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PALLIATIVE MEDICINE (A JATOI, SECTION EDITOR)

A Comprehensive Review of Cannabis in Patients with Cancer: Availability in the USA, General Efficacy, and Safety

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Abstract

Purpose of Review As the legalization of medical cannabis continues across the USA, oncology care providers will be increasingly asked to provide recommendations regarding its use in the cancer setting. In this article, we review recent literature that analyzes cannabis use specifically in patients with cancer and provide an accessible guide for clinicians, researchers, and patients.

Recent Findings We aimed to answer questions about the availability of cannabis in the USA, the trials supporting its use in the cancer setting, and the important factors to consider related to safety. Thirty states plus the District of Columbia have established comprehensive medical cannabis programs, each with different regulations and products available. In June 2018, Epidiolex, a cannabis extraction product containing 99% CBD, was approved to treat refractory seizures; however, whole-plant products and non-prescription extraction products dominate the market. Recent randomized, placebo-controlled studies of nabiximols (Sativex) in patients with refractory cancer-pain have largely shown no significant benefits. Conversely, large observational studies suggest patients with cancer using cannabis report significant improvement of many common symptoms. Cannabis use appears well tolerated, with few serious adverse effects reported.

Summary Though prospective clinical trials are needed to provide the robust data required to establish the proper role of cannabinoid and cannabis-based therapy in cancer patients, physicians can draw upon the knowledge currently available to have informed discussions with their patients.

Keywords Cannabis · Marijuana · Cancer · Palliative care

Case Scenario

A 55-year-old man being treated with fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) for metastatic pancreatic cancer presents to your clinic with a plethora of symptoms, including nausea and vomiting, pain, insomnia from steroids, and constipation from opioids. To combat his nausea and vomiting, the patient is currently taking ondansetron and lorazepam. For pain management, the patient is taking 30 mg of morphine sulfate controlled release twice daily and 5 to 10 mg of oxycodone every 3 h as needed. The patient is taking senna and polyethylene glycol for constipation and trazodone as a sleep aid. Despite all these palliative medications, the patient's symptoms persist.

Willing to try anything to alleviate his symptoms, the patient asks you about cannabis. The patient, knowing that cannabis has been used by humans for centuries and is appearing frequently in the news, believes cannabis could be a safe and effective choice for palliation of his symptoms. As his oncology provider, how do you respond? Do you recommend use of cannabis? If so, for which symptoms? Is cannabis safe for this patient? Is it even legal?

This article is part of the Topical Collection on *Palliative Medicine*

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Introduction

Cannabis (marijuana) use is becoming more prevalent in patients with cancer [1••]. However, only 30% of oncologists feel that they have sufficient training to make informed

recommendations about cannabis [2••] and 85% want more education about it [3]. Previous review articles have attempted to outline the benefits and risks of cannabis use in patients with cancer [4, 5, 6•]; however, they often include studies that are outdated, compare cannabis with drugs that are no longer used, or extrapolate data from patients without cancer.

In this article, we aim to provide a comprehensive and accessible review of cannabis and its palliative effects exclusively in the cancer population. We focus on a series of common questions that patients, clinicians, and researchers face when considering cannabis for relief of cancer symptoms (Fig. 1). While the emphasis of this review is the palliative effects of cannabis, we address other important questions, such as accessibility and safety (Fig. 1). In addition, we provide online sources that are constantly updated and easily accessed, allowing clinicians, patients, caretakers, and policymakers to stay current on the ever-changing landscape of cannabis research.

Cannabis Availability

What Are the Laws and Regulations in My State?

At the federal level, cannabis (including all derivatives of the plant that come from the flowering tops, resin, and leaves) remains classified as a Schedule I substance under the Controlled Substances Act. Schedule I substances are considered to have no currently accepted medical use and a high potential for abuse, making distribution of cannabis a federal offense. At the state level, however, legalization of cannabis use (for both medical and recreational reasons) has generally been gaining momentum over the past decade. As of June 1, 2018, 30 states plus the District of Columbia (DC), Guam, and Puerto Rico have established comprehensive medical cannabis programs. Legalization occurred in 2007 or later in 21 of the states, with some of these programs not yet operational. An additional 16 states allow possession of certain cannabidiol-rich, low-tetrahydrocannabinol (THC) cannabis products, with some programs allowing no means of production or distribution of these products within the state. Since 2012, nine states and the DC have expanded beyond a comprehensive medical cannabis program: eight have legalized recreational use and allow retail distribution; one state and DC allow recreational use and cultivation but have no regulated production or sales [7•].

Each state medical cannabis program is different, so clinicians must review information from a reliable source for states where they practice. Each state program maintains a website with information. The websites for the National Conference of State Legislatures and Americans for Safe Access have links to state program websites as well as their own formatted program descriptions for each state [7•], https://www.safeaccessnow.org/state_and_federal_law. The programs vary greatly in a number of ways, including types of products allowed, enrollment processes and fees, qualifying medical conditions, clinician's role, reciprocity (if any), required product testing and labelling, retail purchase mechanisms, designating caregivers to provide assistance, information collected from patients on benefits and harms, taxes collected (if any), and program oversight mechanisms.

