

Using Medical Cannabis in an Oncology Practice

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Introduction

As oncologists, we treat patients who have devastating diagnoses with potent therapies. Hence, we demand solid evidence before recommending any intervention. Unfortunately, when it comes to supporting the use of cannabis in clinical situations, we are frustrated by a dearth of convincing evidence. Data from gold-standard prospective randomized controlled clinical trials are virtually nonexistent. One reason for this is that the only legal source of cannabis for research in the United States is the National Institute on Drug Abuse (NIDA). NIDA has a congressional mandate to study substances of abuse *only* as substances of abuse and not as therapeutic interventions. Although NIDA can supply cannabis for clinical trials to assess its effectiveness, funding must come from elsewhere. However, in this era of gene therapy and nanotechnology, few investigators are interested in studying this ancient botanical medicine. In addition, just as cancer is many diseases, cannabis is many different strains, so standardization of cannabis medicine is a challenge.

How Has Medical Cannabis Been Utilized in Clinical Practice?

Delta-9-tetrahydrocannabinol (THC) is the most psychoactive of the 100 or so of the plant's 21-carbon-containing terpenophenolic compounds known as cannabinoids.[1] A number of other cannabinoids are thought to have medicinal benefit as well. Cannabidiol (CBD), for example, is believed to be analgesic and anti-inflammatory but is not psychoactive.[2] THC has been available as a licensed medicine in the United States since 1986, when dronabinol was approved for the treatment of chemotherapy-induced nausea and vomiting (CINV). The indication was expanded in 1992 to include treatment of anorexia associated with the AIDS wasting syndrome. Nabilone is another synthetic THC that became available in the United States in 2006 for the treatment of nausea and vomiting. Nabiximols is a whole plant extract delivered as an oromucosal spray that contains THC and CBD in a 1:1 ratio.[3-5] Nabiximols is approved in most of the European Union and Canada and continues to

undergo clinical trials in the United States. Most of the available published research on the use of cannabis-based medicines involves these pharmaceutical agents, as studying the whole plant has been difficult, based on the reasons stated previously.

Dronabinol was approved 30 years ago for the treatment of CINV, and as such, it would stand to reason that the parent compound might also have activity for this indication. Again, most of the trial-generated data come from evaluation of the licensed pharmaceuticals and not the botanical itself. Only three trials have investigated cannabis, and in two of those trials the cannabis was only made available after dronabinol had failed.[6-8] Data from systematic reviews are generally more supportive of a benefit from cannabinoids.[9-12] My clinical experience as an oncologist practicing in San Francisco for 35 years is that cannabis is an effective antiemetic, even in situations where other pharmaceuticals have failed. Many patients choose cannabis over serotonin antagonists in hopes of avoiding the troublesome constipation often associated with those medications. Cannabis is also the only antiemetic that is an appetite stimulant. However, no clinical trials have been conducted to date evaluating the effect of the botanical therapy on cancer-related anorexia/cachexia syndrome. A trial of dronabinol found enhanced chemosensory perception of food in the treatment group compared with placebo, but larger studies with appetite and weight change endpoints were not impressive.[13] Nonetheless, patients employing cannabis in clinical practice often benefit from its orexigenic effect.

Our bodies have an intricate system of cannabinoid receptors and endogenous cannabinoids, known as endocannabinoids.[14] It has been postulated that the function of this system is to help us to process pain. Cannabis-based medicines have been tested in a number of pain models, and recent meta-analyses and systematic reviews suggest that they are beneficial in patients with chronic pain syndromes.[12,15,16] Patients with cancer pain as well as neuropathic pain from a number of causes have been included in these reviews. There is a con-

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vincing body of evidence showing cannabis itself is effective in a number of neuropathic pain syndromes, and cannabinoids seem to be able to treat, as well as prevent, chemotherapy-induced peripheral neuropathy caused by vinca alkaloids,[17] platinum, [18] and taxanes [19] in rodent models; however, only one small study of nabiximols has been published investigating this indication.[5]

has been accumulating that confirms the early observations.[1,2,22-27] Internet testimonials abound from patients claiming to have cured their cancer by using highly concentrated oil extractions of cannabis, enriched for THC, CBD, or both. These reports have generated an interest in some patients to forego conventional cancer therapies and to treat their cancer with cannabis oil alone. This is a

