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Cannabis and the Cancer Patient

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Abstract

Session 2 of the National Cancer Institute's Cannabis, Cannabinoids, and Cancer Research Workshop opened with testimony from a lymphoma survivor who detailed medicinal cannabis-related improvements in nausea, low appetite, insomnia, and mental health and the limited clinical counsel she received regarding cannabis use. Discussion next turned to the evolution of the legal landscape of cannabis in the United States, one in which state and federal laws frequently conflict and the Controlled Substance Act renders cannabis Schedule I. This legal climate creates conundrums for US medicinal cannabis researchers who contend with limited funding opportunities, avenues to source trial drug, and procedural red tape and for oncology clinicians who recommend medicinal cannabis to patients with some frequency while perceiving themselves as ill equipped to make such clinical recommendations. Ultimately, it creates challenges for cancer patients who find themselves turning to nonmedical and anecdotal information sources. The risks of cannabis use by the cancer patient were discussed next. These include infection, pharmacodynamic and pharmacokinetic drug-botanical interactions, cyclic nausea and vomiting, e-cigarette or vaping product use–associated illness, legal issues, and high cost. The session concluded with a broad survey of the research supporting oncologic cannabinoid use, conclusive evidence for chemotherapy-induced nausea and vomiting, and suggestive evidence for cancer-related pain.

Between December 15 and 20, 2020, the National Cancer Institute (NCI) held a first-ever 4-day conference on the role cannabis and cannabinoids play in oncology care. The Trans-National Institutes of Health Cannabis, Cannabinoids and Cancer Research Symposium offered as its second session "Cannabis and the Cancer Patient," cochaired by Andrew Freedman, chief of the Clinical and Translational Epidemiology Branch of NCI's Epidemiology and Genomic Research Program, and Ilana Braun, MD, assistant professor of psychiatry at Harvard Medical School and chief of the Division of Adult Psychosocial Oncology at the Dana Farber Cancer Institute. The session also included Stacey Blansky, a recent Cornell University graduate and cancer survivor; Steven Pergam, MD, MPH, associate professor of medicine at the University of Washington School of Medicine and Fred Hutchinson Cancer Research Center as well as medical director of infection prevention at Seattle Cancer Care Alliance; and Donald Abrams, MD, professor emeritus of medicine at University California San Francisco and an oncologist at both Zuckerberg San Francisco General Hospital and the University California San Francisco Osher Center for Integrative Medicine. The session provided an introduction to topics covered in greater depth later in the conference program. This article summarizes the session and offers some potential future directions.

A Cancer Survivor's Experience

The "Cannabis and the Cancer Patient" session opened with eloquent testimony from Stacey Blansky, a recent Cornell

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University graduate and stage IV Hodgkin's lymphoma survivor who had used medicinal cannabis to manage an array of cancer-related symptoms. She was initially drawn to medicinal cannabis because she viewed it as "natural" and holistic as well as a means of shifting locus of symptom control away from the medical community and toward herself. She recounted the limited clinical counsel she received regarding her decision to use medicinal cannabis; her oncologist was not well versed in cannabis literature and could not say with confidence whether the drug would aid in managing her side effects. In fact, she was referred to a separate oncologist within the practice for formal approval to receive medical cannabis. Ms Blansky described the personnel at the New York medicinal cannabis dispensary she frequented as professional and helpful. She presented a constellation of target symptoms to a dispensary pharmacist (New York law requires that pharmacists staff medicinal cannabis dispensaries), who guided her toward products with particular ratios of active ingredients and modes of use (eg, a cannabidiol [CBD]-based oil and a delta-9-tetrahydrocannabinol [THC]–predominant vaping pen). Ms Blansky's target symptoms included nausea, poor appetite, insomnia, and mental health concerns such as anxiety and dysphoria. In addition to the positives, Ms Blansky described the negatives of using medicinal cannabis. These included a measure of stigma in her medical and personal lives. She detailed awkward conversations with physicians in which she worked to convince them that her desire for medicinal cannabis was legitimately health related and not for diversion to friends on her college campus. She discussed having conversations with campus administrators about how she might use cannabis in her smoke- and vape-free dormitory without violating university regulations. She also discussed the considerable out-of-pocket expense (eg, $150 for a 30-mL bottle of CBD and $80 for a vaping pen with cartridge). She reported that, now in remission, she is no longer authorized by her medical team to use medicinal cannabis despite continuation of poor appetite. Ms Blansky reported that this barring was ultimately "fine because cannabis isn't the be-all-and-end-all answer to all issues … [I] was using it for 6 months just to deal with a lot of really horrible side effects of chemotherapy." That said, her goal in presenting to the NCI conference was to change the narrative and unwind preconceived notions among the medical community and conference audience of using medicinal cannabis.