Most programs allow the sale of dried cannabis plant material for smoking or vaporization, and some allow registered patients to grow a limited number of cannabis plants. Several programs do not permit dried cannabis plant material of any kind and sell only cannabis extract liquids packaged into a combination of oral solutions, capsules or tablets, tinctures, vaporization oils, and topical agents.

Clinicians serve as gatekeepers in each state's program, but the nature of their determination and action and the type of clinician eligible vary considerably. Importantly, no program has the familiar prescription mechanism, because that would place the clinician too squarely in violation of federal law, putting their Drug Enforcement Agency license at risk.

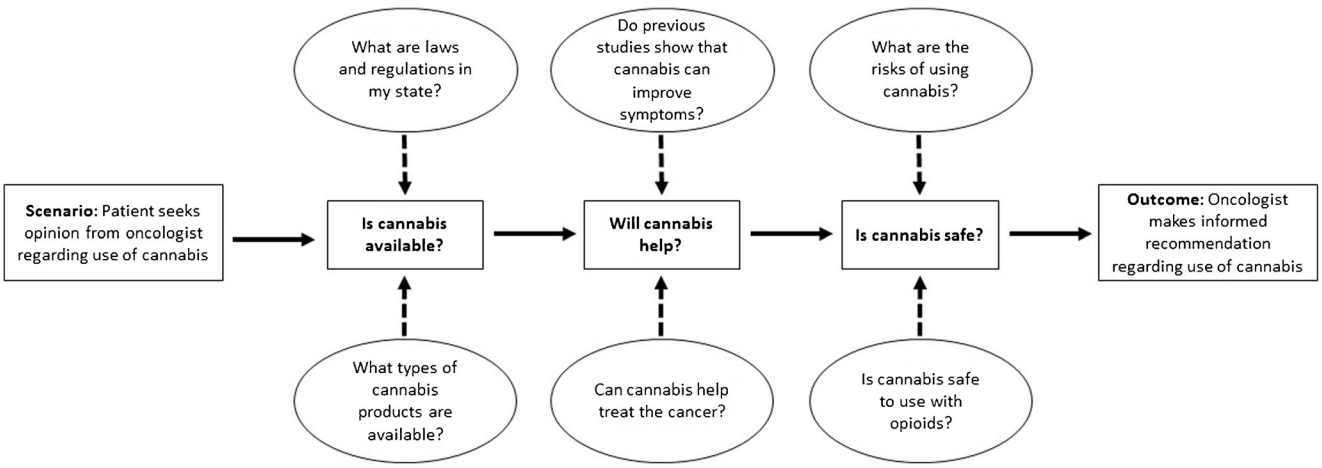

Fig. 1 Key questions to address when discussing availability, effectiveness, and safety of cannabis with patients

Instead, the formal role of the clinician is certifying that the patient has one of the program's qualifying conditions and, for some programs, an additional attestation. The additional component is typically attesting belief that the patient could benefit from medical cannabis or that the potential benefits outweigh the potential risks. In a few programs, the clinician has an option to specify the type of product they think most appropriate for the patient or an obligation to specify the maximum amount of product that can be sold. Clinicians eligible to participate in the program are in many programs limited to physicians (MD or DO), but in some states, advanced practice registered nurses, physician assistants, and homeopathic/naturopathic physicians are also eligible.

What Types of Cannabis Products Are Available?

The history of *Cannabis sativa* use, along with the chemical makeup and signaling mechanisms, has been well described [8••]. The category of chemicals most relevant to therapeutic use of cannabis is the cannabinoids. THC and cannabidiol (CBD) are the most studied; however, many other cannabinoids and compounds (e.g., a variety of terpenes) have been identified in the plant and may have important pharmacologic properties. Fig. 2 categorizes products by THC/CBD ratios and general product types (e.g., prescription medications, extraction products, whole plant products) to help clinicians better understand patient options when considering using "cannabis."

Synthetic THC dronabinol (Marinol) and THC analog nabilone (Casamet) were approved by the U.S. Food and Drug Agency (FDA) for nausea and vomiting associated with cancer chemotherapy in 1985 and 2006, respectively [32, 33]. Dronabinol and nabilone are single chemical drugs containing no CBD. CBD is felt to have anti-inflammatory, anti-seizure, and anti-anxiolytic properties and helps compete with THC for CB1 and CB2 receptors to mitigate some of THC's intoxicating effects [34]. Perhaps due to their lack of CBD, dronabinol and nabilone are often tolerated poorly, and to date have not been adopted widely in treating patients with cancer. Nabiximols (Sativex) is produced through a cannabis extraction process that results in a product with roughly equal amounts of THC and CBD. While nabiximols has been extensively evaluated for a cancer pain approval, it is currently available only in Canada for this purpose. In June 2018, Epidiolex, a cannabis extraction product containing 99% CBD, was approved by the FDA for treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome [35].

