior to achieving its current illicit substance status. Cannabinoids, the active components of *Cannabis sativa*, mimic the effects of the endogenous cannabinoids (endocannabinoids), activating specific cannabinoid receptors, particularly CB1 found predominantly in the central nervous system and CB2 found predominantly in cells involved with immune function. Delta-9-tetrahydrocannabinol, the main bioactive cannabinoid in the plant, has been available as a prescription medication approved for treatment of cancer chemotherapy-induced nausea and vomiting and anorexia associated with the AIDS wasting syndrome. Cannabinoids may be of benefit in the treatment of cancer-related pain, possibly synergistic with opioid analgesics. Cannabinoids have been shown to be of benefit in the treatment of HIV-related peripheral neuropathy, suggesting that they may be worthy of study in patients with other neuropathic symptoms. Cannabinoids have a favorable drug safety profile, but their medical use is predominantly limited by their psychoactive effects and their limited bioavailability.

Although long recognized for its medicinal values and widely used by millions throughout the world, cannabis receives little attention in the standard literature because of its status as a controlled substance and classification in the United States as a Schedule I agent with a high potential for abuse and no known medical use. Data on the potential effectiveness of medicinal cannabis is difficult to find due to the limited numbers of clinical trials that have been conducted to date. As a botanical, cannabis shares those difficulties encountered in the study of plants that are grown in many climates and environments from diverse genetic strains and harvested under variable conditions.

CANNABIS AS MEDICINE: A BRIEF HISTORY

The use of cannabis as medicine dates back nearly 3,000 years.[1] Employed widely on the Indian subcontinent, cannabis was introduced into Western medicine in the 1840s by W.B. O'Shaughnessy, a surgeon who learned of its medicinal benefits first-hand while working in the British East Indies Company. Promoted for reported analgesic, sedative, antiinflammatory, antispasmodic, and anticonvulsant properties, cannabis was said to be the treatment of choice for Queen Victoria's dysmennorhea. In the early 1900s, medicines that were indicated for each of cannabis' purported activities were introduced into the Western armamentarium, making its use less widespread.

Physicians in the United States were the main opponents to the introduction of the Marihuana Tax Act by the Treasury Department in 1937. The legislation was masterminded by Harry Anslinger, director of the Federal Bureau of Narcotics from its inception in 1931 until 1962, who testified in Congress that "Marijuana is the most violence-causing drug in the history of mankind." The Act imposed a levy of one dollar an ounce for medicinal use and one hundred dollars an ounce for recreational use, which in 1937 dollars was a prohibitive cost. By using the Mexican name for the plant and associating it with nefarious South-of-the-Border activities, the proponents fooled many physicians. The Act was singly opposed by the American Medical Association, who felt that objective evidence that cannabis was harmful was lacking and that its passage would impede further research into its medical utility. In 1942, cannabis was removed from the U.S. Pharmacopoeia. In 1970, with the initiation of the Controlled Substances Act, marijuana was classified as a Schedule I drug. Where both Schedule I and Schedule II substances have a high potential for abuse, Schedule I drugs are distinguished by having no accepted medical use. Other Schedule I substances include heroin, LSD, mescaline, methylqualone, and, most recently, gammahydroxybutyrate (GHB). Despite efforts to change the scheduling of cannabis, it remains a Schedule I substance at this time.

Delta-9-THC is one of the ~100 cannabinoids found in the cannabis plant and is felt to be the main psychoactive component. Overall, the plant contains about 400 compounds derived from its secondary metabolism, many of which may contribute to its medicinal effect. Synthetic delta-9-THC in sesame oil (dronabinol, Marinol) was first licensed and approved in 1986 for the

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Received 5 January 2015; accepted 9 March 2015; advance online publication 16 March 2015. doi:10.1002/cpt.108

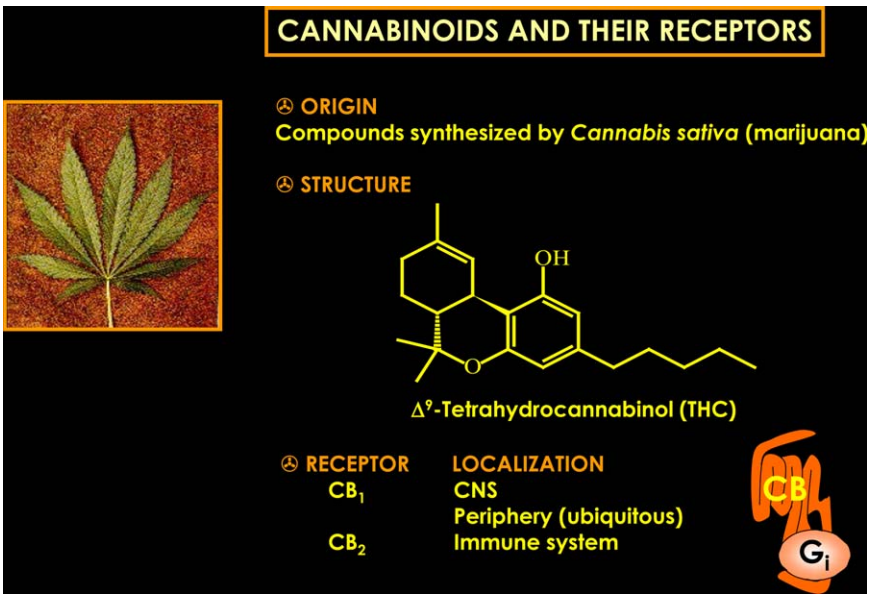

Figure 1 Cannabinoids are a group of 21 carbon terpenophenolic compounds produced by *Cannabis* species. The phytocannabinoids complex with two receptors, CB1 and CB2, to produce their physiologic effects.

treatment of chemotherapy-associated nausea and vomiting. Clinical trials done at the time determined that dronabinol was as effective, if not more so, than the available antiemetic agents.[2] Dronabinol was investigated for its ability to stimulate weight gain in patients with the AIDS wasting syndrome in the late 1980s. Results from a number of trials suggested that although patients reported an improvement in appetite, no statistically significant weight gain was appreciated.[3,4] Nabilone (Cesamet) is another synthetic delta-9-THC that is also available by prescription. More recently, nabiximols (Sativex), a whole plant extract delivered as an oromucosal spray, has been developed and approved for medical use in Europe and Canada. This article will review the biology and pharmacology of cannabis and cannabinoids and focus on their use in symptom management, particularly in patients with cancer.