KEY POINTS

- **The current dearth of convincing evidence supporting the use of cannabis in clinical situations is because it has been difficult to get access to the plant to study as a therapeutic intervention.**
- **Cannabis can be an effective anti-emetic and appetite stimulant and may also be beneficial for cancer patients with chronic pain and neuropathy.**
- **Internet testimonials about possible anti-cancer effects of cannabis have caused some patients to forego conventional cancer therapies; oncologists should emphasize that this is not a recommended course of action, especially in patients with a potentially curable malignancy.**
- **It is important that oncologists educate themselves about the use of medical cannabis, including mode of administration, appropriate strain, and potential side effects for patients with comorbidities.**

If I have a single medicine that I can recommend to assist with nausea, anorexia, insomnia, depression, and pain rather than prescribing five or six pharmaceuticals that may interact with each other or the patient's chemotherapy, I consider it an attractive option for my patients

In the 16-patient placebo-controlled crossover trial, 5 responders reported a greater than 2-point decrease in their pain on a 0 to 10 numeric rating scale. Hence, further clinical trials of cannabis-based therapies in chemotherapy-induced peripheral neuropathy are warranted.

In animal models, cannabinoids appear to be synergistic with opioids in producing analgesia. Based on these preclinical observations, we conducted a small pharmacokinetic interaction study. [20] Although we saw no effect on plasma concentration of morphine or oxycodone when adding vaporized cannabis to steady-state dosages of sustained-release preparations, we did appreciate synergistic pain relief, although the study was too small to make a definitive statement about a pain endpoint. That said, in my clinical practice I have seen many patients decrease their dose of narcotics or wean off them altogether with the addition of cannabis to their regimen. Pain relief, with or without opiates, is another area where cannabis may be quite useful. In a number of the published pain studies, medicinal cannabis has also been reported to be effective in improving sleep quality. Patients report that CBD-rich products may be particularly effective for insomnia.

Investigators at the National Cancer Institute first published results of in vitro and animal studies demonstrating the inhibitory effects of cannabinoids—delta-9-THC, delta-8-THC, and CBD—on cancer cell growth and proliferation.[21] This line of research subsequently moved to Spain and Italy, where an increasing body of preclinical evidence

distressing situation, especially when faced with a patient with a potentially curable malignancy who chooses to go down this alternative pathway. As yet, there have been no clinical trials investigating highly concentrated cannabis products as anticancer agents, so patients must be reminded that what is observed in the test tube or animal models does not necessarily translate into benefit in humans.

Does Mode of Administration (Inhalation vs Oral Consumption) Matter?

When cannabis is inhaled, either as combusted or vaporized plant matter, the peak concentration of THC occurs in 2 to 5 minutes, with a rapid drop-off. The kinetics of inhaled oils, as one might find in the electric portable devices, may not yet be fully known. When ingested by mouth, the oral bioavailability is low and variable, estimated to be 5% to 20% of the ingested dose. In studies we conducted, the peak plasma concentration of THC taken by mouth was achieved at 2.5 hours and declined much more slowly. The terminal half-life of orally ingested THC is 25 to 30 hours, and when delta-9-THC passes through the liver it is metabolized into a psychoactive 11-hydroxy-THC, which may be even more psychoactive than the delta-9-THC. This is why people eating cannabis-baked products or capsules report a more significant psychoactive effect compared with those who inhale it (since in the second case, less of the secondary psychoactive metabolite is formed). A study investigating the pharmacokinetics of nabiximols delivered as

an oromucosal spray found values similar to those of orally administered THC.[28] The metabolism of sublingual highly concentrated extracts and oils currently being used by patients seeking an anti-cancer effect is not known at this time.

In view of these kinetics, I generally advise patients that if they want better control over the onset, depth, and duration of the effect, inhalation may be the better mode of delivery. However, I have heard from some patients who feel that while eating is a normal function, inhalation is not and may present additional health problems. As a result, they chose to go to a dispensary, where they were instructed to eat only a quarter of a cannabis cookie, but when the effects weren't felt right way, they ate the entire cookie. For a number of patients this created a degree of psychoactivity that was uncomfortable or frightening, sometimes necessitating medical evaluation and intervention. However, for sustained effects or overnight benefits, oral ingestion may be a more convenient mode of delivery than inhalation once proper dosing has been ascertained.

What Are the Obstacles to Obtaining Medical Cannabis?

Cannabis is now available for medical use in 23 states and the District of Columbia. California was the first state to approve medicinal cannabis in 1996. Over the past 2 decades, half of the states, accounting for 86% of the US population, have acquired access to cannabis as medicine. My patients in the San Francisco Bay Area have a wide assortment of dispensaries where they are able to obtain cannabis. It requires a letter from a physician (one hopes, the patient's own personal provider) recommending cannabis to the patient and stating that the physician will monitor the patient should he or she choose to use it. Alternatively, patients can pay a small fee and register with the state to obtain an identification card that allows them to access any dispensary.

