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Cannabis Use in Patients With Cancer: A Clinical Review

Brooke Worster, MD[1,2]; Emily R. Hajjar, PharmD[3]; and Nathan Handley, MD, MBA[1,2,4]

abstract

Cannabis use and interest continues to increase among patients with cancer and caregivers. High-quality research remains scant in many areas, causing hesitancy or discomfort among most clinical providers. Although we have limitations on hard outcomes, we can provide some guidance and more proactively engage in conversations with patients and family about cannabis. Several studies support the efficacy of cannabis for various cancer and treatment-related symptoms, such as chemotherapy-induced nausea and cancer pain. Although formulations and dosing guidelines for clinicians do not formally exist at present, attention to tetrahydrocannabinol concentration and understanding of risks with inhalation can reduce risk. Conflicting information exists on the interaction between cannabis and immunotherapy as well as estrogen receptor interactions. Motivational interviewing can help engage in more productive, less stigmatized conversations.

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Mr Jones is a 55-year-old man with a medical history of hypertension, gastrointestinal reflux disease and ulcerative colitis who presented to a local hospital with weight loss and jaundice. He received a diagnosis of metastatic cholangiocarcinoma, underwent stent placement, and recently began systemic chemotherapy. He is six feet tall and originally weighed 215 lbs. When he comes in for treatment today, his weight has decreased to 192 lbs. He reports that he has pain with anything he tries to eat. He does not like how much constipation resulted from opiates, so he is using only sparingly. He currently takes acetaminophen, famotidine, amlodipine/hydrochlorothiazide senna, and oxycodone as needed. He asks you what can be done for his appetite and pain.

INTRODUCTION

Of the 15.5 million Americans living with cancer,[1] moderate to severe pain (0-10 numerical rating score ≥ 5) is experienced by more than a third because of consequences of cancer, its treatments, or both.[2] According to a large, longitudinal study done by the American Cancer Society, pain was among the top three symptoms contributing the greatest negative impact to patients' quality of life (QoL).[3]

Although improving QoL in patients with cancer remains a top priority, we continue to struggle with effective and safe interventions for many of the cancer and cancer treatment–related side effects including pain and anorexia. Given the increasing awareness of risks associated with long-term or high-dose opioid use, many patients now want to limit or avoid opioid use when possible.[4,5] Recent surveys report that between 25% and 40% of patients with cancer use cannabis in any form, from a state-regulated dispensary or obtained from illicit sources,[6,7] and among those, a large majority report using it to manage symptoms such as pain or anxiety.[8]

At least 36 states and the District of Columbia have approved cannabis for medical use, and 18 have laws allowing legal recreational access.[9] Understanding the terminology associated with cannabis is important to have a basis for composition, safety, or availability. The US government created the distinction between high (> 0.3% tetrahydrocannabinol [THC]) and low THC (< 0.3% THC) cannabis as a regulatory mechanism. The Farm Bill[10] of 2018 deregulated low THC cannabis, known as hemp. Hemp is often referred to as cannabidiol (CBD); however, this nomenclature is inaccurate, as hemp contains numerous compounds, including THC. Subsequently, innumerable CBD-based products flooded the marketplace with little to no regulation in content or quality.[11] Although patients have online or even convenience store access to these CBD products, there is minimal assurance of composition (Table 1).

There remains wide discrepancy between state-to-state regulation and operational procedures surrounding cannabis. Rapid expansion of legislation allows greater access, but high-grade scientific

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Author affiliations and support information (if applicable) appear at the end of this article.

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TABLE 1. Distinguishing Factors: Cannabis, Marijuana, and Hemp

***Cannabis* = taxonomic term referring to a genus of flowering plants that are members of the family Cannabaceae, consisting of 1,000s of phytochemicals, divided into three species (*Cannabis sativa, Cannabis indica,* and *Cannabis ruderalis*)**

	Marijuana[a]	Hemp
United States law defines as		
Plant components	Leaves, flowers, and viable seeds of cannabis	Stalks, stems, and sterilized seeds of cannabis
Δ9-THC = main psychoactive component	> 0.3%	< 0.3%
CBD	Any	Any

Abbreviations: CBD, cannabidiol; THC, tetrahydrocannabinol.