CANNABINOID CHEMISTRY AND BIOLOGIC EFFECTS

Cannabinoids are a group of 21 carbon terpenophenolic compounds produced uniquely by *Cannabis sativa* and *Cannabis indica* species.[1] With the discovery of endogenous cannabinoids and to distinguish them from pharmaceutical compounds, the plant compounds may also be referred to as phytocannabinoids. Although delta-9-THC is the primary active ingredient in cannabis, there are a number of non-THC cannabinoids and noncannabinoid compounds that also have biologic activity. Cannabidiol (CBD), cannabinol, cannabichromene, cannabigerol, tetrahydrocannabivirin, and delta-8-THC are just some of the additional cannabinoids that have been identified. It is postulated that the secondary compounds may enhance the beneficial effects of delta-9-THC, for example by modulating the THC-induced anxiety, anticholinergic, or immunosuppressive effects, and may reduce the unwanted effects of delta-9-THC, for example by attenuating seizures, psychoses, or motor discoordination. In addition, cannabis-associated terpenoids and flavonoids may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens, and provide antiinflammatory activity.[1,5]

The neurobiology of the cannabinoids has only been identified within the past 25 years, during which time an explosion of knowledge has occurred.[1] In the mid-1980s, researchers developed a potent cannabinoid agonist to be used in research investigations. In 1986 it was discovered that cannabinoids inhibited the accumulation of 3′-5′ cyclic adenosine monophosphate (cAMP), suggesting the presence of a receptor-mediated mechanism. By attaching a radiolabel to the synthetic cannabinoid, the first cannabinoid receptor, CB1, was pharmacologically identified in the brain in 1988. The CB1 receptor is coupled to G_i proteins (**Figure 1**). Its engagement inhibits adenylyl cyclase and voltage-gated calcium channels, and stimulates rectifying potassium conductances and mitogen-activated protein kinase cascades. By 1990, investigators had cloned the CB1 receptor, identified its DNA sequence, and mapped its location in the brain, with the largest expression being in the basal ganglia, cerebellum, hippocampus, and cerebral cortex. Nowadays, CB1 is known to be a ubiquitous protein that is present in basically all body tissues. In 1993 a second cannabinoid receptor, CB2, was identified outside the brain. Originally detected in macrophages and the marginal zone of the spleen, the highest abundance of CB2 receptors is located on the B lymphocytes and natural killer cells, suggesting a role in immunity.

The existence of cannabinoid receptors has subsequently been demonstrated in most animal species, all the way down to invertebrates. Are these receptors present in the body solely to complex with ingested phytocannabinoids? The answer came in 1992 with the identification of a brain constituent that binds to the cannabinoid receptor. Named anandamide from the Sanskrit word for bliss, the first endocannabinoid had been discovered.

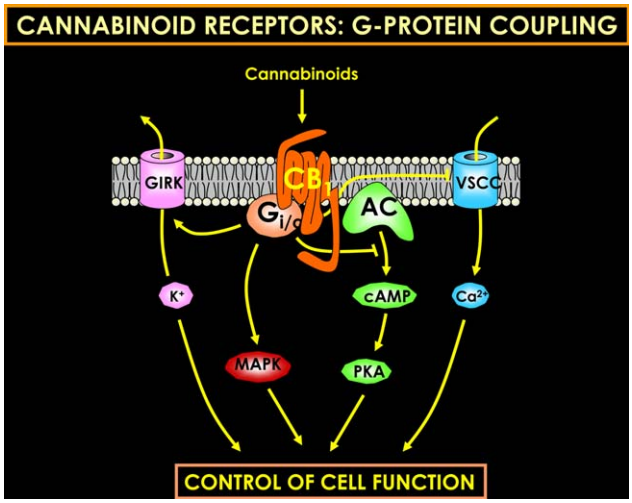

Figure 2 Signaling pathways coupled to the CB_1 cannabinoid receptor. Cannabinoids exert their effects by binding to specific G_i protein-coupled receptors. The CB_1 cannabinoid receptor signals to a number of different cellular pathways. These include, for example, (i) inhibition of the adenylyl cyclase (AC)cyclic AMPprotein kinase A (PKA) pathway; (ii) modulation of ion conductances, by inhibition of voltage-sensitive Ca^{2+} channels (VSCC) and activation of G_i protein-coupled inwardly rectifying K^+ channels (GIRK); and (iii) activation of mitogen-activated protein kinase (MAPK) cascades. Other less established cannabinoid receptor effectors and the crosstalk among the different pathways have been omitted for simplification.

Subsequently, 2-arachidonoylglycerol (2-AG) has also been confirmed as part of the body's endogenous cannabinoid system. These endocannabinoids function as neuromodulators. As the ligands for the 7-transmembrane domain cannabinoid receptors located in presynaptic nerve terminals, binding of the endocannabinoid leads to G-protein activation and the cascade of events transpires resulting in the opening of potassium channels, which decreases cell firing and the closure of calcium channels that decreases neurotransmitter release (**Figure 2**).

The functions of the endogenous cannabinoid system in the body are becoming more appreciated through advances in cannabinoid pharmacology.[6,7] The identification of the cannabinoid receptors has led to a host of agonists and antagonists being synthesized. Utilizing these tools, investigators are discovering that the system is likely to be important in the control of many biological functions, such as modulation of pain and appetite, suckling in the newborn, and the complexities of memory, to mention just a few. In addition to being utilized to learn more about the natural function of the endocannabinoid system, a number of these cannabinoid receptor agonists and antagonists are being developed as potential pharmaceutical therapies. In the meantime, dronabinol, nabilone, and cannabis are the currently available cannabinoid therapies in the US. Levonantradol (Nantrodolum) is a synthetic cannabinoid administered intramuscularly, not used as much clinically since the oral agents became available. Nabiximols, a standardized whole-plant extract delivered as an oromucosal spray with an ~1:1 ratio of THC and cannabidiol, is available in Canada and some European countries and is undergoing late-phase testing in the US and other countries.

Through the receptors described above, cannabis delivered by way of inhalation, orally, or oromucosally can produce a host of biologic effects.[8] The 1999 Institute of Medicine report, Marijuana and Medicine: Assessing the Science Base, makes the following general conclusions about the biology of cannabis and cannabinoids.[9]

- Cannabinoids likely have a natural role in pain modulation, control of movement, and memory.
- The natural role of cannabinoids in immune systems is likely multifaceted and remains unclear.
- The brain develops tolerance to cannabinoids.
- Animal research has demonstrated the potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine, or nicotine.
- Withdrawal symptoms can be observed in animals but appear mild compared with those of withdrawal from opiates or benzodiazepines.