United States' Legal Landscape for Medicinal Cannabis: Research and Clinical Implications

Dr Ilana Braun described the United States as amid a legal sea change regarding cannabis law, leading federal and state laws to frequently conflict. The degree of enforcement of the federal prohibition has varied by administration. These fluctuations, as well as the divide between state and federal law, has affected medicinal cannabis clinical care and research, leaving medicinal cannabis at times a conundrum for patients, caregivers, clinicians, and researchers. Clinicians, then, should routinely ask their patients about medicinal cannabis in order to guide care in this domain (1).

Cannabis' legal history in the United States is marked by 2 key inflection points (2–5). Until the early decades of the 20th century, state and federal laws agreed in their permissive stance toward medicinal cannabis, and the botanical existed in patented formulas for analgesics and other remedies.[2] Fueled in part by xenophobic sentiments (eg, the term "marijuana" has entered the lexicon, linking cannabis to Mexican immigrants) as well as by the timber interest (eg, hemp was a competitor to wood in paper manufacturing), several states began to restrict or ban cannabis use (6). Harry Jacob Anslinger, the first Federal Bureau of Narcotics chief, and newspaper publisher William Randolph Hearst launched a media campaign racializing cannabis and linking its use with criminality and insanity. In 1937, the Marihuana Tax Act was proposed and passed. Of note, the American Medical Association lobbied against the tax and advocated for greater cannabis research; the act passed nonetheless (2). Global interest in cannabinoid research persisted and, in response, the United States appointed the University of Mississippi the official grower of cannabis for research purposes in 1968; it remains so to this day. In 1970, Richard Nixon signed the Controlled Substance Act into existence. This act assigned cannabis a Schedule I designation, indicating that the botanical was not acceptable for medical use, lacked a safety profile acceptable for medicinal use even under medical supervision, and possessed a high abuse potential (7). The same act rendered cocaine Schedule II, so classified cannabis is more dangerous than cocaine (7).

State Initiatives to Legalize Cannabis

Another inflection point occurred in the mid-1990s when, spurred by a ballot initiative, California became the first state to legalize medicinal cannabis, and many states gradually followed suit (2–5). In 2004, in a fight between federal and state's rights, the United States Supreme Court ruled that the federal government could prosecute patients abiding by their state medicinal cannabis laws, indicating that medicinal cannabis users were not completely shielded from federal legal exposure (5). By 2012, there were about 12 medicinal cannabis laws on state books. In that year, Colorado and Washington became the first 2 states to approve adult-use (ie, recreational) cannabis laws (5). Under the Obama administration, 2 important developments occurred: first, the US Department of Justice (DOJ) issued a memo in which the DOJ was prohibited from using its funds to intervene in the implementation of state cannabis laws (5). Under the Trump administration, by contrast, the DOJ took a harder line toward cannabis, blocking more than 24 requests to grow cannabis alongside the University of Mississippi for research purposes (8). Between 2018 and 2019, the first herbal cannabinoid was approved by the US Federal Drug Administration (FDA) and, in this context, rescheduled from Schedule I to V, which the FDA would ultimately deschedule, allowing it to stock pharmacy shelves. Legislation commonly referred to as the "Farm Bill" legalized cannabis high in CBD and low in THC (ie, hemp) (5). Although hemp and hemp-derived products are now legal, many federal, state, and local regulatory uncertainties continue.

As of the 2020 election cycle, 36 states in the United States have comprehensive medical cannabis laws on their books, and 15 of those states have in parallel adult-use cannabis laws (5). The District of Columbia has both such laws as well (5). Eleven additional states have more limited forms of medicinal cannabis legislation (5). Typically, these more restrictive laws allow for products high in CBD and low in THC. Currently, there are only 3 states in the United States that have no public access to nonpharmaceutical cannabinoids (5).