[a]Used interchangeably with cannabis; given the range of possible patient products used, the term cannabis is more accurate and inclusive in this setting.

evidence remains limited.[12] Thus, it is not surprising that national guidelines lack recommendations about possible therapeutic uses of cannabis, which creates clinical challenges for clinicians.[13] A recent nationally representative sample of medical oncologists found that 70% of oncologists did not feel equipped to make clinical recommendations regarding cannabis, and only 46% had recommended its use.[13]

Mr Jones reports a desire to avoid higher-dose opioids and denies significant nausea as the cause of his poor appetite. In conversation with his care team, cannabis use is brought up as a potential treatment. He does not feel comfortable smoking or inhaling anything and wonders if there is another way for him to use cannabis.

FORMULATIONS, PHARMACOKINETICS, AND THE ENDOCANNABINOID SYSTEM

It is important to understand both the endocannabinoid system, where phytocannabinoids are primarily active, and the range of cannabis-based products available to patients, as the potency, tolerability, and pharmacokinetics can vary widely (Table 2).

TABLE 2. Potential Benefits and Risks of Cannabis on the Basis of Formulation

Formulation	Potential Benefit	Potential Risk
Inhalation	Rapid relief of pain or anxiety Help with sleep latency	Cough Irritation of oral mucosa Dry mouth Dizziness
Oral/sublingual	Extended duration of pain, anxiolytic, antiemetic effect Help with sleep maintenance	Adverse taste Potential aggravation of nausea Dry mouth Diarrhea
Topical	Localized pain relief	Contact dermatitis Urticaria

Although there are more than 100 known phytocannabinoids, the most well recognized are Δ9 THC and CBD. The two best-studied targets for cannabinoids in the human body are the endocannabinoid system receptors CB_1 and CB_2.[14] There are other receptors that both THC and CBD activate or antagonize; however, these remain less mapped than the CB_1 and CB_2 receptors. CB_1 is found predominantly in the central and peripheral nervous system, whereas CB_2 has a more limited distribution in the immune and hematopoietic system.[15]

There are four main methods of ingesting cannabis: inhalation (vaporization or smoking), oral, sublingual, and topical. Each method has unique pharmacokinetics and other considerations that may make it more or less tolerable to specific patients (Table 3). Cannabis is metabolized by the liver and primarily excreted in feces. Metabolites are highly lipophilic, leading to a very long half-life in humans (up to 70 days).[16]

Inhalation

Inhalation remains the most common method of cannabis consumption in the Unites States and worldwide.[17] This can include smoking, which is the burning of the dried flower and inhaling the components that are released. Smoking can occur via several forms (eg, rolled cigarette joint *v* pipe bong). Vaporization is similar; however, the plant is not burned, but instead heated to a temperature at which the active ingredients in the plant are released as vapor that is inhaled by the consumer. Although much is still unknown about long-term side effects of inhalation of cannabis via vaporization, a meta-analysis from 2018 published in *Annals of Internal Medicine* showed minimal impact on pulmonary function with short-term cannabis vaporization.[18] However, vaporizers use concentrated oil extracted from the plant and can contain up to as much as 90% THC, which can result in serious side effects for a novice consumer. Inhaling high THC concentrations, via either smoking or vaporizing, may increase risk for arrhythmia or myocardial infarction in susceptible patients.[19] Common side effects specific to inhalation include sore throat, irritation of oral mucosa, and cough. A potential benefit of inhalation is both rapid onset of action (helpful when nausea is a prominent symptom) and ability to easily titrate one's dose, making overconsumption less likely.[20]

Oral/Sublingual

Oral ingestion is rapidly becoming a more prominent form of cannabis ingestion, and much research and development has gone into formulations of cannabis-infused candy, beverages, and other food products.[21] Formulations include pills, edibles (food-based products and candies), and beverages. Sublingual ingestion includes sprays, dissolvable strips, tinctures, and lozenges. The largest limitation in oral or sublingual ingestion is poor