PHARMACOLOGY OF CANNABIS

When taken by mouth, there is a low (6–20%) and variable oral bioavailability.[1,8] Peak plasma concentrations occur after 1–6 hours and remain elevated with a terminal half-life of 20–30 hours. When consumed orally, delta-9-THC is initially metabolized in the liver to 11-OH-THC, also a potent psychoactive metabolite. On the other hand, when inhaled, the cannabinoids are rapidly absorbed into the bloodstream with a peak concentration in 2–10 minutes that rapidly declines over the next 30 minutes. Inhalation thus achieves a higher peak concentration with a shorter duration of effect. Less of the psychoactive 11-OH-THC metabolite is formed. When nabiximols is taken oromucosally, no pharmacokinetic interactions seem to occur between its two major cannabinoid constituents: THC and CBD, and the pharmacokinetic properties of the THC present in nabiximols are similar to those of oral THC.[10]

Cannabinoids can interact with the hepatic cytochrome P450 enzyme system.[1] CBD, for example, can inactivate CYP3A4. After repeated doses, some of the cannabinoids may induce P450 isoforms. The effects are predominantly related to the CYP1A2, CYP2C, and CYP3A isoforms. The potential for a cannabinoid interaction with cytochrome P450 and, hence, possibly metabolism of pharmaceutical agents has led to a small amount of data on the possibility of botanical:drug interactions. For example, in one study 24 cancer patients were treated with intravenous irinotecan (600 mg, $n = 12$) or docetaxel (180 mg, $n = 12$), followed 3 weeks later by the same drugs concomitant with medicinal cannabis taken as an herbal tea for 15 consecutive days, starting 12 days before the second treatment.[11] The carefully conducted pharmacokinetic analyses showed that cannabis administration as a tea did not significantly influence exposure to and clearance of irinotecan or docetaxel.

CANNABINOIDS AND CANCER SYMPTOM MANAGEMENT

Antiemetic effect

The nausea and vomiting related to cancer chemotherapy continues to be a significant clinical problem even in light of the newer

agents that have been added to our armamentarium since the 1970s and 1980s, when clinical trials of cannabinoids were first conducted.[12] In those days, phenothiazines and metoclopramide were the main antiemetic agents used. Dronabinol (synthetic THC) and nabilone (a synthetic analog of THC) were both tested as novel oral agents in a number of controlled clinical trials. Nabilone was approved in Canada in 1982, but only recently became available in the US. Dronabinol was approved as an antiemetic to be used in cancer chemotherapy in the US in 1986.

Numerous meta-analyses confirm the utility of these THC-related agents in the treatment of chemotherapy-induced nausea and vomiting. Tramer *et al.* [13] conducted a systematic review of 30 randomized comparisons of cannabis with placebo or antiemetics from which dichotomous data on efficacy and harm were available. Oral nabilone, oral dronabinol, and intramuscular levonantradol were tested. No smoked cannabis trials were included. In all, 1,366 patients were involved in the systematic review. Cannabinoids were found to be significantly more effective antiemetics than prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride. In this analysis, the number of people needed to treat for one person to have an effect (NNT) for complete control of nausea was 6; the NNT for complete control of vomiting was 8. Cannabinoids were not more effective in patients receiving very low or very high emetogenic chemotherapy. In crossover trials, patients preferred cannabinoids for future chemotherapy cycles. Tramer *et al.* identified some "potentially beneficial side effects" that occurred more often with cannabinoids including the "high," sedation, or drowsiness, and euphoria. Less desirable side effects that occurred more frequently with cannabinoids included dizziness, dysphoria, or depression, hallucinations, paranoia, and hypotension.

A later analysis by Ben Amar[14] reported that 15 controlled studies had compared nabilone to placebo or available antiemetic drugs. In 600 patients with a variety of malignant diagnoses, nabilone was found to be superior to prochlorperazine, domperidone, and alizapride, with patients clearly favoring nabilone for continuous use. Nabilone has also been shown to be moderately effective in managing the nausea and vomiting associated with radiation therapy and anesthesia after abdominal surgery.[13,15] In the same meta-analysis, Ben Amar reported that in 14 studies of dronabinol involving 681 patients, the cannabinoid antiemetic effect was equivalent or significantly greater than chlorpromazine and equivalent to metochlopramide, thiethylperazine, and haloperidol. It is noted that the efficacy of the cannabinoids in these studies was sometimes outweighed by the adverse reactions and that none of the comparator antiemetics were of the serotonin receptor antagonist class that is the mainstay of treatment today.

A small pilot, randomized, double-blind, placebo-controlled phase II trial was conducted to investigate the whole-plant cannabis-based medicine, nabiximols, added to standard antiemetics in the treatment of chemotherapy-induced nausea and vomiting.[16] Seven patients were randomized to receive the mixture of delta-9-THC and CBD, and nine added placebo to their standard of care antiemetic regimen. Five of the seven nabiximols recipients compared to two of the nine on placebo experienced a complete response with a mean daily dose of 4.8 sprays (~13 mg THC and 12 mg CBD) in both groups without serious adverse effects. Further larger studies of the potential of nabiximols as an antiemetic are warranted.

There have been only three controlled trials evaluating the efficacy of smoked cannabis in chemotherapy-induced nausea and vomiting.[14] In two of the studies, the smoked cannabis was only made available after patients failed dronabinol. The third trial was a randomized, double-blind, placebo-controlled, crossover trial involving 20 adults where both smoked cannabis and oral THC were evaluated. One-quarter of the patients reported a positive antiemetic response to the cannabinoid therapies. On direct questioning of the participants, 35% preferred the oral dronabinol, 20% preferred the smoked marijuana, and 45% did not express a preference. Four participants receiving dronabinol alone experienced distorted time perception or hallucinations which were also reported by two with smoked marijuana and one with both substances. Both dronabinol and nabilone are US Food and Drug Administration (FDA)-approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic therapy. Nabilone's extended duration of action allows for twice a day dosing of one or two mg commencing 1–3 hours prior to receiving chemotherapy. A dose of 1 or 2 mg the night before administration of chemotherapy might also be useful. It is recommended to commence dronabinol at an initial dose of 5 mg/m^2, also 1–3 hours prior to the administration of chemotherapy, then every 2–4 hours after chemotherapy, for a total of 4–6 doses/day. Should the 5 mg/m^2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m^2 increments to a maximum of 15 mg/m^2 per dose. Nabilone, with fewer metabolites and a lower dose range, may be associated with fewer side effects. The need to dose 1–3 hours prior to chemotherapy is one factor that drives patients to prefer inhaled cannabis where the delivery and effect peak within minutes. Patients also prefer the ability to more tightly titrate the dose of cannabinoids they receive when inhaling compared to oral ingestion.

The National Comprehensive Cancer Network antiemesis guidelines recommend cannabinoids among other therapies to consider as a breakthrough treatment for chemotherapy-induced nausea and vomiting (http://www.nccn.org).

Appetite stimulation

Anorexia, early satiety, weight loss, and cachexia are some of the most daunting symptom management challenges faced by the practicing oncologist. There are very few tools in the toolbox for addressing these concerns. For many the hormonal manipulation with megestrol acetate (synthetically derived progesterone) may be contraindicated or the side effects undesirable. Two small controlled trials demonstrated that oral THC stimulates appetite and may slow weight loss in patients with advanced malignancies.[14] In a larger randomized, double-blind, parallel group study of 469 adults with advanced cancer and weight loss, patients received either 2.5 mg of oral THC twice daily, 800 mg of oral megestrol daily, or both. In the megestrol monotherapy group, appetite increased in 75% and weight in 11% compared to 49% and 3%, respectively, in the oral THC group. These differences

were statistically significant. The combined therapy did not confer additional benefits. A smaller randomized placebo-controlled trial of dronabinol in cancer patients demonstrated enhanced chemosensory perception in the treatment group.[17] In the patients receiving cannabinoids, food was reported to taste better, appetite improved, and the proportion of protein calories was increased compared to the placebo group.

