Cannabinoids and Cancer

Evidence from cell culture systems and animal models indicates that THC and other cannabinoids may inhibit the growth of some tumors by the modulation of signaling pathways.

By Donald I. Abrams and Manuel Guzman

Although long-recognized for its medicinal values and widely used by millions throughout the world, marijuana 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. However, the potential benefits of medicinal cannabis have not been lost on a large number of people living with cancer, some of whom have been quite vocal in attributing their ability to complete their prescribed course of chemotherapy to the anti-emetic effects of smoked cannabis.

In the practice of integrative oncology, the provider is frequently faced with situations where being able to recommend medicinal cannabis seems like the right thing to do. A growing body of preclinical evidence suggests that cannabis may not only be effective for symptom management, but may have a direct antitumor effect as well. This article will review the role of cannabinoids in cancer.

Key Concepts

• Cannabis has been used in medicine for thousands of years prior to achieving its current status as an illicit substance.

• Cannabinoids, the active components of Cannabis sativa, mimic the effects of the endogenous cannabinoids (the so-called endocannabinoids), activating specific cannabinoid receptors, particularly CB1 found predominantly in the central nervous system and CB2 found in cells involved with immune function.

Delta-9-tetrahydrocannabinol, the main psychoactive cannabinoid in the plant, has been available as a prescription medication approved for chemotherapy-induced nausea and vomiting and treatment of anorexia associated with the AIDS wasting syndrome.

• In addition to treatment of nausea and anorexia, cannabinoids may be of benefit in the treatment of cancer-related pain, possibly in a synergistic fashion 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 chemotherapy-related neuropathic symptoms.

• Cannabinoids have a favorable drug safety profile, medical use predominantly limited by their psychoactive effects and their limited bioavailability.

• There is no conclusive evidence that chronic cannabis use leads to the development of any malignancies; some preclinical studies actually suggest a protective effect.

• Cannabinoids inhibit tumor growth in laboratory animal models by modulation of key cell-signaling pathways, inducing direct growth arrest and tumor cell death, as well as by inhibiting tumor angiogenesis and metastasis.

• Cannabinoids appear to be selective antitumor compounds as they kill tumor cells without affecting their non-transformed counterparts.

• More basic and clinical research is needed to ascertain not only the role of cannabinoids in palliative cancer care, but to delineate their role as potential anti-cancer agents with activity at a number of sites by way of multiple mechanisms of action.

CANNABIS AS MEDICINE: A BRIEF HISTORY

Use of cannabis as medicine dates back at least 2000 years.[1-4] Widely employed 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, anti-inflammatory, antispasmodic and anticonvulsant properties, cannabis was said to be the treatment of choice for Queen Victoria's dysmen-norhea. 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 $1 an ounce for medicinal use and $100 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.

Mayor Fiorello LaGuardia of New York commissioned an investigation into the reality of the potential risks and benefits of cannabis that reported in 1944 that the substance was not associated with any increased risk of criminal activity, addiction or insanity as had been claimed. The LaGuardia Commission Report, as well as subsequent similar investigations that have been commissioned nearly every decade since, went largely ignored.

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).

In 1973, President Nixon's investigation into the risks and benefits of marijuana, the Shafer Commission, concluded that it was a safe substance with no addictive potential that had medicinal benefits. Despite the fact that it was deemed to have no medical use, marijuana was distributed to patients by the United States government on a case-by-case basis by way of a Compassionate Use Investigational New Drug (IND) program established in 1978.

In the late 1980s and early 1990s, many people living with human immunodeficiency virus-1 (HIV) developed a wasting syndrome as a pre-terminal event.[5] The wasting syndrome, characterized by anorexia, weight loss of greater than 10 percent body weight, and frequently, fever and diarrhea, created hordes of cachectic individuals in search of any potential therapeutic intervention. Many turned to smoking marijuana.[6-8]

Fearful that there might be a run on the Compassionate Use program, the Bush administration shut it down in 1992, the same year that dronabinol (delta-9-tetrahydrocannabinol, Marinol(r)) was approved for treatment of anorexia associated with the AIDS wasting syndrome.

Delta-9-tetrahydrocannabinol is one of the approximately 70 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 was first licensed and approved in 1986 for the 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.[9] The potent class of serotonin receptor antagonists which have subsequently revolutionized the ability to administer emetogenic chemotherapy had not yet come to market.

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.[10-11] In one trial evaluating megestrol acetate and dronabinol alone and together, the cannabinoid seemed to negate some of the weight increase seen in those only receiving the hormone.[12]

CANNABINOID CHEMISTRY AND BIOLOGIC EFFECTS

Cannabinoids are a group of 21 carbon terpenophenolic compounds produced uniquely by Cannabis sativa and Cannabis indica species.[13-14] 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 non-cannabinoid compounds that also have biologic activity. Cannabinol, cannabidiol, cannabichromene, cannabigerol, tetrahydrocannabivarin 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. In addition, cannabis-associated terpenoids and flavonoids may increase cerebral blood flow, enhance cortical activity, kill respiratory pathogens and provide anti-inflammatory activity.

The neurobiology of the cannabinoids

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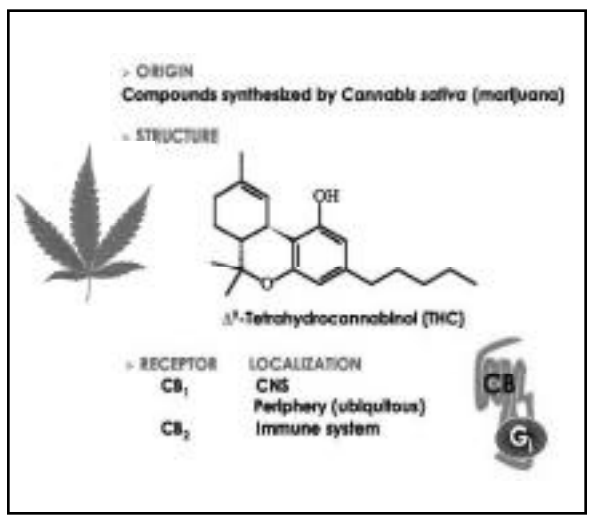

CANNABINOIDS are a group of 21-carbon terpenophenolic compounds. Delta-9-tetrahydrocannabinol (THC) is the most potent of the phytocannabinoids produced by the Cannabis species. The cannabinoids complex with two receptors, CB1 and CB2, to produce physiologic effects.

