Cannabis 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

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

• Delta-9-tetrahyrocannabinol, 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 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 favourable safety profile, with relatively few side effects 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 modulating 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 anticancer agents with activity at a number of sites by way of well defined mechanisms of action.

CANNABIS AS MEDICINE: A BRIEF HISTORY

Use of cannabis as medicine dates back at least 2000 years. 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 dysentery, fever and diarrhea, created 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 anti-tumor effect as well. This article will review the role of cannabinoids in cancer.

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 uses. Data on the potential effectiveness of medicinal cannabis is difficult to find due to the limited numbers of medical 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 grown in a wide range of conditions. However, the potential benefits of medicinal cannabis have not been lost on a large number of people suffering from cancer, some of whom have been quite vocal in attributing their ability to touch the reality of the potential risks and benefits of cannabis that reported in 1944 with any increased risk of criminal activity or insurmountable prohibitive cost.

By 1938, cannabis was classified as a Schedule I drug. Where both Schedule I and Schedule II substances have high potential for abuse, Schedule I drugs are distinguished by having no accepted medical use. Other Schedule I substances include heroin, LSD, and the methamphetamines.

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than chlorpromazine and equivalent to metoclopramide, thiethylperazine and haloperidol.

It is noted that the efficacy of the cannabinoid in these studies was sometimes outweighed by the adverse reactions: in non-clinical studies, cannabinoid anxiolytic and anticonvulsant effects were seen in a dose-dependent manner. Patients frequently experienced a range of unwanted effects, including dizziness, dry mouth, blurred vision, and increased appetite.

The University of California at Los Angeles conducted a clinical trial comparing smoked marijuana, oral dronabinol, and placebo. In this study, patients who received smoked marijuana experienced a significant reduction in nausea and vomiting compared to the placebo group. The study was approved by the FDA for the treatment of nausea and vomiting associated with chemotherapy.

In a double-blind, placebo-controlled trial conducted by the University of California, patients with advanced cancer who were unresponsive to conventional anti-emetic therapy were randomized to one of three treatment groups: smoked marijuana, oral dronabinol, or placebo. The results showed that patients who received smoked marijuana had a significant reduction in nausea and vomiting compared to the placebo group. The study was designed to compare the efficacy of smoked marijuana and oral dronabinol in the treatment of chemotherapy-induced nausea and vomiting.

In conclusion, the evidence suggests that cannabinoids may be effective in the treatment of chemotherapy-induced nausea and vomiting. Further research is needed to determine the optimal dose and formulation of cannabinoids for this indication.
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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 shown to be of potential benefit in an animal model of neuropathic pain.6 Neuropathic pain is a common 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 among illicit 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.6 Smoked cannabis reduced daily pain by 34% compared to 17% with placebo (p < 0.03). Greater than 60% of patients who smoked cannabis re-duced chronic pain by a median of 72% compared to 15% with placebo (p < 0.001). Cannabis also reduced experimental pain by both brush and von Frey hair stimuli (p < 0.05) in a heat-capacitance 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 cannabinoids for central neuropathic pain associated with multiple sclerosis produced results similar to the previous study. In contrast, a synthetic delta-9-THC alone or combined with cannabinol showed a 41% pain reduction with active drug compared to a 22% reduction with placebo.6 In this study, the cannabinol alone preparation was ineffective in pain relief. Improvement in sleep quality was also reported with the sublingual spray. Timing of administration and other factors of the study design may have influenced the effectiveness of cannabinoid preparations in chemotherapy-induced neuropathic pain.

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.10,11 The antinociceptive effects of opioids are acutely mediated by mu receptors but may be enhanced by delta-9-THC activation of kappa and delta opioid receptors.10 It has been further postulated that the cannabinoid opioid interaction may occur at the level of their signal transduction mechanisms.10,11 Receptors for both classes of molecules are coupled to similar intracellular signaling mechanisms that lead to a decrease in cAMP production by G-protein activated adenylate cyclase.

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 con-}

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over the follow-up period. In the men who smoked cannabis alone or addition to marijuana, the risk of lung cancer was increased 10-fold. In the over one hundred twelve incident cancer cases (611 lung, 303 oral, 108 esopha-gus, 100 pharynx, 90 larynx) were matched to 1040 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 one year. Cross-sectional analyses also requested information on the use of other drugs including hashish, tob-acco (all forms) and alcohol, sociodemographic, psychological, and educational 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 (age, gender, and frequent heavy use and pack/years). The results showed that although marijuana use for > 30 years was associated with a modest increase in the crude analysis with each cancer except pharyngeal, no positive associations were found when adjusting for several confounding factors. The authors concluded that marijuana use, including exposure to smoke, is not associated with an increased risk of any of the cancers evaluated.

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 develop-}
Cannabinoids and Cancer

There has been an increasing body of evidence over the past decade that canna
binoids may have a role in cancer therapy. Evidence from cell culture systems as well as animal models have suggested that THC and its endogenous cannabinoids may inhibit the growth of some tumors by the modulation of signaling pathways and induce cell death as well as by inhibition of angiogenesis and metastasis. The antiproliferative effects were originally demonstrated in human colon cancer cell lines and were later generalized to many other tumor cell lines. Since the late 1990s, several plant de
rived (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 from original lung adenocarcinoma study, other tumor cells that have been shown to be sensitive to cannabinoid-induced growth inhibition include glioma, breast, epine
leukemia/myeloma, neuroblastoma, skin, uterus, breast, gastric, colorectal, pancreatic and prostate car
cinomas.1-8

Perhaps even more compelling, canna
binoid administration to nude mice slows the growth of various tumor xenografts including lung and skin carcino
mas, thyroid epitheliomas, melanoma, pancreatic carcinomas, lymphomas and colon adenocarcinomas of CB1 and/or CB2 receptors for the antitumor effect has been shown by various bio
chemical and functional assays. Local topical ap
proaches already mentioned and the cu
mulative effects of CB signaling in the control of cell fate are expected to have 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 inhibi
tion of transformed-cell growth and inhi
bition of tumor angiogenesis and me	astasis.9-12 A desirable property of anti
tumor compounds is their preferential targeting of malignant cells over normal cells. Cannabinoids appear to kill tumor cells but do not affect their non-transformed coun
terparts and may even protect them from cell death. This is best exemplified by glial cells.