Many animal studies have previously demonstrated that THC and other cannabinoids have a stimulatory effect on appetite and increase food intake. It is felt that the endogenous cannabinoid system may serve as a regulator of feeding behavior. For example, anandamide in mice leads to a potent enhancement of appetite.[18] It is felt that the CB1 receptors, present in the hypothalamus where food intake is controlled and in the mesolimbic reward system, may be involved in the motivational or reward aspects of eating. This led to the development of the pharmaceutical CB1 antagonist rimonabant (Acomplia), which was approved in Europe for the treatment of obesity on the basis of phase III clinical trials where it was shown to induce a 4–5 kg mean weight loss with improved glycemic and lipid profiles.[19] However, Acomplia was never approved in the US and was ultimately withdrawn from the European market because it was found to induce anxiety and depressive disorders that were deemed high risk, often leading to patient suicide.

Anecdotal as well as clinical trial evidence also supports the appetite-stimulating effect of inhaling cannabis. In classic trials conducted in the 1970s in healthy controls, it was found that, especially when smoked in a social/communal setting, cannabis inhalation led to an increase in caloric intake, predominantly in the form of between-meal snacks, mainly in the form of fatty and sweet foods. In cancer patients with anorexia as well as chemotherapy-induced nausea, it is worth noting that cannabis is the only antiemetic that also has orexigenic action. Although cannabis thus provides two potential benefits to the patient with cancer, the appetite stimulation does not always reverse the cancer cachexia which is a function of energy wasting in addition to decreased food intake. Interestingly, an increasing body of epidemiologic evidence suggests that instead of being overweight, the general noncancer population of cannabis users has a lower prevalence of obesity than nonusers, with smaller waist circumferences and lower fasting insulin levels.[20,21]

Analgesia

Our understanding of the possible mechanisms of cannabinoid-induced analgesia has been greatly increased through study of the cannabinoid receptors, endocannabinoids and synthetic agonists and antagonists. The CB1 receptor is found in the central nervous system as well as in peripheral nerve terminals. Elevated levels of the CB1 receptor, like opioid receptors, are found in areas of the brain that modulate nociceptive processing.[1,22] In contrast, CB2 receptors are located in peripheral tissue and are present at very low expression levels in the central nervous system (CNS). Of the endogenous cannabinoids identified, anandamide has high affinity for CB1 receptors, whereas 2-AG has high affinity for both CB1 and CB2 receptors. With the development of receptor-selective antagonists (for example, SR141716 for CB1 and SR144528 for CB2), additional information has been obtained regarding the roles of the receptors and endogenous cannabinoids in modulation of pain. Where the CB1 agonists exert analgesic activity in the CNS, both CB1 and CB2 agonists have peripheral analgesic actions. Cannabinoids may also contribute to pain modulation through an antiinflammatory mechanism—a CB2 effect with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents such as histamine and serotonin and on keratinocytes to enhance the release of analgesic opioids.[23,24]

Cannabinoids are effective in animal models of both acute and persistent pain. The central analgesic mechanism differs from the opioids in that it cannot be blocked by opioid antagonists. The potential for additive analgesic effects with opioids as well as the potential for cannabinoids to reduce nausea and increase appetite make a strong case for the evaluation of marijuana as adjunctive therapy for patients on morphine.[25] Unfortunately, although the medical literature cites evidence of cannabinoids' ability to reduce naturally occurring pain, few human studies have been performed. Early studies of cannabinoids on experimental pain in human volunteers produced inconsistent results. In some cases, the administration of cannabinoids failed to produce observable analgesic effects; in others, cannabinoids resulted in an increase of pain sensitivity (hyperalgesia). Institute of Medicine reviewers noted that these studies suffered from poor design and methodological problems and dubbed their findings inconclusive.[9]

Encouraging clinical data on the effects of cannabinoids on chronic pain come from three studies of cancer pain. Cancer pain results from inflammation, mechanical invasion of bone or other pain-sensitive structure, or nerve injury. It is severe, persistent, and often resistant to treatment with opioids. Noyes *et al.*[26] conducted two studies on the effects of oral THC on cancer pain. Both studies used standard single-dose analgesic study methodology and met the criteria for well-controlled clinical trials of analgesic efficacy. The first trial measured both pain intensity and pain relief in a double-blind, placebo controlled study of 10 subjects. Observers compared the effects of placebo and 5, 10, 15, and 20 mg doses of delta-9-THC over a 6-hour period. Researchers reported that 15 and 20 mg doses produced significant analgesia, as well as antiemesis and appetite stimulation. The authors cautioned that some subjects reported unwanted side effects such as sedation and depersonalization at the 20 mg dose level. In a follow up single-dose study of 36 subjects, Noyes *et al.*[27] reported that 10 mg of THC produced analgesic effects over a 7-hour observation period comparable to 60 mg of codeine, and that 20 mg of THC induced effects equivalent to 120 mg of codeine. The authors noted that respondents found higher doses of THC to be more sedative than codeine. However, in a separate publication, Noyes and Baram[28] reported that patients administered THC had improved mood, sense of well-being, and less anxiety.

A more recent study investigated the effects of whole-plant extract preparations in patients with intractable cancer pain.[29] In all, 177 patients experiencing inadequate analgesia despite chronic opioid use were randomized to receive the THC:CBD extract ($N = 60$), the THC extract ($N = 58$), or placebo ($N =$

59) in a 2-week, multicenter, double-blind trial. Pain relief was superior in the THC:CBD group, with twice as many patients in the combination arm achieving a greater than 30% reduction in pain when compared to placebo. The THC alone group fared more or less the same as the placebo recipients. No change from baseline at a median dose of opioids or need for breakthrough medication was seen.