As the cannabis industry grows, an increasing number of states are mandating that cannabis be extracted and/or formulated into products with defined amounts of THC and CBD. While ratios can vary significantly, they typically come as THC dominant (THC/CBD > 5:1), balanced (THC/CBD 1:1), or CBD dominant (CBD/THC > 10:1). The most common routes of administration include oral (pills and liquids/oils), inhalational (vaporized oil), and topical (creams or gels). As an example, the many different products currently available from the two licensed cannabis manufacturers in the Minnesota Medical Cannabis Program are easily found online [36, 37]. Other states have similar programs and products.

Whole-plant products likely remain the most commonly used form of cannabis, especially in states where cannabis has been legalized for recreational use. In these forms, amounts and ratios of THC and CBD are often unknown or unreliable. Different strains (including percentage of THC) of the *Cannabis sativa* plant, along with differences in bioavailability, account for the potency of a single joint [38]. As such, calculating the exact amount (and cost) of THC in a single joint is challenging (e.g., a 0.33-g joint that costs $3.50 and has 8% THC would equate to a THC dose of about 26 mg) [39]. Furthermore, there has been an explosion of use of hemp/CBD-only oils [40, 41]. Hemp is defined as *Cannabis sativa* with < 0.3% THC. While the legality of CBD-only oils continues to be discussed, various products are now sold over the counter, both online and in stores, throughout the country without the need for a prescription/certification. As an unregulated product, both the marketing claims and the chemical composition of these products remain questionable [42, 43].

Cost for the various cannabis products is often hard to calculate and compare. Estimates are provided in Fig. 2 based on costs per milligram of THC and/or CBD. Regardless of the possible benefit, the costs for extraction products and whole-plant products remain largely a patient responsibility because insurance does not cover these expenses. Yearly costs for regular cannabis users can exceed $3000 [44], and a year's supply of Epidiolex is estimated to be more than $30,000 [45].

Cannabis Efficacy

Do Previous Studies Show That Cannabis Can Improve Symptoms?

While cannabis has been used by humans for centuries, research into its palliative effects specifically for cancer patients started in the 1970s [4, 46]. Early researchers investigated its analgesic potential, finding that it could manage pain without significant side effects when administered at low doses [47, 48]. However, before our current era of excellent antiemetics, most work focused on cannabis' ability to manage nausea and vomiting. A foundational paper by Sallan et al. found that THC was better than placebo at eliminating chemotherapy-induced nausea and vomiting [49]. Still, not all studies have found cannabis to be beneficial; in one study, patients preferred the side effects from chemotherapy to those from cannabis [50].

Table 1 Studies assessing the impact of cannabis in patients with cancer since 2000

Symptom	Year	First author	Type of study	No. of patients	Product	Results and takeaways
Pain	2010	Johnson [9]	Double-blind RCT	177	THC:CBD vs. THC vs. Placebo	"This study shows that THC:CBD extract is efficacious for relief of pain in patients with advanced cancer pain not fully relieved by strong opioids." The THC extract alone did not significantly reduce pain. Patients were permitted to self-titrate during week 1 of treatment. Memory and concentration were significantly better in placebo group. Opioid dosing did not change from baseline in three groups. Treatment lasted only 2 weeks, limiting understanding of long-term effectiveness
	2012	Portenoy [10]	Double-blind RCT	360	Nabiximols (at 3 doses) vs. placebo	"Overall, the study supports the conclusion that nabiximols has analgesic efficacy when used as add-on therapy in a population of cancer patients with pain that is poorly responsive to opioids." Sleep was also improved in the low- and medium-dose groups, albeit via a non-validated measure. Patients were allowed to titrate but had to remain within dosing range for their cohort. Only 66% of the high-dose group continued on the study. Adverse events were comparable with placebo in the low- and medium-dose groups. Physicians were encouraged to keep opioid dosing constant, preventing analysis of any opioid-sparing effect
	2013	Johnson [11]	Open-label continuation	43	THC:CBD and THCc	"Long-term use of THC/CBD spray was generally well tolerated, with no evidence of a loss of effect [of pain relief] with long-term use. Furthermore, patients who kept using the study medication did not seek to increase their dose of this or other pain-relieving medication over time, suggesting that the adjuvant use of cannabinoids in cancer-related pain could provide useful benefit." Extension of Johnson et al. (2010). Patients could self-titrate to optimal dose, unlike previous trial. Authors warn that conclusions should be drawn carefully due to the open-nature aspect of trial and high death rate (13 patients)
	2014	Lynch [12]	Double-blind crossover trial	16	Nabiximols vs. Placebo	"In conclusion, this pilot trial supports that it will be worthwhile to study nabiximols in a full randomized controlled trial of chemotherapy-induced neuropathic pain." While there was no significant difference in pain when analyzing entire group, five patients experienced a clinically significant decrease in pain. In addition, there were no serious adverse events. Patients allowed to self-titrate dosing. Relatively small sample size decreases impact
	2017	Fallon [13]	Double-blind RCT	Study 1: 399 Study 2: 216	Nabiximols vs. placebo	"While Sativex did not demonstrate superiority to placebo in reducing self-reported average pain on the Numeric Rating Scale (NRS), […] Sativex treatment was numerically better than placebo in US patients, especially in those younger than 65, for average pain NRS score." Patients were allowed to self-titrate. Study 2 initially had 540 patients, who self-titrated nabiximols over 2 weeks. Only those obtaining $\geq 15\%$ improvement in pain were randomly assigned ($n = 216$). The benefit observed in the US cohort was potentially ascribed to a lower opioid dose, allowing increased synergy between cannabinoid and opioid receptors. Stable dosing of other pain medications prevents analysis of opioid sparing. Study also limited by daily fluctuations in NRSs