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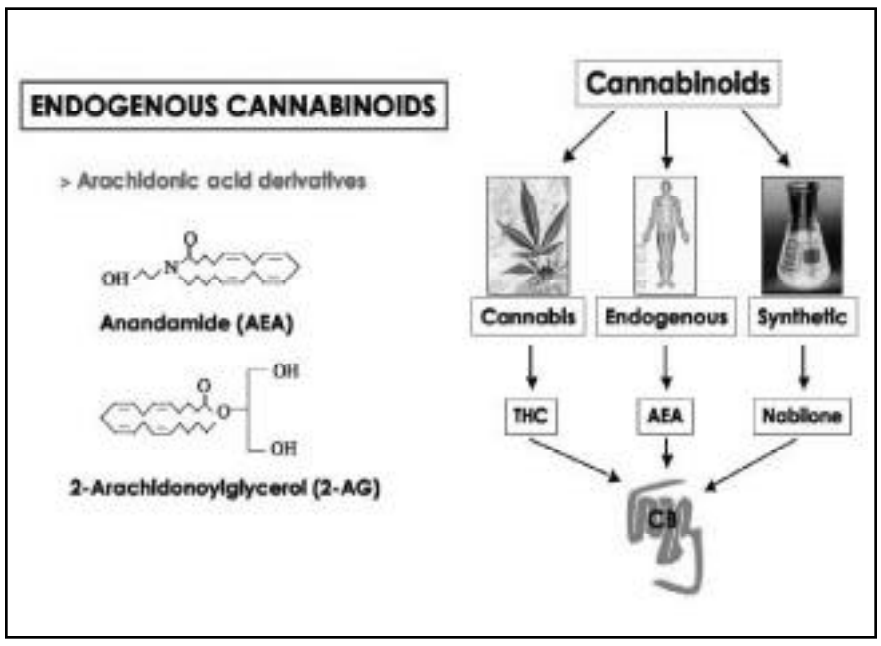
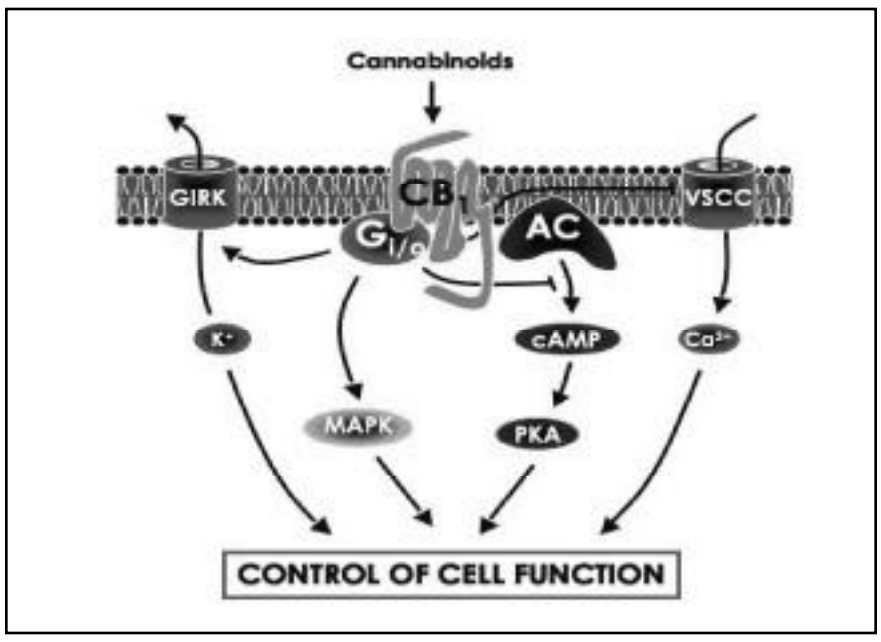


ENDOGENOUS CANNABINOIDS, anandamide (AEA) and 2-arachidonoylglycerol (2-AG), function as neurotransmitters. Synthetic cannabinoids have also been produced as pharmaceutical agents. Cannabinoids exert their effects by binding to specific Gi/o protein-coupled receptors.



SIGNALING PATHWAYS COUPLED TO THE CB1 CANNABINOID RECEPTOR are outlined above. The CB1 cannabinoid receptor signals to a number of different cellular pathways. These include (i) inhibition of the adenylyl cyclase (AC)-cyclic AMP-protein kinase A (PKA) pathway; (ii) modulation of ion conductances, by inhibition of voltage-sensitive Ca2+ channels (VSCC) and activation of G 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 cross-talk among the different pathways have been omitted for simplification.

has only been identified within the past 20 years during which time an explosion of knowledge has occurred.[15-18] In the mid-1980's, researchers developed a potent cannabinoid agonist to be used in research investigations.

In 1986 it was discovered that cannabinoids inhibited the accumulation of 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 Gi/o proteins. Its engagement inhibits adenylyl cyclase and voltage-gated calcium channels, and stimulates rectifying potassium conductances and mitogen-activated protein kinase activity.

By 1990, investigators had cloned the CB1 receptor, identified its DNA sequence and mapped its location in the brain, with the largest concentration being in the basal ganglia, cerebellum, hippocampus and cerebral cortex.

In 1993 a second cannabinoid receptor, CB2, was identified outside the brain.

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 concentration of CB2 receptors is located on the B lymphocytes and natural killer cells, suggesting a possible role in immunity.