Neuropathy

Cannabinoids have also been shown to be of potential benefit in an animal model of neuropathic pain.[30] Neuropathic pain is a troubling symptom in cancer patients, especially those treated with platinum-based chemotherapy or taxanes. A painful sensory peripheral neuropathy is also commonly encountered in patients with HIV infection either as a consequence of HIV itself or antiretroviral drugs used in treatment of the infection. We completed a randomized, controlled trial of smoked cannabis compared to placebo in 50 subjects with HIV-related peripheral neuropathy.[31] Smoked cannabis reduced daily pain by 34% compared to 17% with placebo ($P = 0.03$). A greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group ($P = 0.04$). The first cannabis cigarette reduced chronic pain by a median of 72% compared to 15% with placebo ($P < 0.001$). Cannabis also reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli ($P \leq 0.05$) in a heat-capsaicin experimental pain model used to anchor the more subjective response of the chronic neuropathic pain. No serious adverse events were reported. The NNT in this study was 3.6, which was virtually identical to the NNT in other studies of inhaled cannabis in HIV and other neuropathic syndromes.[32–34]

Two placebo-controlled studies of cannabinoids for central neuropathic pain associated with multiple sclerosis produced results similar to the aforementioned study. In a crossover trial of synthetic delta-9-THC up to 10 mg/day, a NNT of 3.5 was reported.[35] A trial of the sublingual spray containing delta-9-THC alone or combined with CBD showed a 41% pain reduction with active drug compared to a 22% reduction with placebo.[36] In this study, the CBD-alone preparation was ineffective in pain relief. Improvement in sleep quality was also reported with the sublingual spray. Nabiximols is currently approved in Canada for treatment of neuropathic pain related to multiple sclerosis as well as cancer-related pain. A small clinical trial has been conducted investigating nabiximols in 16 patients with chemotherapy-induced neuropathic pain, with results suggesting that larger follow-on clinical trials in this patient population are warranted.[37]

In an animal model of paclitaxel-induced neuropathic pain, chronic administration of the nonpsychoactive cannabinoid CBD prevented the onset of chemotherapy-induced neurotoxicity in mice.[38] The investigators suggested that adjunct treatment with CBD during taxane chemotherapy may be safe and effective in the prevention or attenuation of chemotherapy-induced neuropathic pain, although human studies are certainly required.

Cannabinoid:opioid interactions

Synergism between opioids and cannabinoids has been postulated and subsequently demonstrated in a number of animal models.[39] The antinociceptive effects of morphine are predominantly mediated by mu-opioid receptors but may be enhanced by delta-9-THC activation of kappa and delta-opioid receptors. It has been further postulated that the cannabinoid:opioid interaction may occur at the level of their signal transduction mechanisms. Receptors for both classes of drugs are coupled to similar intracellular signaling mechanisms that lead to a decrease in cAMP production by way of G_i protein activation. There has also been some evidence that cannabinoids might increase the synthesis or release of endogenous opioids, or both. With this background, we conducted a pharmacokinetic interaction study to investigate the effect of concomitant cannabis on disposition kinetics of opioid analgesics.[40] Ten patients with chronic pain on a stable dose of sustained-release morphine and 11 on sustained-release oxycodone had their opioid concentration over time curves evaluated before and after 4 days of exposure to vaporized cannabis. No adverse side effects of combining cannabinoids and opioids were observed over the course of the in-patient evaluation. There were no significant alterations in the area under the curves for the opioids after the addition of vaporized cannabis. Although the study was not powered for pain as an endpoint, evidence of potential synergistic relief of pain was appreciated. If cannabinoids and opioids were shown to be synergistic in a larger follow-on controlled clinical trial, it is possible that lower doses of opioids would be effective for longer periods of time with fewer side effects, clearly a benefit to the patient with pain.

Anxiety, depression, and sleep

In clinical trials of cannabis, euphoria is often scored as an adverse effect. Although not all patients experience mood elevation after exposure to cannabis, it is a frequent outcome. Much depends on the "set and setting" and the individual's prior experience with cannabis. Some people develop dysphoria with or without paranoia upon exposure to cannabis; for them, cannabis or its constituents may not be clinically useful. Sleepiness is another common side effect which can easily be recast as improved sleep quality, as has been reported in trials of nabiximols as well as inhaled cannabis.[41,42] For the cancer patient suffering from anorexia, nausea, pain, depression, anxiety, and insomnia, a single agent that can address all of these symptoms would be a valuable addition to the armamentarium. Cannabis may therefore be particularly useful in supportive or palliative care situations. [43]

CANNABINOIDS AS ANTICANCER AGENTS

There has been an increasing body of evidence over the past decade that cannabinoids may have a role in cancer therapy.[1,44–46] Evidence from cell culture systems as well as animal models has shown that THC and other cannabinoids may inhibit the growth of some tumors by the modulation of signaling pathways that lead to growth arrest and cell death as well as by inhibition of angiogenesis and metastasis. The antiproliferative effects were originally reported in 1975 by Munson *et al.*,[47] who demonstrated that delta-9-THC, delta-8-THC, and cannabinol inhibited Lewis lung adenocarcinoma cell growth *in vitro* as well as in mice. Curiously, there was no real follow-up of these findings for 20 years when the line of investigation was

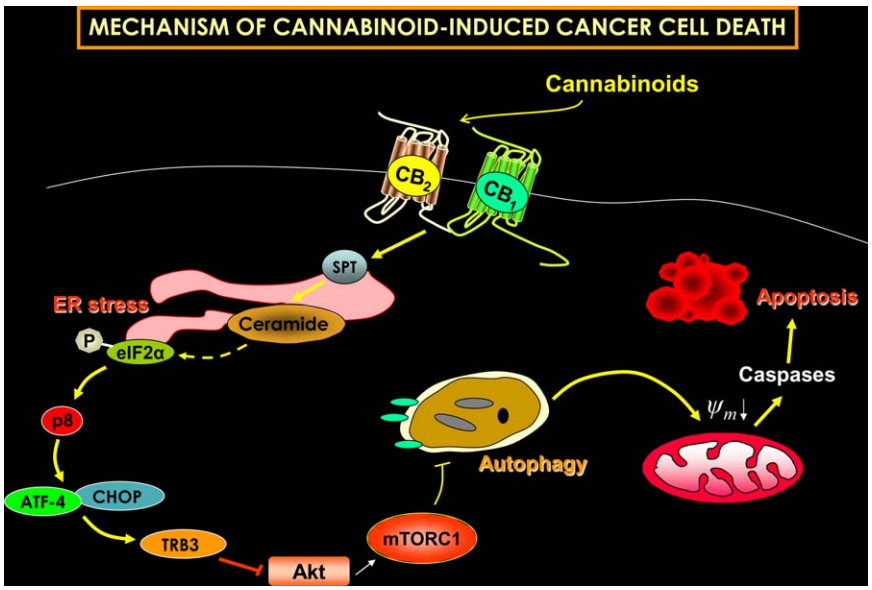

Figure 3 Mechanism of cannabinoid-induced cancer cell death. Cannabinoid agonists bind to CB_1 and/or CB_2 receptors to stimulate *de novo* synthesis of ceramide via induction of the enzyme serine palmitoyltransferase (SPT). This triggers the induction of an eIF2a-mediated endoplasmic reticulum (ER) stress response that promotes the up-regulation of the transcription factor p8 and several of its downstream targets, including the transcription factors ATF-4 and CHOP and the pseudokinase TRB3. This favors the interaction of TRB3 with the prosurvival protein AKT, thus leading to the inhibition of the AKT -mTORC1 axis and the subsequent induction of autophagy. Autophagy is upstream of intrinsic mitochondrial apoptosis in the process of cannabinoid-induced cell death.