Table 1 (continued)

Symptom	Year	First author	Type of study	No. of patients	Product	Results and takeaways
	2017	Lichtman [14]	Double-blind RCT	397	Nabiximols	"In conclusion, this Phase 3, randomized placebo-controlled study in advanced cancer patients with chronic uncontrolled pain did not find a positive treatment effect for nabiximols compared to placebo on the primary endpoint (percent change in the average pain NRS score)." Study design is nearly identical to study 1 in Fallon et al. 2017 paper
Nausea/vomiting	2006	Zutt [15]	Open-label	7	Dronabinol	"Loss of appetite and nausea due to liver metastases of malignant melanoma can be treated in individual cases supportively with Dronabinol." All patients experienced dizziness but not enough to stop drug. Small number on trial negatively affects impact of trial. Originally published in German with an English abstract
	2007	Meiri [16]	Double-blind RCT	64	Dronabinol vs. ondansetron vs. combination vs. placebo	"Dronabinol or ondansetron was similarly effective for the treatment of chemotherapy-induced nausea and vomiting. Combination therapy [..] was not more effective than either agent alone. Active treatments were well tolerated." Flexible dosing of dronabinol was allowed after fixed doses on day 1 and day 2 and had a median dosage of 20 mg/day during flexible period. Trial lasted only 5 days, limiting results on long-term effectiveness
	2010	Duran [17]	Double-blind RCT	16	Whole-plant cannabis (THC and CBD) + SOC vs. placebo + SOC	"Compared with placebo, CBM added to standard antiemetic therapy was well tolerated and provided better protection against delayed [chemotherapy-induced nausea and vomiting]." Patients were allowed to increase dosing over a short time period. More adverse events were reported in the cannabis group, but they were not serious. Again, sample size is limiting
Anorexia/cachexia	2002	Jatoi [18]	Double-blind RCT	469	Megestrol acetate vs. dronabinol vs. combination	"Megestrol acetate is superior to dronabinol in the treatment of cancer-associated anorexia, and the addition of dronabinol […] does not confer additional benefit." Megestrol acetate and dronabinol also did not differ significantly with respect to managing nausea and vomiting. Of note, dosing was relatively low (2.5 mg twice daily) and was not titrated up or down to patient preference
	2005	Walsh [19]	Open-label continuation	6	Dronabinol	"Dronabinol is another therapeutic option for cancer anorexia, and titration should be done to subjective patient benefit as is customary with megestrol acetate." Of the six patients, five reported stable or improved symptom management for all subjective measures (appetite, intake, feel, and energy). As a case study, the conclusions are weaker than those of RCTs
Global symptoms	2006	Strasser [20]	Double-blind RCT	243	Cannabis extract (THC and cannabidiol) vs. THC vs. placebo	"No differences in patients' appetite or QOL were found either between CE, THC, and PL or between CE and THC at the dosages investigated." Compared with placebo, cannabis extract had a higher hazard ratio for adverse events. Study limited due to lack of dose escalation and 6-week treatment period. Also, only 164 (67%) completed the entire study
	2008	Maida [21]	Observational case study	112	Nabilone	"This study demonstrated that patients who used nabilone enjoyed significantly improved management of pain, nausea, total distress, and anxiety when compared with untreated patients. Nabilone use also was associated with lower overall

Table 1 (continued)