Changes to federal law may be imminent, as then-US Senator from California Kamala Harris and Jerrold Nadler, Congressman from New York's 10th District, proposed the Marijuana Opportunity, Reinvestment, and Expungement Bill (9,

10). This act promises to decriminalize cannabis, expunge prior cannabis convictions from the record, and impose a 5% federal tax on cannabis sales, with revenue directed toward communities most affected by the war on drugs. As Vice President, Kamala Harris has been vocal that the Biden administration aims to decriminalize cannabis use.

State Medical Cannabis Laws

The 36 state comprehensive medicinal cannabis laws are defined by key features. These laws protect the user from state criminal penalties (9). They enable access to medicinal cannabis (eg, through dispensary systems or home cultivation) (9). They allow for a variety of products to be sold or used and for a variety of modes of administration, including smoking or vaping using an electronic device (9).

Most importantly, they ensure that medicinal cannabis is available to the general public (ie, not just through a pilot program) (9). Comprehensive medicinal cannabis laws are generally structured to identify medical conditions that qualify for cannabis (9). They tend to allow health-care providers to issue formal recommendations that medicinal cannabis be used but not write actual prescriptions. This unique procedure has been put in place to protect health professionals from federal legal exposure.

Comprehensive medicinal cannabis laws often stipulate permissible possession amounts, and these vary dramatically from state to state (11). The laws tend to establish state registries and the issuance of identification cards (9). The health conditions that qualify for medicinal cannabis vary substantially from state to state, with the exception of HIV/AIDS and cancer, which exist in almost every state law (11). This commonality is one of the reasons that a medicinal cannabis conference is so important in the oncology realm.

Medicinal cannabis dispensaries vary in nature from state to state (11). In general, they are not obligated to offer pharmaceutical-grade products. They are regulated in many ways, but important aspects such as the potency of the products they offer may not be regulated. In most states, medicinal cannabis dispensaries are mainly staffed by nonmedical personnel who advise patients on topics such as dosing and delivery method.

In many states, several differences between a traditional prescription and a typical medicinal cannabis recommendation exist. In the case of a traditional prescription, a health-care provider stipulates the active ingredient(s). By contrast, with a medicinal cannabis recommendation, a health-care provider does not usually specify active ingredient(s) in the same manner because most medicinal cannabis products are not comprised of 1 active ingredient but hundreds that operate through complicated inhibitory and synergistic interactions (12). Further, medicinal cannabis recommendations do not always specify route, dose, and frequency of use–decisions that may ultimately be made at the dispensary counter or that patients might determine through personal experimentation.

Research and Clinical Implications of the US Legal Landscape

The Schedule I designation carries important research and clinical implications. In the research domain, this designation leads to challenges in accessing federal funding to carry out the research, being able to source the study drug, and negotiating red tape. It leads cannabis researchers to assume a degree of personal, criminal, and financial liability in carrying out such research. In the clinical realm, clinicians sometimes assume a contradictory stance toward medicinal cannabis. On one hand, health-care professionals recommend the agents to their patients, with greater than 2% of the population in several states holding medicinal cannabis licenses (13). On the other hand, most professional medical associations offer little clinical guidance around medicinal cannabis (14). Most medical practice infrastructure ignores the reality of medicinal cannabis (14). For instance, the Epic electronic medical record system (which has dominant share in the United States) does not offer a convenient way for medicinal cannabis to be added to a patient's medication list (14). Some clinicians who recommend medicinal cannabis to their patients acknowledge that they do not understand the agent well enough to make the recommendations they are making, and research has also shown that some patients who use medicinal cannabis perceive a lack of clinical oversight for their use.