picked up by scientists in Spain and Italy, who have remained at the forefront of this emerging field.[1,44–46,48] Since the late 1990s, several plant-derived (THC and CBD), synthetic (WIN-55,212-2 and HU-210), and endogenous cannabinoids (anandamide and 2-arachidonoylglycerol) have been shown to exert antiproliferative effects of a wide variety of tumor cells in culture systems. In addition to the original lung adenocarcinoma study, other tumor cells that have been shown to be sensitive to cannabinoid-induced growth inhibition include glioma, thyroid epithelioma, leukemia/lymphoma, neuroblastoma, and skin, uterus, breast, gastric, colorectal, pancreatic, and prostate carcinomas.[1,46,49–53] Perhaps even more compelling, cannabinoid administration to nude mice slows the growth of various tumor xenografts or genetically initiated tumors including lung, breast, colorectal, and skin carcinomas, thyroid epitheliomas, melanomas, pancreatic carcinomas, lymphomas, and gliomas. The requirement of CB1 and/or CB2 receptors for the antitumor effect has been shown by various biochemical and pharmacological approaches, and the cumulative effects of cannabinoid receptor signaling in the control of cell fate are expected to have important implications in the potential of cannabinoids for regulating tumor cell growth.

Cannabinoids may exert their antitumor effects by a number of different mechanisms, including direct induction of transformed cell death, direct inhibition of transformed-cell growth, and inhibition of tumor angiogenesis and metastasis (**Figure 3**). A desirable property of antitumor compounds is their preferential targeting of malignant cells. Cannabinoids appear to kill tumor cells but do not affect their nontransformed counterparts, and may even protect them from cell death. This is best exemplified by glial cells. Thus, cannabinoids have been shown to induce apoptosis of glioma cells in culture and regression of glioma cells in mice and rats by activating CB1 and CB2 receptors. In

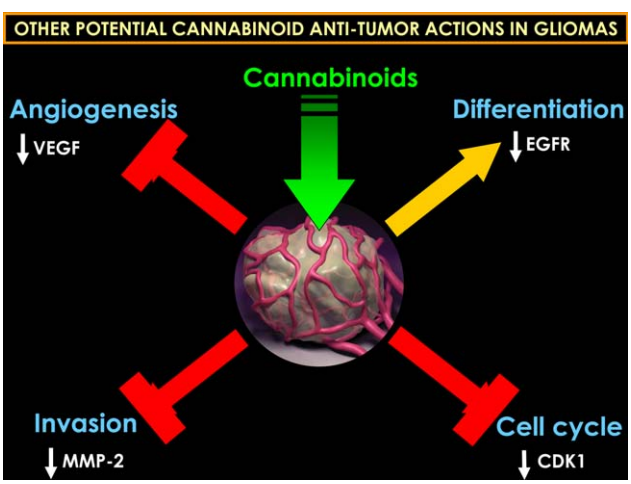

Figure 4 Other antitumor effects of cannabinoids. Besides inducing apoptosis of tumor cells, cannabinoid administration can decrease the growth of gliomas by other mechanisms, including at least: (i) reduction of tumor angiogenesis, by inhibition of the vascular endothelial growth factor (VEGF) pathway; (ii) inhibition of tumor cell invasion, by down-regulation of matrix metalloproteinase-2 (MMP-2) expression; (iii) induction of tumor cell differentiation, by down-regulation of epidermal growth factor (EGF) receptor expression; and perhaps (iv) arrest of the cell cycle, by down-regulation of cyclin-dependent kinase-1 (CDK1) expression. The relative contribution of these processes to the inhibition of tumor growth depends on various factors such as the type of tumor under study, the experimental model used and the intensity of cannabinoid signaling.

contrast, cannabinoids protect normal glial cells of astroglial and oligodendroglial lineages from apoptosis mediated by the CB1 receptor.

Immunohistochemical and functional analyses in mouse models of gliomas, skin carcinomas, and other tumors have demonstrated that cannabinoid administration alters the vascular hyperplasia characteristic of actively growing tumors into a pattern characterized by small, differentiated, impermeable capillaries, thus thwarting angiogenesis. This is accompanied by a reduced expression of vascular endothelial growth factor (VEGF) and other proangiogenic cytokines, as well as of VEGF receptors. Activation of cannabinoid receptors in vascular endothelial cells inhibits cell migration and survival, also contributing to impaired tumor vascularization. Cannabinoid administration to tumor-bearing mice decreases the activity and expression of matrix metalloproteinase 2, a proteolyic enzyme that allows tissue breakdown and remodeling during angiogenesis and metastasis. This supports the inhibitory effect of cannabinoids in inhibiting tumor invasion in animal models (**Figure 4**).

The use of combination anticancer therapies has a number of theoretical advantages over single-agent-based strategies as they allow the simultaneous targeting of tumor growth, progression, and/or spreading at different levels. In line with this idea, recent observations suggest that the combined administration of cannabinoids with other anticancer drugs acts synergistically to reduce tumor growth in mice. For example, the administration of THC and temozolomide (the benchmark agent for the management of glioblastoma) exerts a strong antitumor action in glioma xenografts, an effect that is also evident in temozolomide-resistant tumors.[54]

An additional approach has been to combine THC with CBD, a cannabinoid that reduces the growth of several types of tumor xenografts in mice through a still poorly defined mechanism. Combined administration of THC and CBD enhances the anticancer activity of THC and reduces the doses of THC needed to induce its tumor growth-inhibiting activity.[54,55] Moreover, the combination of THC and CBD together with temozolomide produces a striking reduction in the growth of glioma xenografts even when low doses of THC are used.[54] CBD is also known to alleviate some of the undesired effects of THC administration, such as seizures, incoordination, and psychotic events, and therefore improves the tolerability of cannabis-based medicines.[6] As *Cannabis sativa* contains an estimated 100 different cannabinoids, some of the other cannabinoids present in addition to CBD might also attenuate the psychoactive side effects of THC or even produce other therapeutic benefits. Thus, we believe that clinical studies aimed at analyzing the efficacy of cannabinoids as antitumor agents should be based not only on the use of both pure substances, such as THC and CBD, but also of cannabis products containing controlled amounts of THC, CBD, and other cannabinoids.

So with the body of evidence increasing, where are the clinical trials in humans with malignant disease? True, cannabinoids have psychoactive side effects, but these could be considered to be within the boundaries of tolerance for the toxicity profiles of cytotoxic chemotherapeutic and targeted small molecule therapies widely used in oncology. Ten years ago, a pilot clinical trial was carried out in collaboration between the Tenerife University Hospital and the Guzman laboratory in Madrid (Spain) to investigate the effect of local administration of THC intracranially through an infusion catheter on the growth of recurrent glioblastoma multiforme.[56] In this ground-breaking pilot study, THC administration was shown to be safe and associated with decreased tumor cell progression—as assessed by magnetic resonance imaging and biomarker expression criteria—in at least two of the nine patients studied. Two clinical studies aimed at evaluating the antitumoral activity of cannabinoids are currently ongoing (ClinicalTrials.gov Identifiers: NCT01812616 and NCT02255292).