Symptom	Year	First author	Type of study	No. of patients	Product	Results and takeaways
						use of drugs such as opioids" and other drugs. This study is limited by the lack of blinding. In addition, baseline symptoms were significantly greater (other than shortness of breath) in the untreated group
	2011	Brisbois [22]	Double-blind RCT	46	THC vs. placebo	"Our pilot study demonstrates that THC, compared with placebo, improved and enhanced chemosensory perception, altered macronutrient preference, and improved appeal of savory foods, appetite, relaxation, and quality of sleep for advanced cancer patients with chemosensory alterations." Of note, patients were allowed to increase dosage of THC up to 20 mg/day. Twenty-one (46%) patients completed the study. Six patients in each arm were withdrawn due to serious adverse events, one possibly due to drug
	2013	Bar-Sela [23]	Interviews	211	Cannabis	"The positive effects of cannabis on various cancer-related symptoms are tempered by reliance on self-reporting for many of the variables. Although studies with a control group are missing, the improvement in symptoms should push the use of cannabis in palliative treatment of oncology patients." Patients with prolonged usage reported memory lessening. Because the study involved self-reporting, it is possible the effects were more psychological than physiological. Study lacked control group
	2016	Cote [24]	Double-blind RCT	56	Nabilone vs placebo	"At the dosage used, nabilone was not potent enough to improve patients' quality of life over placebo." However, dosage was determined to be tolerable with limited toxicity. Limited by large number of patients who quit (24, of which 9 were receiving nabilone) from an already small study
	2018	Bar-Lev Schleider [25]	Interviews and questionnaire	2970	Cannabis	"Cannabis as a palliative treatment for cancer patients seems to be a well-tolerated, effective, and safe option to help patients cope with the malignancy-related symptoms." About 70% of participants (compared with 20% at baseline) reported good quality of life after 6 months of cannabis. Lack of a control group is limiting, but impressive sample size. The time delay from ending a chemotherapy regimen may also explain the improved symptoms
	2018	Zhang [26]	Prospective cohort study	148	Cannabis	"Recreational use of *C sativa* potentially alleviates anxiety, depression, pain, and nausea and improves general well-being in patients with newly diagnosed [head and neck cancer]." Despite the findings that cannabis was very beneficial in this population, the study had severe limitations; namely, the users were recreational and were not randomly assigned to take cannabis. Second, QOL measures were assessed once at baseline, preventing the researchers from gaining a better understanding of cannabis' long-term effects
	2018	Anderson [27]	State-mandated survey data	1120	Cannabis	"Cancer patients enrolled in Minnesota's medical cannabis program showed significant reduction across all 8 symptoms assessed within 4 months of program participation. Medical cannabis was well-tolerated, and some patients attained clinically meaningful and lasting levels of improvement." This large survey adds further evidence to the variety of

Table 1 (continued)

Symptom	Year	First author	Type of study	No. of patients	Product	Results and takeaways
						symptoms that can be managed using medical cannabis, as well as the low prevalence of adverse events (10.5%) among patients. Like other survey-based studies, this paper is limited by response bias and the lack of control that is seen in a RCT
Antitumor	2006	Guzman [28]	Open-label study	9	THC	"[THC] inhibited tumor-cell proliferation in vitro and decreased tumor cell Ki67 immunostaining when administered to 2 patients" and exhibited a "fair safety profile." Due to the small sample size and lack of control group, the effect on overall survival is unknown. However, this study provides a base for further studies
	2011	Foroughi [29]	Case report	2	Inhaled cannabis	The report "documented 2 cases of spontaneous regression of residual pilocytic astrocytoma in the forniceal region and discussed the possible role of cannabis inhalation in promoting the regression." The report discusses other possibilities that affect the development and regression of tumors, such as lifestyle changes and hormonal changes. Rare tumors
	2013	Singh [30]	Case report	1	Cannabinoid resin extract	"Cannabinoid resin extract is used as an effective treatment for acute lymphoblastic leukemia with a positive Philadelphia chromosome mutation and indications of dose-dependent disease control. The clinical observation in this study revealed a rapid dose-dependent correlation." Implications severely limited due to sample size of 1. However, authors argue response is not spontaneous remission due to achievement of a dose-response curve
	2017	Twelves [31]	Part 1: Safety study Part 2: Double-blind RCT	Part 1: 6 Part 2: 20	Part 1: CBD: THC oro-mucosal spray adjunct to temozolomide Part 2: CBD: THC spray + temozolomide or placebo + temozolomide	"This randomized study provides preliminary evidence that 1:1 CBD/THC offers some efficacy in patients with recurrent glioblastoma multiforme when used as an adjunct to dose-intense temozolomide and confirms the safety and feasibility of individualized dosing." While the results are significant, the sample size limits its conclusiveness. The publication is also an abstract, limiting information on the study

Research into cannabis began to wane with the introduction of more powerful serotonin receptor antagonists such as ondansetron in the early 1990s [51]. This decline was further exacerbated by strict drug laws in the USA. While research into cannabis and synthetic cannabinoids has begun to increase once again as patients and providers look to alternatives for symptom management, it remains severely limited. In this comprehensive review of the literature, we found only 23 articles published since 2000 that examined cannabis in cancer patients for palliative or anti-cancer effects (Table 1). Only ten studies were double-blind randomized controlled trials (RCTs) (Table 1). However, with the expanding availability and use of cannabis in the past 5 years, a number of larger studies have begun to provide valuable insight into the potential palliative benefits of cannabis.