The existence of cannabinoid receptors has subsequently been demonstrated in 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. Subsequently 2-arachidonoylglycerol (2-AG) has also been confirmed as part of the body's endogenous cannabinoid system.

These endocanabinoids function as neurotransmitters. As the ligands for the 7-transmembrane domain cannabinoid receptors, 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 which decreases neurotransmitter release.

The function of the endogenous cannabinoid system in the body is becoming more appreciated through advances in cannabinoid pharmacology. 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 modulation of pain and appetite, suckling in the newborn and the complexities of memory. (Michael Pollan in *"The Botany of Desire"* gives a particularly entertaining description of the natural function of endocannabinoids in memory.[19])

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 (Cesamet(r), a synthetic cannabinoid) and cannabis are the currently available cannabinoid therapies in the United States. Levonantradol (Nantrodolum (r)) is a synthetic cannabinoid administered intramuscularly, not used as much clinically since the oral agents became available.

A whole cannabis extract (Sativex(r)) delivered as an oro-mucosal spray with varying combinations of THC and cannabidiol is available in Canada and undergoing late phase testing in the US and other countries.

Through the receptors described above, cannabis delivered by way of inhalation or orally can produce a host of biologic effects. The Institute of Medicine report makes the following general conclusions about the biology of cannabis and cannabinoids:[2]

• 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 aminals but appear mild compared with those of withdrawal from opiates of benzodiazepines.

Pharmacology of Cannabis

When taken by mouth, there is a low (6-20%) and variable oral bioavailability.[13-20] 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 smoked, the cannabinoids are rapidly absorbed into the bloodstream with a peak concentration in 2-10 minutes which rapidly declines over the next 30 minutes. Smoking thus achieves a higher peak concentration with a shorter duration of effect. Less of the psychoactive 11-OH-THC metabolite is formed.

Cannabinoids can interact with the hepatic cytochrome P450 enzyme system.[21-22] Cannabidiol, for example, can inactivate CYP 3A4. 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 chemotherapeutic agents has lead to a small amount of data on the possibility of botanical:drug interactions.

In one study, 24 cancer patients were treated with intravenous irinotecan (600 mg, n = 12) or docetaxel (180 mg, n = 12), followed three 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.[23] The carefully conducted pharmacokinetic analyses showed that cannabis administration did not significantly influence exposure to and clearance of irinotecan or docetaxel.

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.[24]

In those days, phenothiazines and metoclopropramide 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.* conducted a systematic review of 30 randomized comparisons of cannabis with placebo or antiemetics from which dichotomous data on efficacy and harm were available.[25] Oral nabilone, oral dronabinol, and intramuscular levonantradol were tested. No smoked cannabis trials were included. Thirteen hundred sixty-six 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 needed to treat (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 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 reported that 15 controlled studies compared nabilone to placebo or available antiemetic drugs.[26] In 600 patients with a variety of malignant diagnoses, nabilone was found to be superior to prochlorperazine, domperidone and alizapride, with patients clearly favoring the 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.[25-28] In the same meta-analysis, Ben Amar reports that in 14 studies of dronabinol involving 681 patients, the cannabinoid antiemetic effect was equivalent or significantly greater

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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.

There have been only three controlled trials evaluating the efficacy of smoked marijuana in chemotherapy-induced nausea and vomiting.[26] 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 marijuana 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.

The University of California Center for Medicinal Cannabis Research also approved and funded a double-dummy design clinical trial to compare smoked cannabis, oral dronabinol or placebo in patients with delayed nausea and vomiting, a condition for which the serotonin receptor antagonists are ineffective.[29]

Unfortunately the trial was launched concurrently with the first release of aprepitant (Emend (r)), the first commercially available drug from the new class of agents, the Substance P/neurokinin NK-1 receptor antagonists, which are approved for the treatment of delayed nausea.[30] The cannabis trial never accrued and the funding was withdrawn.

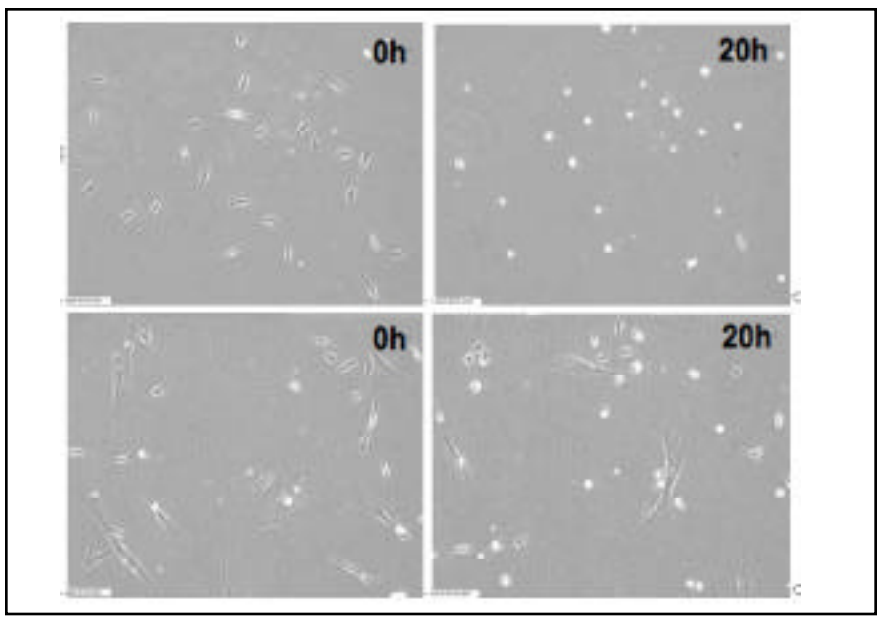
Both dronabinol and nabilone are FDA-approved for the treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic therapy. Nabilone's extended duration of action allows for twice-a-day dosing of one or two milligrams commencing 1 to 3 hours prior to receiving chemotherapy. A dose of 1 or 2 milligrams the night before administration of chemotherapy might also be useful.