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TABLE 3. Cannabis Pharmacokinetics

Form	Onset of Action	Peak Effect	Duration of Effect
Inhalation (includes vaporization or smoking)	0-10 minutes	3-10 minutes	2-4 hours
Oral	1-3 hours	1-2 hours	6-12 hours
Sublingual	15-60 minutes	45 minutes	4-6 hours
Topical	5-120 minutes	Variable	Variable

pharmacokinetics: bioavailability is low (between 6% and 25%) because of the lipophilic nature of the bioactive substances and absorption is erratic, as it can be delayed and otherwise affected by other stomach contents.[22] This makes oral ingestion difficult to effectively titrate as well as more prone to overconsumption, especially with high-THC products, in that patients may need to wait longer than expected for the onset of effect and assume they need more. Overingestion of THC can lead to nausea, anxiety, paranoia, disorientation, and short-term psychosis.[23] Additionally, most edible products are potentially appealing to children or pets (candy, cookies, and flavored drinks); so, caution must be used in storage.

Sublingual use may improve bioavailability and absorption. Sativex (nabiximols), the one plant-based cannabinoid medication, approved for medical use in Canada and parts of Europe but not yet in the United States, includes the entire spectrum of natural cannabinoids and is delivered as a sublingual spray. The time of onset is similar to those seen in general oral consumption; however, some studies have reported an earlier onset.[22]

Topical

A final common way to consume cannabis is topical use in the form of lotions, salves, oils, and patches. Topical administration of cannabis potentially allows a steady infusion of a drug to be delivered over a prolonged period of time, while also minimizing the adverse effects of higher drug peak concentrations because of limited systemic availability, which can reduce unwanted side effects. Topical administration is potentially ideal for localized symptoms, such as those found in dermatologic conditions and arthritis. However, local skin irritation can occur, and the absorption capacity of both the cannabis preparation and the additives may not be well described.[24] Topical use is often popular in novice users or older adults who wish to avoid the intoxicating effects of cannabinoids.

Rick Simpson Oil

Rick Simpson oil (RSO) refers to a full-spectrum extract that is known to be high in THC. These products are highly potent and have a viscous consistency.[25] Because of the activation of the THC in the extraction process, RSO can be ingested orally, sublingually, or topically. It does not need to be heated to work like other preparations require.[26] Although RSO products have the same considerations as other formulations listed above, special consideration should be noted on the potency, as unintentional overdose can occur more frequently with this type of product. Although some believe the topical application of RSO products may cure cancers, this is only supported by anecdotal stories.[27]

Risks

It is important to consider risks and side effects of cannabis use when counseling patients. Cannabis smoke carries many of the same carcinogens found in tobacco smoke. However, large cross-sectional and longitudinal studies have not found a link between cannabis smoking and long-term pulmonary consequences, such as chronic obstructive pulmonary disease and lung cancer.[28,29]

More recent evidence highlights cardiovascular concerns among cannabis users as well. Randomized controlled trials evaluating the therapeutic use and safety of cannabis are lacking, but a growing body of evidence suggests that marijuana consumption may be associated with adverse cardiovascular risks.[30] There is much to be learned, and most studies now are retrospective analyses with confounding variable such as high prevalence of tobacco use in the populations as well.[31]

Data regarding the relationship between cannabis use and psychiatric disorders are incompletely understood, often in conflict, and vary on the basis of cannabinoid type, potency, and composition, with synthetic, illicit THC products carrying a much higher risk than whole plant or extract.[32]

Mr Jones has an appointment with the interprofessional Supportive Oncology team. The team evaluates his perceptions and prior experiences surrounding cannabis use in an effort to create open dialogue about his fears and interest in using cannabis. He admits that a friend gave him a gummy that was helpful for both pain and appetite but made him somewhat dizzy. He is not sure what the composition of that product was. The physician certifies him for the state-approved medical cannabis program, and the social worker helps guide him through the cost, payment, and dispensary access, reminding him that these are all state-specific. Recommendations given for a tincture to use for both pain and appetite with initial use of a 2.5 mg dose of THC and to prioritize formulations that also have CBD.