Despite these impressive *in vitro* and animal model findings regarding the potential antitumor effects of cannabinoids, there is still no solid basis for ongoing claims by proponents of highly concentrated cannabis extracts or oils that these preparations can "cure cancer." Increasing numbers of patients in North America are seeking oils high in THC and/or CBD due to testimonials that patients have used these preparations either topically to eradicate skin cancers or systemically to eliminate nonskin cancers. This has led to a number of patients seeking to forego or postpone potentially curative conventional cancer therapies in favor of self-medicating with high-potency cannabis oils. Many patients claiming to be cured of their cancers have used the products in addition to conventional cancer therapies, thus obfuscating the issue further. Although the *in vitro* and animal evidence is intriguing, there have not yet been any robust human studies investigating cannabis as an anticancer agent that would warrant advising patients to forego conventional therapy in favor of using a high-potency cannabis extract. Patients who choose to delay conventional therapies in the hopes of benefiting from a trial of cannabis oil against their cancer risk the possibility of having a potentially treatable cancer become incurable. As the preclinical evidence suggests that cannabinoids might enhance the antitumor activity of conventional chemotherapeutic agents as well as ameliorate associated side effects, the addition of cannabinoid-based preparations to standard cancer therapy should not be discouraged by the treating oncologist.

CANNABIS AND CANCER RISK

A study conducted by the National Toxicology Program of the US Department of Health and Human Services on mice and rats suggested that cannabinoids may have a protective effect against tumor development.[57] In this 2-year evaluation, rats and mice were given increasing doses of THC by gavage. A dose-related decrease in the incidence of both benign and malignant tumors was observed. Animals receiving THC dosing also survived longer than those receiving vehicle alone.

The biology of mice and rats is certainly different from that of humans, and gavage is not equivalent to smoking a combusted botanical product. Many would find the combustion and inhalation of a therapeutic agent to be an undesirable and perhaps counterintuitive way to deliver a drug. Most of the evidence available on the risk of cancer from marijuana smoking comes from epidemiologic studies, naturally, as prospective, randomized

control trials are not possible. Over the years, reports of increased risks of lung cancer, oropharyngeal cancers, and prostate and cervical cancer have been most consistently reported. For each trial suggesting a possible increase in cancer incidence in chronic marijuana users, others have been published that appear to refute the association.

A 40-year cohort study of Swedish military conscripts evaluated for cannabis use in 1969–1970 found that in those who reported use of cannabis more than 50 times in their life, their risk of lung cancer in 2009 was increased 2-fold.[58] As tobacco use was nearly universal in this cohort, the association was present even after adjusting for tobacco use.

Another retrospective cohort study evaluated 64,855 Kaiser Permanente healthcare members seen between 1979 and 1985, and followed through 1993.[59] Men aged 15–49 were divided into four cohorts based on their use of tobacco and marijuana: never smoked either, smoked only cannabis, smoked only tobacco, smoked tobacco and cannabis. There were 5,600–8,200 men in each cell followed for an average of nearly 9 years. In the men who never smoked, there were two cases of lung cancer diagnosed over the follow-up period. In the men who smoked tobacco, either alone or in addition to marijuana, the risk of lung cancer was increased 10-fold. In the over 50,000 person-years of follow-up of men who only smoked marijuana, there were no documented cases of lung cancer; less than in the never smokers.

A population-based case–control study of the association between marijuana use and the risk of lung and upper aerodigestive tract cancers was performed in Los Angeles.[60] In all, 1,112 incident cancer cases (611 lung, 303 oral, 108 esophagus, 100 pharynx, 90 larynx) were matched to 1,040 cancer-free controls on age, gender, and neighborhood. A standardized questionnaire used during face-to-face interviews collected information on marijuana use expressed in joint-years, where 1 joint-year is the equivalent of smoking one marijuana cigarette per day for 1 year. The interviews also requested information on the use of other drugs including hashish, tobacco (all forms), and alcohol, sociodemographic factors, diet, occupational history, environmental factors including exposure to smoke, medical history, and family history of cancer. Data were presented as crude odds ratios and adjusted odds ratios using three models of covariate adjustment (with only Model 3 including tobacco use and pack/years). The results showed that although using marijuana for $\geq$30 joint-years was positively associated in the crude analysis with each cancer except pharyngeal, no positive associations were found when adjusting for several confounders including cigarette smoking. In fact, in the Model 3 analysis for lung cancer, the cohort who reported >0 to <1 joint-years of marijuana use had a 37% reduction in the risk of developing lung cancer compared to those who never smoked marijuana. Although this was the only cohort where the reduction in lung cancer risk reached statistical significance, in the model all levels of marijuana use (including $\geq$60 joint-years) had adjusted odds ratios (ORs) less than 1.0. The authors report adjusted ORs <1 for all cancers except oral cancer and found no consistent association of marijuana use with any malignant outcome. In what appears to be an overly aggressive attempt to delineate the possible limitations of their work that could have led to such a consistent yet startling result, the authors mention that "it is possible that marijuana use does not increase cancer risk.... Although the adjusted ORs < 1 may be chance findings, they were observed for all non-reference exposure categories with all outcomes except oral cancer. Although purely speculative, it is possible that such inverse associations may reflect a protective effect of marijuana."

A systematic review evaluating 19 studies that involved persons 18 years or older who smoked marijuana and examined premalignant or cancerous lung lesions concluded that observational studies failed to demonstrate significant associations between marijuana smoking and lung cancer after adjusting for tobacco use.[61] The authors site the selection bias, small sample size, limited generalizability, and overall young participant age in stating that because of the biological plausibility of an association of marijuana smoking and lung cancer, physicians should still caution patients regarding potential risks until further rigorous studies permit definitive conclusions. A more recent pooled analysis of six international case–control studies involving 2,159 lung cancer cases and 2,985 controls found weak associations between cannabis smoking and lung cancer in never tobacco smokers, but the authors suggested that the results provide little evidence of increased risk of lung cancer among habitual or long-term users while again cautioning that the possibility of adverse effect for heavy consumption cannot be excluded.[62]

Postulating that chronic use of cannabis impacts negatively on endocrine and reproductive systems, three recent investigations suggest an association between cannabis and testicular tumors.[63–65] These population-based case–control studies reported an association between marijuana use and elevated risk of especially nonseminomatous germ cell tumors. Although lacking good dose information and adequate sample sizes, the trends warrant further follow-up. A recent analysis from the California Men's Health Study reported that cannabis use may be inversely associated with bladder cancer risk in a study of 84,170 men aged 45–69.[66] A review of 34 epidemiologic studies acknowledges the possible association of cannabis use with testicular cancers, agrees that the data regarding lung cancer is confounded by concomitant tobacco use, and concludes that for other cancer sites the data are still insufficient to make any conclusions.[67] Finally, a comprehensive review from Health Canada concluded that although concerns exist, the epidemiologic evidence of a link between use of cannabis and cancer remains inconclusive (http://www.hc-sc.gc.ca/dhp-mps/marihuana/med/infoprof-eng.php).