It is recommended to commence dronabinol at an initial dose of 5 mg/m2, also 1 to 3 hours prior to the administration of chemotherapy, then every 2 to 4 hours after chemotherapy, for a total of 4 to 6 doses/day. Should the 5 mg/m2 dose prove to be ineffective, and in the absence of significant side effects, the dose may be escalated by 2.5 mg/m2 increments to a maximum of 15 mg/m2 per dose.

Nabilone, with fewer metabolites and a lower dose range may be associated with fewer side effects. The need to dose one to three hours prior to chemotherapy is one factor that drives patients to prefer smoked 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 smoking compared to oral ingestion.

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 tool-box for addressing these concerns. Patients are not only disturbed by the disfigurement associated with wasting, but also by their inability to engage in the social interaction associated with breaking bread and partaking of a meal. 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.[26]



DELTA-9-THC KILLS BRAIN TUMOR CELLS at a concentration that is nontoxic to normal brain cells. Images obtained through a time-lapse microscope illustrate the selective induction of cell death in cultures of human Glioblastoma multiforme cells *(upper left)* compared to normal human glial cells *(lower left)*. After 20 hours of treatment, death of nearly all of the GBM cells is evidenced by cells shrinking to inanimate white spheres *(upper right)*. The normal cells exposed to the same concentration of delta-9-THC continue to migrate and divide (lower right). Photo by McAllister and Yount.

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.

Similar studies in patients with HIV-associated wasting syndrome also found that cannabinoids were more effective in improving appetite than in increasing weight. In our own study of the safety of smoked and oral cannabinoids in patients with HIV on protease inhibitor regimens, we did find an increase in weight in both cannabinoid groups compared to the placebo recipients; however the study was not powered with weight gain as an endpoint.[31-32]

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.[33]

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 has led to the development of the pharmaceutical CB1 antagonist rimonabant (Acomplia (r)), 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. [34]

This first of a new class of agents has not yet been approved in the US because it was found to induce anxiety and depressive disorders that were deemed high risk.

Anecdotal as well as clinical trial evidence also supports the appetite-stimulating effect of smoking cannabis. In classic trials conducted in the 1970s in healthy controls, it was found that, especially when smoked in a social/communal setting, cannabis ingestion 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.

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.[35]

In contrast, CB2 receptors are located in peripheral tissue and are present at very low expression levels in the CNS. Of the endogenous cannabinoids identified, anandamide has high affinity for CB1 receptors, whereas 2-AG has affinity for both CB1 and CB2 receptors.

With the development of receptor-specific antagonists (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.[36-37]

Where the CB1 agonists exert analgesic activity in the CNS, both CB1 and CB2 agonists have peripheral analgesic actions.[38-39]

Cannabinoids may also contribute to pain modulation through an anti-inflammatory 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.[40-42]

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.

Medical literature cites evidence of cannabinoids' ability to reduce naturally occurring pain, but 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). Upon review, Institute of Medicine researchers noted that these studies suffered from poor design and methodological problems and dubbed their findings inconclusive.[2]

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.

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 and colleagues 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 experiment measured both pain intensity and pain relief in a double-blind, placebo controlled study of 10 subjects.[43] 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 anti-emesis and appetite stimulation. 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 reported that 10 mg of THC produced analgesic effects over a seven-hour observation period comparable to 60 mg of codeine, and that 20 mg of THC induced effects equivalent to 120 mg of codeine.[44] Authors noted that respondents found higher doses of THC to be more sedative than codeine. However, in a separate publication, Noyes *et al* reported that patients administered THC had improved mood, sense of well-being, and less anxiety.[45]

A study by Staquet and colleagues on the effects of a THC nitrogen analogue on cancer pain yielded similar results.[46] Authors found the THC analogue equivalent to 50 mg of codeine and superior to both placebo and 50 mg of secobarbital in subjects with mild, moderate and severe pain.

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Neuropathic pain is a troubling symptom in cancer patients, especially those treated with platinum-based chemotherapy or taxanes.

Cannabinoids have also been shown to be of potential benefit in an animal model of neuropathic pain.[47] 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.[48] Smoked cannabis reduced daily pain by 34% compared to 17% with placebo (p=0.03). 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≤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.

Two recent placebo-controlled studies of cannabinioids for central neuropathic pain associated with multiple sclerosis produced results similar to the present study. In a crossover trial of synthetic delta-9-THC up to 10 mg/day, an NNT of 3.5 was reported.[49]

A trial of a sublingual spray containing delta-9-THC alone or combined with cannabidiol showed a 41% pain reduction with active drug compared to a 22% reduction with placebo.[50] In this study, the cannabidiol alone preparation was ineffective in pain relief. Improvement in sleep quality was also reported with the sublingual spray. To date, no clinical trials have examined the effectiveness of cannabinoid preparations in chemotherapy-induced neuropathic pain.

If cannabinoids and opioids are synergistic, it is possible that lower doses of opioids may be effective for longer periods of time with fewer side effects

Synergism between opioids and cannabinoids has been postulated and subsequently demonstrated in a number of animal models.[51-55] The antinociceptive effects of morphine are predominantly mediated by mu receptors but may be enhanced by delta-9-THC activation of kappa and delta opioid receptors.[55]

It has been further postulated that the cannabinoid:opioid interaction may occur at the level of their signal transduction mechanisms.[56-57] Receptors for both classes of drugs are coupled to similar intracellular signaling mechanisms that lead to a decrease in cAMP production by way of Gi protein activation.[58-60]

There has also been some evidence that cannabinoids might increase the synthesis or release of endogenous opioids, or both. With this background, we are conducting a pharmacokinetic interaction study to investigate the effect of concomitant cannabis on disposition kinetics of opioid analgesics. If cannabinoids and opioids are synergistic, it is possible that lower doses of opioids may be effective for longer periods of time with fewer side effects, clearly a benefit to the cancer 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 the sublingual spray cannabis-based medicine.[61] 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.