Nabiximols has been a heavy focus of cannabis research in cancer patients (Fig. 2). After initially publishing a double-blind RCT in 2010, Johnson et al. conducted an open-label continuation study with 43 patients looking at nabiximols and THC-only sprays [9, 11]. Key findings included the following: (1) Pain relief/control was deemed "adequate" by patients, (2) doses of nabiximols and other pain medications did not increase over time, and (3) while many investigators considered the pain relief inadequate, only 7% of participants withdrew due to a lack of efficacy. This trial points to the potential long-term benefit of adjuvant cannabis use in managing pain without developing a tolerance to opioid therapy.

In 2014, Lynch et al. compared nabiximols to placebo in a double-blind crossover trial [12]. While the trial found no significant difference in neuropathic pain between groups, five individuals found nabiximols to effectively relieve pain.

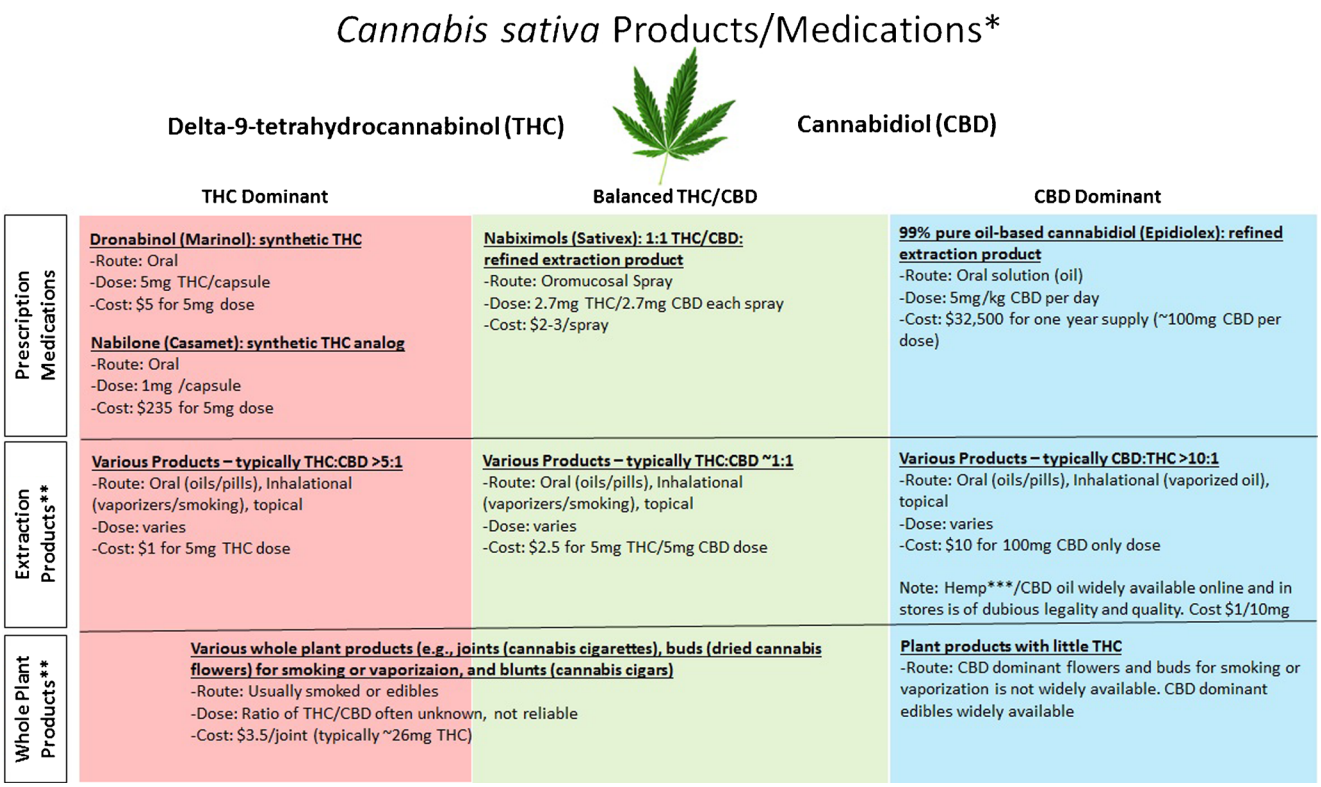

Fig. 2 Types of *Cannabis sativa* products/medications available. *Under prescription medications, nabiximols (Sativex) is not U.S. Food and Drug Administration-approved. It is available in Canada for cancer pain and multiple sclerosis. Costs estimated as of June 2018 using (a) retail pricing where available, (b) average pricing from Minnesota's medical cannabis companies, and (c) online sources. **Extraction products are commonly produced through state programs. Whole-plant products are available in state programs and on the open market ("street"). ***Hemp = *Cannabis sativa* with < 0.3% THC component

Fallon et al. also compared nabiximols to placebo, albeit with a much larger sample [13••]. This trial also showed that nabiximols did not decrease pain in the overall cohort. However, nabiximols was significantly better than placebo in certain subgroups, namely younger patients from the USA. The results of both trials perhaps point to the varying benefits of cannabis between individuals. Rather than serving as a panacea, it may only benefit certain patients.