SAFETY AND SIDE EFFECTS

Cannabinoids have an extremely favorable drug safety profile.[1,9,12,44] Unlike opioid receptors, cannabinoid receptors are not located in brainstem areas controlling respiration, so lethal overdoses due to respiratory suppression do not occur. The LD_{50} has been estimated to be 1,500 pounds smoked in 15 minutes as extrapolated from animal studies where the median lethal dose was estimated to be several grams per kilogram of body weight (http://www.fcda.org/pdf/young88.fcda.pdf).

The administration of cannabinoids to laboratory animals and humans does result in psychoactive effects. In humans, the central nervous system effects are both stimulating and depressing and are divided mainly into four groups: affective (euphoria and easy laughter); sensory (temporal and spatial perception alterations and disorientation); somatic (drowsiness, dizziness and motor incoordination); and cognitive (confusion, memory lapses and difficulty concentrating).

As cannabinoid receptors are not just located in the CNS but are present in tissues throughout the body, additional side effects of note include tachycardia and hypotension, conjunctival injection, bronchodilation, muscle relaxation, and decreased gastrointestinal motility. Tolerance to the unwanted side effects of cannabis appears to develop rapidly in laboratory animals and humans. This is felt to occur due to a decrease in the number of total and functionally coupled cannabinoid receptors on the cell surface, with a possible minor contribution from increased cannabinoid biotransformation and excretion with repeated exposure.

Although cannabinoids are considered by some to be addictive drugs, their addictive potential is considerably lower than other prescribed agents or substances of abuse. The brain develops tolerance to cannabinoids and animal research demonstrates a potential for dependence. Dependence is reported to develop in 9% of cannabis users according to the criteria in the *DSM-IV*.[68] The Institute of Medicine report puts this into context noting that, with 46% of the US population ever having used cannabis with 9% becoming dependent, the risk is much lower than that of nicotine, heroin, cocaine, and alcohol, and equivalent to the proportion of those dependent on anxiolytics.[9] Withdrawal symptoms—irritability, insomnia with sleep EEG disturbance, restlessness, hot flashes, and rarely nausea and cramping—have been observed, but are usually mild compared with the withdrawal from opiates or benzodiazepines and usually dissipate after a few days. Unlike other commonly used drugs, cannabinoids are stored in adipose tissue and excreted at a low rate (half-life 1–3 days), so even abrupt cessation of THC intake is not associated with rapid declines in plasma concentration that would precipitate withdrawal symptoms or drug craving.

The Institute of Medicine report addressed the frequent concern that marijuana is a "gateway drug" leading to use of other subsequent more potent and addictive substances of abuse.[9] The report recounts that marijuana is the most widely used illicit drug and, predictably, the first most people encounter. Not surprisingly, most users of other illicit drugs have used marijuana first. However, most drug users begin with alcohol and nicotine before marijuana; hence, marijuana would very rarely be the first "gateway" drug. The report summarizes that there is no conclusive evidence that the drug effects of marijuana are causally linked to the subsequent abuse of other illicit drugs and cautions that data on drug use progression cannot be assumed to apply to the use of drugs for medical purposes, which is certainly pertinent to the discussion of cannabis in cancer patients.

GUIDELINES FOR PROVIDERS

The Institute of Medicine is aware that the development and acceptance of preferred smokeless marijuana delivery systems "may take years; in the meantime there are patients with debilitating symptoms for whom smoked marijuana may provide relief." So what is a provider to do? Patients with cancer have a number of symptoms that may be responsive to cannabinoid therapies. As enumerated, these include nausea, vomiting, anorexia, pain, insomnia, anxiety, and depression. Many providers would frown upon the use of a relatively benign inhaled psychotropic agent while freely writing prescriptions for pharmaceutical agents with significantly greater cost, potential for addiction or abuse, and more negative societal impact overall.

A Medical Board of California Action Report from 2004 provides a model for how states with medical marijuana legislation should advise physicians (http://www.caldocinfo.ca.gov). "The intent of the board at this time is to reassure physicians that if they use the same proper care in recommending medical marijuana to their patients as they would any other medication or treatment, their activity will be viewed by the Medical Board just as any other appropriate medical intervention."

The Board recommends following the accepted standards that would be used in recommending any medication. A history and physical examination should be documented. The provider should ascertain that medical marijuana use is not masking an acute or treatable progressive condition. A treatment plan should be formulated. A patient need not have failed all standard interventions before marijuana can be recommended. The physician may have little guidelines in actually recommending a concrete dose for the patient to use.[69] As there are so many variables associated with effect, the physician and patient should develop an individual self-titration dosing paradigm that allows the patient to achieve the maximum benefit with tolerable side effects. Discussion of potential side effects and obtaining verbal informed consent are desirable. Periodic review of the treatment efficacy should be documented. Consultation should be obtained when necessary. Proper record keeping that supports the decision to recommend the use of medical marijuana is advised.

The controlled medical use of cannabis preparations is currently legal in Austria, Canada, Czech Republic, Finland, Germany, Israel, Italy, the Netherlands, Portugal, and Spain. Although 23 states and the District of Columbia now have legislation allowing physicians to recommend medicinal cannabis to patients, it is still illegal on the federal level, causing many physicians to think twice before offering their patients this option. It is estimated that 70% of the US population lives in jurisdictions where they can access medical cannabis. Unfortunately, most physicians currently practicing medicine have been schooled during the prohibition era and have little or no knowledge of the biological actions of (endo)cannabinoids and the medicinal qualities of cannabis. Much of the discussion is dominated by addiction medicine specialists who have a skewed view of the health consequences of cannabis use by virtue of their specialty. Certainly a practicing oncologist is likely to have a much different perception of the risk:benefits of cannabis compared to the addiction medicine specialist (http://www.cancer.gov/cancertopics/pdq/cam/cannabis/healthprofessional/).

Recently, the *New England Journal of Medicine* presented the case of a 68-year-old woman with metastatic breast cancer seeking medicinal cannabis for symptom management.[70] Opposing arguments were presented. In all, 1,446 readers then participated in a poll, the results of which were reported in a subsequent article. The authors remarked "We were surprised by the outcome of polling and comments, with 76% of all votes in favor of the use of marijuana for medicinal purposes—even though marijuana use is illegal in most countries."[71] Hence, there is a suggestion that, with an increased and concerted educational effort aimed at healthcare providers, in the coming years medicinal cannabis may become an option for an even larger percentage of patients who may benefit from its use.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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