SAFETY AND SIDE EFFECTS

Cannabinoids have an extremely favorable drug safety profile.[13, 14, 24, 62] Unlike opioid receptors, cannabinoid receptors are not located in brainstem areas controlling respiration, so lethal overdoses due to respiratory suppression do not occur. The LD50 has been estimated to be 1500 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.[63]

As cannabinoid receptors are not just located in the central nervous system 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.

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. Animal research demonstrates a potential for dependence, but this potential is observed under a narrower range of conditions than with benzodiazepines, opiates, cocaine or nicotine.

Withdrawal symptoms –irritability, insomnia with sleep EEG disturbance, restlessness, hot flashes and rarely nausea and cramping– have been observed, but appear 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.

Most drug users begin with alcohol and nicotine before marijuana.

The 1999 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.[2] 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 is not the most common and is rarely the first "gateway" drug.

The report concludes 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.

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.[64] In this two-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.

Mice and rats are not people 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 counter-intuitive 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 retrospective cohort study of 64,855 Kaiser Permanente health care members seen between 1979-1985 and followed through 1993 yielded an interesting finding.[65] 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 5600-8200 men in each cell followed for an average of nearly nine 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 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.[66]

The authors cite the selection bias, small sample size, limited generalizability and overall young participant 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 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.[67] One thousand one hundred twelve incident cancer cases (611 lung, 303 oral, 108 esophagus, 100 pharynx, 90 larynx) were matched to 1040 cancer-free controls on age, gender and neighborhood.

A standardized questionnaire used during face-to-face interview collected information on marijuana use expressed in joint-years, where 1 joint-year is the equivalent of smoking one marijuana cigarette per day for one 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 > 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 > 60 joint-years) had adjusted odds ratios 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 which 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

continued on next page

Cannabinoids and Cancer *from previous page*

reflect a protective effect of marijuana."

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.[62] Evidence from cell culture systems as well as animal models have suggested 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 and colleagues, 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 twenty years when the line of investigation was picked up by scientists in Spain and Italy who have remained at the forefront of this emerging field.[62. 68. 69]

Since the late 1990s, several plant derived (THC and cannabidiol), 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.[70-81]

Perhaps even more compelling, cannabinoid administration to nude mice slows the growth of various tumor xenografts including lung 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 already mentioned and the cumulative effects of CB 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.[82-83] A desirable property of antitumor compounds is their preferential targeting of malignant cells. Cannabinoids appear to kill tumor cells but do not affect their non-transformed counterparts and may even protect them from cell death. This is best exemplified by glial cells.

Cannabinoids have been shown to induce apoptosis of glioma cells in culture and induce regression of glioma cells in mice and rats. In 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 and skin carcinomas 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 pro-angiogenic 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.

Further support comes from studies in human non-small cell lung cancer cell lines that overexpress epidermal growth factor receptor, in which THC inhibits epidermal growth factor-induced growth, chemotaxis and chemo-invasion.[84]

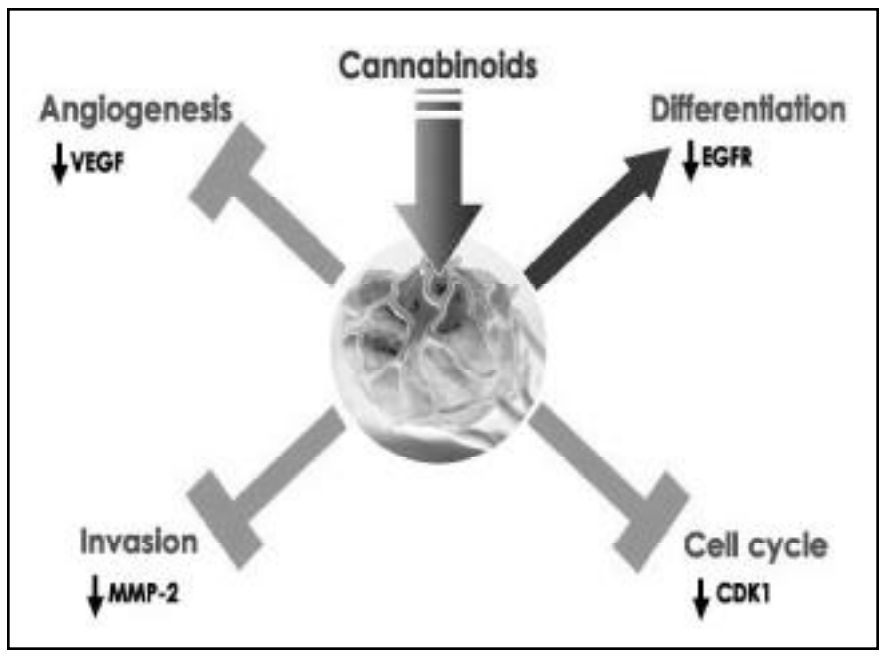
In an in vivo model using severe combined immunodeficient mice, subcutaneous tumors were generated by inoculating the animals with the same cell lines. Tumor growth in THC-treated animals was inhibited by 60% compared with vehicle-treated controls. The inhibition was significant both regarding the subcutaneous xenograft as well as the number and weight of lung metastases. Tumor specimens revealed antiproliferative and antiangiogenic effects of THC.

Most recently, another potential anticancer and particularly anti-metastasis mechanism for cannabinoids has been identified. Id helix-loop-helix proteins control processes related to tumor progression[85] Reducing Id-1 using antisense technology led to significant reductions in breast cancer cell proliferation and invasiveness in in vitro models and metastases in mice. Reducing Id-1 expression with antisense technology is not a possible intervention in humans with breast cancer at this time, however. Cannabidiol has been demonstrated to down-regulate Id-1 expression in aggressive human breast cancer cells. The investigators suggest that cannabidiol represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the down-regulation of tumor aggressiveness.

\Two additional potential mechanisms of anticancer activity warrant brief mention. Cannabinoids, both plant-derived and endogenous, are believed to have anti-inflammatory effects. Inflammation is being increasingly linked to the development of various malignancies. Perhaps one of the most obvious associations is the development of colorectal carcinoma in patients with inflammatory bowel disease.