Beyond nabiximols, Cote et al. analyzed the effects of nabilone versus placebo on overall quality of life (QOL) through a double-blind RCT [24•]. Fifty-six patients were consented; however, 24 patients dropped out. Unfortunately, this large dropout rate severely hampers any conclusions that can be drawn from this trial. Nonetheless, this trial showed that nabilone was tolerable and safe in this cohort of patients receiving treatment for head and neck cancers. Recently, Zhang and colleagues published a prospective, case-matched cohort study, also in head and neck cancer patients [26]. This study was also limited due to the nature of the trial: QOL measures were only taken once, at baseline, and did not track symptoms throughout the treatment course. Nonetheless, this trial found cannabis to relieve a wide variety of symptoms, including pain, depression, anxiety, and overall QOL.

Finally, interviews and questionnaires studying effects of cannabis on a variety of symptoms have generally shown cannabis to be extremely beneficial [23, 25••]. Bar-Sela found a wide applicability for cannabis, with improvement in nausea, vomiting, mood, fatigue, weight loss, and other symptoms of the cancer and its treatment [23]. Bar-Lev Schleider's study included 2970 patients who had received medical cannabis as part of their cancer therapy [25••]. Of the patients who remained in the study after 6 months and replied to the second survey, 95.9% found an improvement in their overall condition. Others have demonstrated that patients with cancer have clinically significant symptom improvement within 4 months of enrolling in a state-sponsored cannabis program [27]. Although selection bias with survey completion is likely, these studies suggest the potential palliative benefits of medical cannabis for cancer patients, as well as the need for further prospective randomized trials to better delineate the patient population and symptoms on which cannabis use may have the best impact.

Can Cannabis Help Treat the Cancer?

Despite anecdotal reports and extensive online websites/blogs claiming that cannabis has a significant antitumor effect, there

is little direct clinical evidence. Only two case reports have been published documenting a potential antitumor impact of cannabis (one in relapsed/refractory acute lymphoblastic leukemia and another in pilocytic astrocytomas) [29, 30].

Evidence of antitumor impact in patients is limited to two main studies, both in glioblastoma multiforme (GBM). In an often-cited study by Guzman et al., nine patients with recurrent and progressive GBM despite surgery and radiotherapy were treated with repeated intratumor dosing of THC [28]. Median survival of the group was 24 weeks, with two patients living nearly 1 year. In addition, three of nine (33%) of patients had clinical and/or radiographic improvement, with two of these patients showing decreased tumor-cell proliferation on repeat biopsies. Taken together, this study demonstrated that THC injected into tumors may affect tumor growth and clinical outcomes. Because patients did not consume cannabis products directly, one cannot assume that more typical use of cannabis would lead to similar outcomes.

A randomized, placebo-controlled study in patients with recurrent GBM using nabiximols in combination with temozolomide has been completed, with results available only in abstract [31]. In this study, patients receiving nabiximols/temozolomide ($n = 12$) vs temozolomide alone ($n = 9$) had improved 6-month progression-free survival (42% vs 33%), longer median survival (> 550 days vs 369 days), and higher 1-year survival rates (83% vs 56%). Dosing and safety data were limited. While the small sample size and lack of final results limit this study, it may show further evidence of a possible anti-tumor impact of cannabis in GBM.

Additional clinical data on cannabis' impact on tumor growth is otherwise lacking. We thoroughly reviewed previous clinical studies for any mention of tumor response or survival rates (Table 1). In addition, a review of all abstracts from the past 3 years of the International Cannabis Research Society's annual meetings did not reveal additional studies.

Even though robust clinical data are lacking, the role of the endocannabinoid system and the complex signaling pathways involved with cannabis use have been better delineated [52]. Most data that suggest a possible antitumor effect comes from in vitro and animal studies. Pioneering studies began in 1975, when Munson et al. demonstrated that oral administration of THC in mice with lung adenocarcinoma resulted in reduced tumor size and longer survival [53]. Subsequent in vitro and animal studies were nicely reviewed by Wilkie et al. [4].

In summary, while in vitro and animal data suggest a possible antitumor impact of cannabis, only two small studies in patients with relapsed GBM demonstrate a possible role. Donald Abrams, MD (an oncologist and expert on cannabis research), summarized things nicely in his 2015 review by stating, "there have not been any robust human studies investigating cannabis as an anticancer agent that would warrant advising patients to forego conventional therapy in favor of using a high-potency cannabis extract," but added the caveat that, "the addition of cannabinoid-based preparations to standard cancer therapy should not be discouraged by the treating oncologist" [54].