Numerous barriers still exist. One is the patient's reluctance to try cannabis because of stigma that they associate with its use, or fear of addiction. I recall one 45-year-old patient with metastatic colon cancer receiving FOLFOX (leucovorin, fluorouracil, and oxaliplatin) who told me that it took him 5 cycles of his treatment to finally get over this stigma and try cannabis. He reported that it did what no other medicine could do—completely eliminate his CINV, and allow him to function quite normally. There are also physicians who have

a persistent phobia about recommending cannabis, and often tell their patients that they receive federal funding and therefore cannot recommend cannabis; however, I find that odd as I have federal funding to do research on cannabis! There is currently a huge knowledge gap for physicians who may be interested in offering cannabis to their patients. Although cannabis has been used as a medicine for nearly 3,000 years, it was removed from the US Pharmacopeia in 1942. Hence, most of us have been trained during a time when cannabis was not an accepted medicine and, as a result, clinicians know very little about what it does and how to use it, nor do they understand what exactly is available for patients in the dispensaries. Even if physicians were aware of the strains and products available, in all likelihood they still would not be comfortable recommending one strain over another because of the total lack of evidence on which to base their decision (eg, whether CBD works for nausea, what the best ratio of THC:CBD is for sleep, or which oil is the most potent for pain relief).

How Can Oncologists Educate Themselves About Medical Cannabis?

Education is critical if we are going to be able to best advise our patients on how they might utilize cannabis, particularly for management of symptoms related to cancer or its treatment. Again, the dearth of evidence hinders our ability to feel confident in counseling patients. We simply do not know the answers to most of the questions our patients are asking about cannabis. I was recently interviewed by a think-tank person working with one of our local dispensaries to improve communications with physicians, who clearly outlined the problem. She remarked that when I see a patient with depression, I might write a prescription for paroxetine 20 mg once daily, bupropion 150 mg twice daily, or sertraline 50 mg once daily. The patient will take the prescription to the pharmacy, and will receive exactly what he or she needs. However, using an analogy to the way cannabis dispensaries work, a physician would write a recommendation for treating depression, and the dispensary would inquire, “do you want paroxetine, bupropion, or sertraline? What dose? How many?” An imperfect system for sure, but that is the way it currently works for medicinal cannabis.

Many things can influence how a person will respond to the use of cannabis medicines. Past experience, “set and setting,” and even pharma-

SUGGESTED RESOURCES

Websites

International Association for Cannabinoid Medicines (IACM)
(www.cannabis-med.org)

International Cannabinoid Research Society
(www.icrs.co)

NCI PDQ CAM Cannabis and Cannabinoids
(www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq)

Patients Out of Time
(www.medicalcannabis.com)

Society of Cannabis Clinicians
(<http://cannabisclinicians.org/>)

The Canadian Consortium for the Investigation of Cannabinoids
(www.ccic.net)

University of California Center for Medicinal Cannabis Research
(www.cmcrc.ucsd.edu)

Books

Backes M.
Cannabis Pharmacy: The Practical Guide to Medical Marijuana

Casarett D.
Stoned: A Doctor's Case for Medical Marijuana

Holland J.
The Pot Book: A Complete Guide to Cannabis - Its Role in Medicine, Politics, Science, and Culture

Pertwee RG.
Handbook of Cannabis

Werner C.
Marijuana Gateway to Health: How Cannabis Protects Us from Cancer and Alzheimer's Disease

cogenomics may all play a role. We recommend a self-titrated dosing regimen for the patient as the safest option, rather than attempting to prescribe an actual dose.^[29] Aside from the psychoactivity of cannabis, which can be a dysphoric experience for some, side effects are generally tolerable. I am cautious about recommending cannabis to elderly patients, however, especially those with underlying heart disease, because cannabis can lower blood pressure and raise the heart rate. Postural hypotension and subsequent falls are also a concern. Colleagues who have studied cannabis in the preclinical setting describe euphoria as a side effect in their animal studies. I do not consider euphoria in my patients to be an adverse event by any means. If I have a single medicine that I can recommend to assist with nausea, anorexia, insomnia, depression, and pain rather than prescribing five or six pharmaceuticals that may interact with each other or the patient's chemotherapy, I consider it an attractive option for my patients. Hopefully, in the near future, more data will be generated from observational or interventional trials, which will allow us to feel even more confident recommending this ancient botanical to our patients.

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