A mouse study has demonstrated that signaling of the endogenous cannabinoid system is likely to provide intrinsic protection against colonic inflammation.[86] This has led to the development of a hypothesis that phytocannabinoids and endocannabinoids may be useful in the prevention and treatment of colorectal cancer.[87]

Kaposi's sarcoma-associated herpesvirus/Human herpesvirus-8 (KSHV/HHV-8) and Epstein-Barr virus (EBV) are related and implicated in the cause of a number of malignant diseases including Kaposi's sarcoma and primary effusion lymphoma (KSHV) and Burkitt's lymphoma, primary central nervous system lymphoma, Hodgkin's disease and nasopharyngeal carcinoma (EBV).



OTHER ANTI-TUMOR 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.

A group of investigators has demonstrated that THC is a potent and selective antiviral agent against KSHV.[88] It is felt that THC may inhibit KSHV replication through the activation of cannabinoid receptors. The authors conclude that further studies on cannabinoids and herpesviruses are important as they may lead to development of drugs that inhibit reactivation of these oncogenic viruses.

Counter to these findings, however, is the recent suggestion that delta-9-THC may actually enhance KSHV infection and replication and foster KSHV-mediated endothelial transformation.[88]

These investigators caution that use of cannabinoids may thus place individuals at greater risk for the development and progression of Kaposi's sarcoma, although epidemiologic data have not supported these in vitro findings.

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.

The Spanish Ministry of Health approved a pilot clinical trial carried out in collaboration between the Tenerife University Hospital and the Guzman laboratory in Madrid to investigate the effect of local administration of THC intracranially through an infusion catheter on the growth of recurrent glioblastoma multiforme.[90]

In this ground-breaking pilot study, THC administration was shown to be safe and associated with decreased tumor cell proliferation in at least two of nine patients studied. Hopefully this pilot trial may open the door to further clinical investigations aimed at assessing the antitumor activity of cannabinoid therapies.

ALTERNATIVE DELIVERY SYSTEMS

And what if clinical trials were to demonstrate that smoked marijuana may be of benefit to patients with a condition like, for example, recurrent glioblastma multiforme?

It is not likely that even a meta-analysis of a number of similar studies in any condition would convince the necessary regulatory bodies that cannabis should be re-instated to the U.S. Pharmacoepia and made widely available to patients who may benefit from its use. The Institute of Medicine Report in 1999 clearly stated that the accumulated data indicate a potential therapeutic value for cannabinoid drugs, particularly in the areas of pain relief, control of nausea and vomiting and appetite stimulation. The authors went on to suggest that the "goal of clinical trials of smoked marijuana would not be to develop it as a licensed drug, but as a first step towards the development of non-smoked, rapid-onset cannabinoid delivery systems." [2]

To this end, we conducted a trial in healthy marijuana-smoker volunteers comparing the blood levels of cannabinoids achieved upon inhaling marijuana that has been vaporized in a device that heated the plant product to below the temperature of combustion and collected the volatilized gases with those obtained upon smoking a comparable dosed cigarette.[91]

Eighteen healthy subjects were evaluated. One dose (1.7, 3.4 or 6.8% tetrahydrocannabinol) and delivery system (smoked cannabis cigarette or vaporization system) was randomly assigned for each of the six inpatient study days. The peak plasma concentrations and six-hour area under the plasma concentration-time curve of THC after inhalation of vaporized cannabis were similar to those of smoked cannabis.

Carbon monoxide levels were substantially reduced with vaporization suggesting less exposure to noxious substances. Neuropsychologic effects were equivalent and participants expressed a clear preference for vaporization as a delivery method.

No adverse events were observed. Vaporization of cannabis is a safe and effective mode of delivery of THC. Consequently, our ongoing evaluation of opioid:cannabinoid interactions is using the vaporizer as a smokeless delivery system.

Another non-synthetic alternative to

continued on next page

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smoked or inhaled cannabis is the sublingual preparation of whole plant extract.[50, 61, 92] Sativex(r) was first approved as a prescription medication in Canada in 2005 for symptomatic relief of neuropathic pain in multiple sclerosis and subsequently as adjunctive therapy for patients with cancer pain on other analgesic medications. The cannabis-based medication is available in Spain, undergoing regulatory review by the European Union and is being evaluated in a Phase II/III clinical trial in patients with cancer-related pain in the U.S..

GUIDELINES FOR PROVIDERS

The Institute of Medicine is aware that the development and acceptance of 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 smoked psychotropic agent while freely writing prescriptions for pharmaceutical agents with significantly greater cost, potential for addiction or abuse, and more negative societal impact overall.

The Medical Board of California in their July 2004 Action Report provides a model for how states with medical marijuana legislation should advise physicians.[93]

"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.... If physicians use the same care in recommending medical marijuana to patients as they would recommending or approving any other medication or prescription drug treatment, they have nothing to fear from the Medical Board."

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.[94]

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.

Despite all these guidelines, the Medical Board of California still reminds physicians that making a written recommendation "could trigger a federal action."

On a more positive note, in a unanimous vote, the Assembly of the American Psychiatric Association recently approved a strongly worded statement supporting legal protection for patients using medical marijuana with their doctor's recommendation.[95] The APA action paper reiterates that "the threat of arrest by federal agents, however, still exists. Seriously ill patients living in these states with medical marijuana recommendations from their doctors should not be subjected to the threat of punitive federal prosecution for merely attempting to alleviate the chronic pain, side effects, or symptoms associated with their conditions or resulting from their overall treatment regimens. ... [We] support protection for patients and physicians participating in state-approved medical marijuana programs."

It behooves the integrative oncologist to follow closely future studies of cannabinoids and cancer. It is likely that these agents will not only prove to be useful in symptom management and palliative care, but as anti-tumor agents as well.