SELECT INDICATIONS AND EVIDENCE BASE

Pain

Very few well-designed, randomized controlled trials exist examining medical cannabis in patients with cancer pain. However, there has been increasing interest in cannabis use for cancer pain, given the lack of safety or tolerability of opioids and other analgesics (eg, renal impairment and nonsteroidal anti-inflammatory drugs, polypharmacy, and risk of addiction). Although evidence is mixed,[33] there appears to be at least a weak indication for cannabis use if standard of care has failed across pain types. Although the evidence is somewhat

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better for neuropathic pain[34] and cancer pain,[34] it is difficult to control for route of administration as well as composition of products. The risks of inhalation as the route of administration often lead many guidelines to steer away from this as a method of consumption.[35]

Therapeutic trials of cannabis for naive users should start with low dose, noninhaled products, possibly with higher CBD component or a CBD:THC 1:1 ratio with slow increases of THC as indicated and tolerable (Table 4). Patients who have had prior exposure to cannabis may be able to tolerate higher THC concentrations. Dosing or oral or sublingual products should start with no higher than 5 mg THC for inexperienced users. Dosing of CBD can be more liberal and is generally well tolerated.

Insomnia

Impaired sleep onset and latency are frequent concerns among patients with cancer and may affect up to 19% of the general population.[36] One very common patient-reported use of cannabis is to treat insomnia. However, research into cannabis use and sleep is very conflicting. There is some evidence that short-term, high-dose CBD may be helpful in decreasing sleep onset and lengthening time asleep[37] possibly through its anxiolytic effects.[38] Conflicting evidence suggests that cannabis cessation after prolonged use can cause or exacerbate insomnia.[39]

Chronic pain affects individuals' ability to get restful sleep. Research, primarily with nabiximols (Sativex THC:CBD 1:1 oromucosal spray), has started to examine the potential role of cannabinoids in addressing sleep disturbances in the context of pain. A significant majority of study patients reported a subjective improvement in sleep quality, although possibly more related to reduced pain levels than a change in biological sleep patterns. Frequent cannabis use, especially with high-THC products, results in tolerance and may trigger self-titration and very high THC use over prolonged exposure for sleep.[40]

TABLE 4. Guidelines for Initial Dosing on the Basis of THC Amount for Cannabis-Naive Users

Initial THC Dosing

Form	Dose	Comments
Inhalation (includes vaporization or smoking)	One short inhalation	Wait 10-15 minutes to see effect Inhale longer-duration puff for stronger effect
Oral	2.5-5 mg	Consider starting with 1/4-1/2 of edible product Wait 1-2 hours to see effect before redosing for desired effect
Sublingual	2.5-5 mg	Wait 45 minutes to see effect before redosing for desired effect
Topical	Liberal amount to affected area	Do not bathe or swim after

Abbreviation: THC, tetrahydrocannabinol.

Although many patients may turn to cannabis for help with sleep impairments, there is little in the way of evidence-based guidance for dosing or composition of product to recommend. Given the longer half-life of oral or sublingual product, this maybe the preferred formulation to help with sleep duration.

Anxiety

Anxiety disorders, as a group, are the most common mental illness in the world, leading to high psychosocial and financial burden.[41] The first-line treatment of anxiety disorders includes various antidepressants (selective seratonin reuptake inhibitor and seratonin and norepinepherine reuptake inhibitor) and benzodiazepines as well as psychotherapy. Up to 40% of patients still experience anxiety symptoms despite this treatment,[42] thus driving interest in additional effective therapeutics. CBD has therapeutic potential as a treatment for anxiety as shown by the burgeoning number of studies and meta-analysis examining use in several anxiety disorders, ranging from post-traumatic stress disorder to public speaking. There is well-supported data that high THC can exacerbate anxiety, induce panic attacks, or even trigger transient psychosis in nonfrequent users or if overingested,[43] whereas CBD has shown tolerability and effectiveness in social anxiety, post-traumatic stress disorder, and general anxiety treatment.[44] Studies have examined both oral and inhaled forms of CBD predominant cannabis with similar efficacy.