Cannabis Safety

What Are the Risks of Using Cannabis?

As with most medications, cannabis is not risk-free. However, adverse events recorded in the cancer population in studies were relatively mild and dose-dependent. In the nabiximols studies, the most common adverse events were dizziness, dry mouth, nausea/vomiting, somnolence, and confusion [55]. The authors acknowledge that other clinical studies have recorded similar adverse events, and it is possible that the study medication is the cause. Numerous studies have also pointed to the dose-related incidence of adverse events: Higher doses of cannabis often have greater frequency and intensity of adverse events [10, 47].

In addition, studies have found some cognitive side effects for cannabis users. Namely, Johnson et al. found that memory and concentration scores deteriorated in individuals receiving nabiximols, while they improved in the placebo group [11]. In their observational study of cannabis in cancer patients, Bar Sela et al. also found a significant worsening of memory in patients with extended usage [23].

Beyond adverse events in studies for cancer patients, other effects have been studied and documented in the general population. Recently, the National Academies of Sciences, Engineering, and Medicine comprehensively outlined many of these risks [8••]. Namely, they found substantial evidence of an increased risk of crashes in motor vehicles, lower offspring birth weight, development of schizophrenia and other psychoses, and worsening of respiratory symptoms. They found moderate evidence of an increased risk for overdose injuries and impaired cognition. Finally, they found limited evidence of an increase in risk of non-seminoma-type testicular germ cell tumors, acute myocardial infarction, chronic obstructive pulmonary disease, pregnancy complications, and a decrease in production of healthy cytokines. Many other symptoms and disorders, such as lung cancer, were found to have no statistically significant association with cannabis usage. Precautions and contraindications associated with cannabis have been outlined and include age younger than 25, pregnancy, schizophrenia, a compromised cardiac state, and a history of substance abuse [56]. In addition, the review addressed the association with hypotension as well as precautions against the use of strong CYP3A4 inhibitors, sedatives, and hypnotics.

With further research into the potential benefits of cannabis usage for cancer patients will come a further understanding of the risks. However, the risks currently seem relatively low in

comparison with many medications commonly prescribed to patients with cancer (e.g., chemotherapy, opioids, benzodiazepines). In patients with metastatic, incurable cancer who have an already high symptom burden from their disease and/or treatments, some cannabis side effects may be of less concern and, in aggregate, the risk-benefit ratio may be perceived as tipping toward the latter.

Is Cannabis Safe to Use with Opioids?

Currently, opioids remain the mainstay in the treatment of cancer-related pain. While their usage in the cancer population remains warranted, opioids have become part of a national conversation due to the epidemic they have caused. In 2016, it was estimated that 116 Americans died daily due to opioid-related overdoses, resulting in more than 40,000 deaths [57]. The impact of the opioid epidemic has become so large that the average life expectancy in the USA has dropped. Policymakers, healthcare providers, researchers, and the general public are actively seeking alternatives, and cannabis is often named as a potential one.

In animal models, studies have found that opioids and cannabis potentially have a synergistic effect, resulting in improved pain management when used together [11, 58]. Studies in cancer patients are less conclusive, but many find that cannabis use in these patients lowers opioid usage, even if results were not statistically significant [9, 13••].

On a larger scale, a recently published analysis of prescribing in the Medicare Part D population showed that states that have legalized and regulated medical cannabis have significant reductions in opioid prescriptions [59•]. The reduction was larger in states with medical cannabis dispensaries than in states that only allowed home cultivation. Another publication found that these states not only had lower opioid prescriptions but also lower opioid overdose mortalities [60]. Among patients enrolled in the Minnesota Medical Cannabis Program for pain, 64% of patients on opioid medications at the onset of cannabis use were able to eliminate or reduce dosage of these medications within 6 months [61]. Although cannabis may not effectively manage symptoms for all cancer patients, its ability to lower opioid usage in a safe manner should be encouraging for patients and physicians alike.

Conclusion

Patient Update

The patient was certified by his treating oncologist in his state's medical cannabis program. He began a regimen using 10 mg of THC-dominant oral capsules each night, which helped his insomnia. He found benefits for pain and nausea using a 5mg THC/5mg CBD balanced solution four times a day as needed. His opioid requirements dropped by 50%, and his constipation improved. Overall, he felt that his QOL improved, and he was able to continue his chemotherapy regimen without dose reductions.

As the number of states legalizing cannabis for medical and recreational use continues to grow, oncologists will be increasingly asked about the merits of cannabis. Through this review, we hope oncologists and other care providers will be better informed to have a thorough discussion with patients regarding cannabis for availability, efficacy, and safety. The National Cancer Institute has a high-quality website of updated information that can help clinicians stay informed [62••]. Despite clinical studies to date, large gaps in knowledge remain. Further prospective clinical trials are needed to provide clinicians the data needed to determine when and where cannabis may best help their patients.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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