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Tashkin Reiterates to Patients Out of Time:

Smoking Cannabis Does Not Cause Lung Cancer

By Fred Gardner

One in three Americans will be afflicted with cancer, we are told by the government (as if it's our immutable fate and somehow acceptable). Cancer is the second-leading cause of death in the U.S. and lung cancer the leading killer among cancers.

You'd think it would have been very big news in June 2005 when UCLA medical school professor Donald Tashkin reported that components of marijuana smoke –although they damage cells in respiratory tissue– somehow prevent them from becoming malignant. In other words, *something in marijuana exerts an anti-cancer effect!*

Tashkin has special credibility. He was the lead investigator on studies dating back to the 1970s that identified the components in marijuana smoke that are toxic. It was Tashkin *et al* who published photomicrographs showing that marijuana smoke damages cells lining the upper airways. It was the Tashkin lab's finding that benzpyrene – a component of tobacco smoke that plays a role in most lung cancers– is especially prevalent in marijuana smoke. It was Tashkin's data showing that marijuana smokers are more likely than non-smokers to cough, wheeze, and produce sputum.

Tashkin reviewed his findings in April 2008, at a conference organized by "Patients Out of Time," a reform group devoted to educating doctors and the public (as opposed to lobbying politicians). Some 30 MDs and nurses got continuing medical education credits for attending the event, which was held at Asilomar, on the Monterey Peninsula.

The National Institute on Drug Abuse, which supported Tashkin's marijuana-related research over the decades, readily gave him a grant in 2002 to conduct a large, population-based, case-controlled study that would prove definitively that heavy, long-term marijuana use increases the risk of lung and upper-airways cancers.

What Tashkin and his colleagues found, however, disproved their hypothesis. (Tashkin is to marijuana as a cause of lung cancer what Hans Blix was to Iraq's weapons of mass destruction –an honest investigator who set out to find something, concluded that it wasn't there, and reported his results.)

Tashkin's team interviewed 1,212 cancer patients from the Los Angeles County Cancer Surveillance program, matched for age, gender, and neighborhood with 1,040 cancer-free controls. Marijuana use was measured in "joint years" (number of years smoked times number of joints per day).

It turned out that increased marijuana use did not result in higher rates of lung and pharyngeal cancer, whereas tobacco smokers were at greater risk the more they smoked. Tobacco smokers who also smoked marijuana were at slightly lower risk of getting lung cancer than tobacco-only smokers.

These findings were not deemed worthy of publication in "NIDA Notes." Tashkin reported them at the 2005 meeting of the International Cannabinoid Research Society. They were published in the October 2006 issue of "*Cancer Epidemiology Biomarkers & Prevention.*"

TASHKIN AT ASILOMAR showed photomicrographs of cells damaged by cannabis smoke. Having identified known carcinogens in the smoke, he was surprised when study results showed that cannabis smoking doesn't lead to lung cancer.

Without a press release from NIDA calling attention to its significance, the assignment editors of America had no idea that "Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study" by Mia Hashibe1, Hal Morgenstern, Yan Cui, Donald P. Tashkin, Zuo-Feng Zhang, Wendy Cozen, Thomas M. Mack and Sander Greenland was a blockbuster story.

I suggested to Eric Bailey of the *L.A. Times* that he write up Tashkin's findings –UCLA provided the local angle if the anti-cancer effect wasn't enough. Bailey said his editors wouldn't be interested for some time because he had just filed a marijuana-related piece. The Tashkin scoop is still there for the taking!

Tashkin Defends His Findings

Investigators from New Zealand recently got widespread media attention for a study contradicting Tashkin's results. "Heavy cannabis users may be at greater risk of chronic lung disease –including cancer– compared to tobacco smokers," is how BBC News summed up the New Zealanders' findings.

The very small size of the study –79 smokers took part, 21 of whom smoked cannabis only– was not held against the authors. In fact, the small New Zealand study was given much more coverage by the corporate press than the large UCLA study that preceded it.

The New Zealand study was portrayed as *the latest word* on this important subject. As if scientific inquiry were some kind of tennis match and the truth just gets truthier with every volley.

Tashkin criticized the New Zealanders' methodology in his talk at Asilomar: "There's some cognitive dissonance associated with the interpretation of their findings. I think this has to do with the belief model among the investigators and –I wish they were here

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to defend themselves– the integrity of the investigators... They actually published another paper in which they mimicked the design that we used for looking at lung function."

Tashkin spoke from the stage of an airy redwood chapel designed by Julia Morgan. He is pink-cheeked, 70ish, wears wire-rimmed spectacles. "For tobacco they found what you'd expect: a higher risk for lung cancer and a clear dose-response relationship. A 24-fold increase in the people who smoked the most... What about marijuana? If they smoked a small or moderate amount there was no increased risk, in fact slightly less than one. But if they were in the upper third of the group, then their risk was six-fold... A rather surprising finding, and one has to be cautious about interpreting the results because of the very small number of cases —fourteen— and controls —four."

Tashkin said the New Zealanders employed "statistical sleight of hand." He deemed it "completely implausible that smokers of only 365 joints of marijuana have a risk for developing lung cancer similar to that of smokers of 7,000 tobacco cigarettes... Their small sample size led to vastly inflated estimates... They had said 'it's ideal to do the study in New Zealand because we have a much higher prevalence of marijuana smoking.' But 88 percent of their controls had never smoked marijuana, whereas 36% of our controls (in Los Angeles) had never smoked marijuana. Why did so few of the controls smoke marijuana? Something fishy about that!"

Strong words for a UCLA School of Medicine professor!

As to the highly promising implication of his own study –that something in marijuana stops damaged cells from becoming malignant— Tashkin noted that an anti-proliferative effect of THC has been observed in cell-culture systems and animal models of brain, breast, prostate, and lung cancer. THC has been shown to promote apoptosis (damaged cells die instead of reproducing) and to counter angiogenesis (the process by which blood vessels are formed —a requirement of tumor growth). Other antioxidants in cannabis may also be involved in countering malignancy, said Tashkin.