A large patient survey in a comprehensive cancer center in the state of Washington demonstrated that of 25% of those surveyed had used cannabis in the past year, mainly targeting physical and neuropsychiatric symptoms. Seventy-four percent had hoped to receive cannabis-related information and education from their health-care providers whereas only 12% had (15). A nationally representative sample of 400 medical oncologists found that 80% discussed medicinal cannabis with patients in the clinic (16). Almost one-half recommended use of medicinal cannabis for their patients in the clinic; however, less than 30% felt knowledgeable enough to make recommendations around medicinal cannabis. The research team's most curious finding was that more than one-half of those who made clinical recommendations fell into the group who did not feel knowledgeable enough to make them. To better understand what might be transpiring in the clinic, this research team went on to conduct qualitative interviews with oncology patients across the United States using cannabis in compliance with their state laws (n = 24) (1). They found that most participants received certification to use medicinal cannabis from a provider new to their care (Ms Blansky recounted a similar experience), typically through a brief transactional encounter. Every participant interviewed disclosed cannabis to their medical team but tended to report that the medical team offered considerably little clinical guidance regarding medicinal cannabis use (similar to Ms Blansky's experience). Left to their own devices, patients relied on personal experimentation and commercial information sources. The team found that most in the sample used medicinal cannabis for symptom management. However, more than one-half used medicinal cannabis as cancer-directed therapy, not infrequently, in lieu of standard treatments. One participant in the study summarized their experience, saying "Most doctors when you mention cannabis, they shut right up, they don't say 2 words to you, they don't give you an opinion."

Risks of Cannabis Use for the Cancer Patient

Steven Pergam, MD, MPH, highlighted that cancer patients often have extensive medication lists and comorbidities and,

depending on disease and treatment, may be highly immunosuppressed. The wide spectrum of modern cancer therapies, which includes novel chemotherapy agents, biologics, and complex treatments such as hematopoietic cell transplantation and immunotherapy, makes evaluating risks of cannabis more difficult in those with cancer. Side effects and/or adverse events that occur with ongoing cancer treatment make determining causality of cannabis and cannabis product complications more difficult. Despite such challenges, the potential benefits of cannabis must be weighed in context with known and potential risks within these patient populations. Dr Pergam discussed data on infections, neuropsychiatric complications, drug interactions, direct side effects, legal risks, and financial implications of use among cancer patients.

Infectious Risks of Cannabis in Cancer Patients

A survey among cancer providers asked, "What is your biggest concern about recommending cannabis to your patients?" Sixty-two percent stated infection risk (17). The most common infections possibly linked to cannabis are invasive molds, which, among patients with hematologic malignancies and patients undergoing hematopoietic cell transplantation, are associated with statistically significant morbidity and mortality (17). Ubiquitous molds, such as Aspergillus species, are common opportunistic pathogens among patients with prolonged neutropenia, viral infections, those receiving high-dose steroids and/or small molecule kinase inhibitors, and other risk factors (18–20). Purported links between cannabis and molds spur from data that demonstrate high levels of fungal contamination on cannabis samples. A study in the Netherlands found that 100% of informally sourced cannabis samples and 64% of commercial cannabis cigarettes were contaminated (21). In another study, 73% of cannabis cigarettes from 26 chronic users were noted to grow Aspergillus, and spores easily passed into air samplers during the smoking process (22). The researchers found 52% of patients in that study had Aspergillus precipitins in their blood compared with only 10% of controls, suggesting high-level exposure. Similarly, 3 types of street cannabis and cannabis grown in government laboratories were positive for Aspergillus spp. (23). In addition, other clinically important fungal pathogens, including highly pathogenic Mucorales spp., have also been described (24).

A study evaluating a large commercially insured population has also linked cannabis use to fungal infections. Using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes, patients diagnosed with fungal infections, with and without concomitant reported cannabis use, were compared. Specific subgroups assessment was limited, but the odds ratio for fungal infection in cannabis users was 3.5 when adjusted for patient age and immunosuppression (25). Persons who used cannabis and had fungal infections were more likely to be older and immunocompromised than those using cannabis without fungal infections. Although this study provides a large overview, the limited data granularity make specific links between cancer, cannabis, and fungal infection more difficult to assess. To date, data causally linking cannabis use to invasive fungal infections among cancer patients remain limited and ripe for research.