Cannabinoids have been shown to induce apoptosis in cell lines in culture and induce regression of glioma cells in mice and rats. In contrast, canna
binoids protect normal glial cells of astro
delial and oligodendroglial lineages from apoptosis mediated by the CB1 re
tector.

Pharmacological 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 endothe
lial growth factor (VEGF) and other pro
ingiogenic cytokines, as well as of VEGF receptors.

Activating cannabinoid receptors in vascular endothelial cells inhibits cell migration and survival, also contribut
ing to impaired tumor vascularization. Cannabinoid administration to tumor bearing mice decreases the activity and expression of matrix metalloproteinase 2 (MMP-2), a protein that allows 2, a proteolytic enzyme that allows tissue breakdown and remodeling during angiogenesis and metastasis. This sup
ports the inhibitory effect of cannab
inoid administration to tumor cell death as well as by inhibition of an
angiogenesis and metastasis.

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 motility, chemotaxis and chemosis-in
vasion.13

In an in vivo model using severe combi
nated immunodeficient mice, subcuta
neous tumor growth was generated by in
jecting the animals with the same cell
tlines. Tumor growth in THC-treated an
imals was inhibited by 60% compared with vehicle-treated controls. The inhibi
tion was significant both regarding the tumor lines. Tumor growth in THC-treated an
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Most recently, another potential anti
cancer and particularly anti-metastasis mechanism for cannabinoids has been identified. Id2 (inhibitor of DNA helix-loop-helix) protein is known to both stimulate tumor progression and mediate metastasis in a variety of tumor specimens. Since the late 1990s, several plant de
rived (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. The antiproliferative effects were originally demonstrated in human colon cancer cell lines and were later generalized to many other tumor cell lines. Since the late 1990s, several plant de
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tions" that has been made between cannabinoids and therapeutic and targeted small molecule therapies widely used in oncology. The Spanish Ministry of Health ap
proved a pilot clinical trial carried out in collaboration between the Tenerife Uni
versity Hospital and the Guzman labo
ratory in Madrid to investigate the ef
fect of local administration of THC in
tracranially through an infusion catheter in patients with malignant ventral cerebrospinal fluid breakdown and remodeling during angiogenesis and metastasis. This sup
ports the inhibitory effect of cannab
inoid administration to tumor cell death as well as by inhibition of an
angiogenesis and metastasis.

With the body of evidence increas
ing, where are the clinical trials in hu
man trials of smoked marijuana? Is it possible to develop a therapeutic agent with the potential to reduce cancer growth and metastasis? Cannabinoids have been shown to inhibit the growth of gliomas and metastasis. This sup
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Tashkin Reiterates to Patients Out of Time:
Smoking Cannabis Does Not Lead to Lung Cancer

By Fred Gardner

One in three Americans will be affected 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 there would have been very big news in June 2005 when UCLA medical school professor Donald Tashkin reported that components of cannabis 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 cannabis smoke that are toxic. He’s conducted thousands of photomicrographs showing that marijuana smoke damages cells lining the upper airways. It was the Tashkin lab’s finding that benzene—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 cancer in lungs of even much-smoked number of joints per day.

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

These findings were deemed worthy of publication in “NIDA Notes.” Tashkin reported them at the 2005 meeting of the International Cannabis

REFERENCES continued

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

Research Society. They were published in the October 2006 issue of “Cancer Epidemiology Biomarkers & Prevention.”

Without a press release from NIDA calling attention to its significance, the assignment editors of “NIDA Notes” had the idea that “Marijuana Use and the Risk of Lung and Upper Aerodigestive Tract Cancers: Results of a Population-Based Case-Control Study” by Mia Hashibe, Hal Morgenstern, Yan Cui, Donald P. Tashkin, Zuo-Feng Zhang, Wendy Cozen, Thomas M. Mack and Sander Greenblatt 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 was as interested in something as 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 went 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 versus 78 non-smokers—was criticized by the corporate press than the large U.S. study that preceded it.

The New Zealand study was portrayed as an anomaly in an already significant subject. As if scientific inquiry were something akin to tennis match and the truth just gets truer with every volley.

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Tashkin Defends His Findings

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A Sociologist Walks Into a Cannabis Club...

At the 2008 Patients Out of Time Conference, sociologist Amanda Reiman described her 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 delivery services, and conducted a focus group with six participants. Excerpts of the study follow.

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

Also mentioned were BPG programs such as acupuncture 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 on Wednesdays. Participants reported getting peer support from other patients at BPG and that patients know they can go to with complaints, questions, suggestions. Perhaps a board could be formed of staff and patients to discuss activities, services and issues related to BPG operations.

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. No more fights in 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. No smoking 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.

Tashkin and controls—four.”

Tashkin spoke from the stage of an airy redwood chapel designed by Julia Morgan. He is pink-cheeked, 70ish, wears wire-rimmed spectacles. “Four people—five, they found you 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 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 355 joints of marihuana 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 98 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?”

Some finding, and one has to be cautious about... the design that we used for looking at... the integrity of O'Shaughnessy’s... not enough chairs in the community room. —Tashkin re COPD

“...must be lifted for them by having access to marijuana...” —Tashkin re COPD

“...much... 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.

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

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