Nausea and Anorexia

There are two US Food and Drug Administration (FDA)–approved delta-9-THC pharmaceutical agents, dronabinol and nabilone, for use in treating nausea and vomiting associated with cytotoxic chemotherapy. A meta-analysis summarizing 28 trials, most completed before 2000, favored these over placebo or other antiemetics available.[45] Additional studies completed more recently also support that although patients reported more frequent side effects, they preferred cannabinoids over other antiemetics.[46] There are no published trials examining the impact of CBD alone on chemotherapy-induced nausea and vomiting. A review published in 2020 demonstrated a small number of smoked or inhaled plant strains with CBD present but no controlled data regarding CBD-predominant cannabis formulations for appetite or nausea currently exist.[12]

Similarly, patients often subjectively report improvements in appetite with cannabis use. Marinol originally received FDA approval for this indication in HIV patients in the 1980s. Studies show that smoked cannabis increase blood levels of ghrelin and leptin, hormones associated with hunger.[47] Small trials of THC supplementation in patients with advanced cancer have shown subjective reports of improved taste and appetite.[48] However, there are minimal studies examining CBD-predominant products in appetite stimulation or weight gain to date.

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It is important to note that of all the antiemetics currently available, cannabis and corticosteroids are the only two options with both antiemetic and orexigenic effects. Balancing risk, benefit, or drug-drug interactions between corticosteroids may limit its use at times, especially in those patients with cancer receiving immunotherapy.

CANCER-SPECIFIC CONCERNS FOR CANNABIS

Immunotherapy

The biological impact of the cannabis is mediated by the endocannabinoid system. Although the two best-studied targets for cannabinoids in the human body are the endocannabinoid receptors CB_1 and CB_2, it is increasingly recognized that additional receptors, enzymes, and endocannabinoid-like lipids appear to be part of an extended endocannabinoid system, or endocannabinoidome.[49-51] This extended system has been implicated in immune system regulation, leading to the hypothesis that cannabis may affect the activity of immunomodulatory agents, including immunotherapy for patients with cancer. Some preliminary data suggest this may be the case. In one retrospective study of 140 patients with melanoma, small-cell lung cancer, and clear cell renal cell carcinoma, receiving either nivolumab alone or nivolumab and cannabis, cannabis use was the only significant factor that decreased response rate (37.5% relative risk in nivolumab alone versus 15.9% in the nivolumab-cannabis group; $P = .016$; odds ratio = 3.13; 95% CI, 1.24 to 8.1). However, cannabis use did not significantly affect either progression-free survival or overall survival.[52] Similarly, a prospective observational study including 102 patients with metastatic disease (68 receiving immunotherapy—pembrolizumab, nivolumab, durvalumab, atezolizumab, or ipilimumab and nivolumab—and 34 receiving immunotherapy plus cannabis) suggested that cannabis users had a lower rate of clinical benefit (39% in users *v* 59% in nonusers, $P = .035$). Similarly, median time to progression was 3.4 months (95% CI, 1.8 to 6.0) for users versus 13.1 months (95% CI, 60 to not available) for nonusers, and median overall survival was 6.4 months versus 28.5 months ($P = .0025$).[53] Cannabis users also had a significant reduction in immune-related adverse events ($P = .057$). Although these studies raise some concerns, additional prospective studies are needed to further examine the association between cannabis use and immunotherapy efficacy.