An important theoretical concern for cannabis use among cancer patients is emergence of Aspergillus resistance to common azole antifungal therapies, which are often used for prevention and treatment of invasive mold infections among high-risk hematologic malignancy patients. Azole antifungals inhibit fungal cell walls (ie, ergosterol biosynthesis) through interference with the activity of 14-α-lanosterol demethylase, which the cyp51A and cyp51B genes encode. Most resistance to date is linked to genetic changes to cyp51A, which can decrease effectiveness of these agents in treating disease; other resistance mechanisms have been documented (26–28). Data primarily from Denmark and Germany have linked the development of azole-resistant Aspergillus spp. due to the use of azoles in agriculture (29). Although associations between resistant fungi and antifungal use are linked to other agricultural products, studies suggest that there is also evidence for azole use in the cultivation of cannabis. In 1 study, 50 illegal cannabis samples taken from community sources were tested for pesticides and herbicides.

Agricultural azoles, tebuconazole, and propiconazole as well as other antifungal agents were all detected (30). In Belgium's illicit cannabis industry, similarly, antifungal agents, including azoles, propiconazole, and tebuconazole, were found in cannabis samples (31). Although some states regulate pesticides, herbicides, and fungicides used in the cannabis industry (eg, Washington, California), illicit dealers or home growers may not follow similar regulations, leading to a potential risk of exposure to azole-resistant fungal pathogens. As of this publication, there are no direct links to cannabis use and azole-resistant fungal infections among cancer patients; however, the detection of agricultural azoles in cannabis samples suggests a potential for emerging resistance and indicates a need for monitoring, reporting, and regulatory control.

Other organisms, particularly bacterial pathogens such as *Klebsiella pneumoniae* and *Enterobacter cloacae*, have been cultured from cannabis (32). Although associations between bacteria on cannabis preparations and infections such as pneumonia are limited, there have been potential outbreaks linked to cannabis described in the literature (33). In addition, anatomic changes to the airway with smoking (eg, decreased function of alveolar macrophages and injury to respiratory cilia) may increase risk for infection, particularly pneumonia (34, 35). In fact, smoking cannabis has been linked to an increased risk of bacterial pneumonia in noncancer populations, presumptively due to such changes (36, 37). Finally, bacterial infections have been linked directly to smoking cannabis, which remains the primary mode of use among cancer patients (15).

One must also consider risk for infections with other modes of use (eg, consumption of edibles). With fungal infections, boiling alone is not sufficient to kill the organism. As one example, Rhizopus spp. grow best at 130°F, and other molds are known to be even more thermotolerant. It has been suggested that baking to at least 300°F for 15 minutes kills *Aspergillus conidia* (as well as any bacteria) but also destroys the THC component of cannabis (38). Due to the wide variety of edible options, both those made in the home and by the cannabis industry, understanding the risk of infection is difficult to assess and available data are limited.

Pharmacodynamic and Pharmacokinetic Drug–Drug Interactions

Pharmacodynamic Interactions. The neurologic effects of cannabis are thought to be some of the potential benefits to patients but must be considered carefully in cancer patients who are often already taking central nervous system depressants for pain, anxiety, or other symptoms. In particular, cannabis effects can be accentuated when combined with barbiturates, opioids, and

benzodiazepines (39). Such interactions may be more apt to occur with edibles, in which THC dosing can be unpredictable in some formulations, and overdose can lead to mental status changes (40, 41). Providers should ask about concomitant cannabis use when prescribing new neuropsychiatric agents. It is also important to caution cancer patients using cannabis (as one does with opioid and benzodiazepine uses) about risks for drowsiness, awareness, and ataxia while driving. More unpredictable, illegally sourced cannabis and cannabis products may be laced with other drugs such as phencyclidine (42). Providers should also be aware that some patients may use cannabis as an alternative to evidence-based pharmaceutical agents that target control of neuropsychiatric symptoms (eg, depression) (15).

Pharmacokinetic Interactions. Tetrahydrocannabinol and CBD undergo hepatic metabolism via cytochrome P450 and, as such, may interfere with other drugs using this metabolic pathway. Drug-to-drug interactions is another concern because cancer patients frequently take several prescription drugs whose therapeutic windows may be affected by cannabis use. For instance, cannabis may inhibit metabolism of the anticoagulant warfarin due to CYP2C9 interactions, resulting in increased plasma concentrations (43). Concurrent cannabis use may also affect the immunosuppressant tacrolimus (44). There are known cannabis–opioid drug–drug interactions (eg, bupronephrine) (45). Most concerning are potential interactions with cancer therapies such as nivolumab (46). Assuring cancer patients discuss use of cannabis products with their medical teams is important so such interactions can be addressed. This is particularly critical because patient patterns of cannabis use may be inconsistent during therapy (eg, outpatient vs inpatient), leading to potential risk of underdosing or overdosing active medications.