COPD

Much of Tashkin's talk was devoted to Chronic Obstructive Pulmonary Disease, another condition prevalent among tobacco smokers. Chronic bronchitis and emphysema are two forms of COPD, which is the fourth-leading cause of death in the United States. Air pollution and tobacco smoke are known culprits. Inhaled pathogens cause an inflammatory response, resulting in diminished lung function. COPD patients have increasing difficulty clearing the airways as they get older.

Tashkin and colleagues at UCLA conducted a major study in which they measured lung function of various cohorts over eight years and found that tobacco-only smokers had an accelerated rate of decline, but marijuana smokers –even if they smoked tobacco as well– experienced the same rate of decline as non-smokers.

"no matter how much marijuana was smoked, the rate of decline was similar to normal." —Tashkin re COPD

"The more tobacco smoked, the greater the rate of decline," said Tashkin. "In contrast, no matter how much marijuana was smoked, the rate of decline was similar to normal."

Tashkin concluded that his and other studies "do not support the concept that regular smoking of marijuana leads to COPD."

Breathe easier, everybody.

A Sociologist Walks Into a Cannabis Club...

At the 2008 Patients Out of Time Conference sociologist Amanda Reiman described a forthcoming study of the Berkeley Patients Group. The BPG, founded in 1999, is one of the few dispensaries that allow medicating on-site —an approach Reiman calls "the social model." Reiman gave a written survey to 350 patients as they arrived at BPG, interviewed five members who received hospice delivery services, and conducted a focus group with six participants. Excerpts of the study follow.

Every patient surveyed agreed that there are benefits from BPG services beyond the medication. All patients mentioned the social support that they got from visiting with other patients and receiving visitors through the hospice program. Patients also mentioned the benefits of having a community room where they could relax and medicate in a safe environment and speak with other patients.

Most patients stressed the importance of regular social contact as being extremely beneficial to their health.

Also mentioned were BPG programs such as acupressure and the different classes and speakers available to patients. Most patients stressed the importance of regular social contact as being extremely beneficial to their health.

One patient described the benefits of having consistency in a life that was otherwise unpredictable; knowing that a visitor would come every Wednesday provided this patient with comfort.

One patient mentioned that in addition to medical help gained from the cannabis, the weekly hospice visits served as peer counseling and allowed her time to vent about her illness and the stresses of being ill.

Patients who are also part of the low-income "Helping Hands" program mentioned the huge financial burden that has been lifted for them by having access to high-grade medicine.

Other patients mentioned the help that they got from medical cannabis to deal with pain, eating and sleep issues.

One patient mentioned that, due to periods of wasting, they would not be here if it were not for their medicine and BPG.

All patients mentioned the social support that they get from other patients and the staff at the dispensary. One patient spoke about how services help her manage the stress of the struggle to stay healthy. She talked about the safe space created at BPG where patients can open up and be vulnerable, which might be hard for some who must maintain a tough exterior to get through their day. She also mentioned that coming to BPG helps get patients out of the house and helps to counteract the isolation that can come along with experiencing a chronic or terminal illness.

Another patient mentioned that hearing about other patients' problems helps him feel like he is not alone and that others are going through the same thing, which can be of great comfort.

One patient mentioned that BPG used to have a daily organic fruit and vegetable delivery service that had to cease operations due to financial reasons. Other patients mentioned that BPG has helped them pay utility bills, and two patients were extremely excited to relate their stories of how BPG gave them Christmas trees when they could not afford them and how much that gesture meant to them.

Patients speak about the staff at BPG as if they are family and express such gratitude for the personal interest that the staff has taken in them, adding to their feelings of importance and self-worth.

Participants reported that they do not purchase cannabis every time they visit BPG and stated that there are many times they visit just to receive services or socialize with other patients.

Participants reported using a range of services at BPG including acupuncture, massage, renter's assistance classes, and recreation activities such as open mic.

Access to free services allows patients to try out an alternative therapy to see if they get relief from it before seeking it out as part of their permanent health care regime. Many participants stated that the services at BPG act as a bridge between the times that they can receive health services elsewhere, either due to the cost of the service or the cost of transportation.

Patients report that losing BPG services would disrupt their entire health care treatment plan. For example, one patient receives acupuncture both at BPG and at a clinic where she receives a more intensive and longer treatment. She reported that she cannot afford these intensive treatments regularly, so she uses the BPG treatments to supplement the more costly ones, as to not interrupt her treatment schedule.

Another participant reported that she lives near BPG and cannot afford the transportation to get to her more intensive treatments on a regular basis, so again, BPG is used to supplement these treatments.

Participants also reported getting peer support from other patients at BPG and forming relationships with other patients for friendship and support. Participants mentioned that exposure to other patients with a range of ailments and circumstances are therapeutic.

Participants who received medicine through Helping Hands reported that they learned of the program through word of mouth and they felt that the criteria should be clearer. Participants reported that most of their other medicines were covered through Medi-Cal or Medicaid.

Suggestions

Participants had several suggestions for how BPG could be more service-oriented and patient-focused:

1. There should be a designated patient liaison that patients know they can go to with complaints, questions, suggestions. Participants felt that they did not know who to approach about problems or suggestions. Perhaps a board could be formed of staff and patients to discuss activities, services and issues related to BPG operations.
2. More arts and crafts.
3. Post the calendar where people can see it while they wait in line.
4. A way to inform folks when time is almost up. Participants felt that sometimes they were rushed out and that sometimes a patient's appearance affected how they were treated when their time was up.
5. Not enough chairs in the community room.
6. There should be a designated counter person for those with lots of questions to speed up the line for those who already know what they want.

Amanda Reiman, MSW PhD, is an academic coordinator/lecturer at the UC Berkeley School of Social Welfare.

PATIENTS OUT OF TIME, ASILOMAR 2008: Al Byrne (who runs a tight meeting), Melanie Dreher, Laura Galli , Juan Sanchez-Ramos, Bill Britt, and MaryLynn Mathre.