Antitumor Characteristics

Several cancer types express cannabinoid receptors in a manner related to the degree of anaplasia and grade of the tumor.[54] In vitro and in vivo cancer models have demonstrated that cannabinoids can modulate tumor growth, although the data remain nascent.[55] Similarly, cell- and animal-based studies have demonstrated similar anticancer effects to plant-derived cannabinoids.[56]

Understanding the process by which cannabinoids regulate cellular processes involved in tumor development remains an important area of research. In 2017, the National Academy of Sciences convened a committee to review the health effects of marijuana.[57] In evaluating potential antitumor characteristics for patients with cancer, the committee found one systematic reviewing focusing specifically on gliomas.[58] The review identified 2,260 studies. Of these, 35 met inclusion, and all were preclinical (with the exception of one small clinical trial); all 16 of the in vivo studies described an antitumor effect of cannabinoids. The committee concluded that there is insufficient evidence to support or refute the conclusion that cannabinoids are an effective treatment for cancers (including glioma), and suggested that signals from the preclinical literature suggest additional clinical research needs to be conducted.

Estrogen Receptor Interactions

Animal models demonstrate that cannabinoids can alter multiple hormonal systems—including suppression of gonadal steroids, growth hormone, prolactin, and thyroid hormone, and activation of the hypothalamic-pituitary-adrenal axis.[59] Crude marijuana extract and condensed marijuana smoke can compete with estradiol for binding to the estrogen receptor; of purified cannabinoids, CBD also demonstrates binding.[60] These observations have led to the hypothesis that cannabis may play a role in hormone-positive breast cancer. Indeed, several studies have demonstrated that THC, CBD, and other CBs can inhibit disease progression in breast cancer models.[61] One study suggests that the effect of a botanical drug formulation may have greater antiproliferative effects than that of pure CBs.[62] Additionally, one study of human breast cancer tissue specimens demonstrated that 75.6% of breast adenocarcinoma expressed CB2, regardless of the subtype (although expression was most highly associated with tumors expressing human epidermal growth factor 2.[63] However, there are not yet clinical data evaluating the effect of either exogenous or endogenous CBs on treatment outcomes or disease prognosis of any breast cancer subtype.[64]

TALKING WITH PATIENTS ABOUT CANNABIS

Given the social, cultural, and regulatory complexity surrounding cannabis, discussing its use with patients can pose a challenge. Motivational interviewing, which seeks to understand a patient's perspective before attempting to impart information, can be an effective tool to have these discussions when a provider senses that cannabis may be of benefit to a patient. In motivational interviewing, a health care provider uses a four-step approach to engage the patient: engaging, focusing, evoking, and planning.[65] In the engaging phase, a provider first listens to the patient to elicit their pre-existing perceptions regarding cannabis. In the

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focusing phase, a provider then clarifies the goal of the treatment (in this case, symptom management). In evoking, the provider then works to understand motivations that may support or inhibit use of cannabis. Finally, in the planning phase, the provider and patient work together to develop a mutually agreeable plan for cannabis use, if appropriate.

In conclusion, improving QoL in patients with cancer remains a top priority. Although the field is early in development, cannabis may play an important role for symptom management in this population. It is important to discuss the potential benefits and adverse effects of cannabis along with counseling points to allow patients to use each dosage form properly.

AFFILIATIONS

[1]Department of Medical Oncology, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA
[2]Sidney Kimmel Cancer Center, Thomas Jefferson University Hospital, Philadelphia, PA
[3]College of Pharmacy, Thomas Jefferson University, Philadelphia, PA
[4]Department of Integrative Medicine and Nutritional Sciences, Thomas Jefferson University, Philadelphia, PA

CORRESPONDING AUTHOR

Brooke Worster, MD, Director, Division of Supportive Oncology, Department of Medical Oncology, Sidney Kimmel Cancer Center (SKCC), 925 Chestnut St, Ste 420a, Philadelphia, PA 19107;
e-mail: Brooke.Worster@jefferson.edu.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cannabis Use in Patients With Cancer: A Clinical Review

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Brooke Worster
Consulting or Advisory Role: Ethos Cannabis (Inst), PAX Therapeutics
Research Funding: Ethos Cannabis (Inst)

Emily R. Hajjar
Consulting or Advisory Role: Prime Therapeutics
Research Funding: Ethos Cannabis (Inst)

Nathan Handley
Research Funding: Nektar (Inst)

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