Other Cannabis Toxicities

Long-term cannabis users may experience cannabis hyperemesis syndrome, which is characterized by cyclic nausea vomiting that tends to be worse in the morning. The syndrome is increasingly recognized in emergency departments in states where cannabis is legal, but pathophysiologic mechanisms remain somewhat unclear (47). Symptoms can be improved by halting cannabis use, taking hot showers and baths, or applying topical capsaicin. Recent reports of an increased risk of severe pulmonary disease associated with vaping products, termed electronic cigarette vaping–associated lung injury, have been linked to nonlicensed cannabis products (48). Electronic cigarette vaping–associated lung injury may be more common in geographies in which cannabis consumers lack legal access to cannabis dispensaries (49). Although not directly related to the cancer patient, reports of children, pets, and other household members accessing edibles can also be a danger (50).

Legal, Employment, and Financial Consequences

Cancer patients should consider the legal ramifications of use in the context of their local jurisdiction, particularly when crossing state lines for treatment. Some workplace environments, such as the military, construction sites, and law enforcement, may require drug testing (51). As noted above, use of cannabis while operating motor vehicles, even if traveling to and from clinic, can place patients at risk for legal issues (52). Having these conversations up front, particularly in areas where cannabis is illegal on the state level, is critical to sidestep avoidable legal complications for patients.

Cancer care remains a major financial burden for patients. Copayments for pharmaceutical agents, limited coverage for care, and yearly deductibles can lead to financial challenges (52). Even in the setting of health insurance, cancer therapy exposes patients and families to statistically significant out-of-pocket health-care costs, and cancer and bankruptcy are unfortunately often linked (54, 55). Currently, regardless of whether they are acquired through formal medicinal cannabis programs or other means, cannabis products are not covered by insurance. All costs are therefore additional out-of-pocket expenses for patients using cannabis. Costs of cannabis can vary widely depending on availability. One ounce of high-quality cannabis in Seattle ranges from $170 for low quality to $234 for higher quality, and costs are nearly twice that in the District of Columbia (56). Excess costs at medicinal cannabis facilities can drive patients to illicit markets. For instance, in a Michigan study, patients were found to obtain cannabis more frequently from illegal community sources due to the high cost of medicinal cannabis distributors (57).

Benefits of Cannabis Use for the Cancer Patient

Individuals with cancer may be confronted with a constellation of symptoms that include nausea and vomiting, loss of appetite, pain, anxiety, depression, and insomnia. When used with the awareness of one's oncologic treatment team, medicinal cannabis may serve as a parsimonious intervention with potential to alleviate all those symptoms as opposed to the prescribing of multiple medications that may interact with each other or with the individual's systemic cancer therapy.

Chemotherapy-Induced Nausea and Vomiting

In the National Academy of Sciences, Engineering, and Medicine's review of the health effects of cannabis and cannabinoids, the strongest therapeutic evidence for cannabinoids in oncology patients pertained to adults with chemotherapy-induced nausea and vomiting.[12] Many clinical trials completed in the 1970s and 1980s with synthetic THC-based products (ie, dronabinol and nabilone) demonstrated that cannabinoids were more effective than available antiemetics at the time. Numerous meta-analyses published since reinforce this conclusion (58, 59). A Cochrane review from 2015 included 23 randomized controlled cannabinoid trials and concluded that cannabinoid-based medications are useful in treating refractory chemotherapy-induced nausea and vomiting as well (60). The 3 most recent meta-analyses and a systematic review of the systematic reviews, however, found the effects of cannabinoids in chemotherapy-induced nausea and vomiting to be less strongly positive; of note, however, they analyzed the same studies from the 1970s and 1980s but drew different conclusions (61–63).

Although THC derivatives have been approved for the chemotherapy-induced nausea and vomiting indication since 1986, controlled trials of whole-plant cannabis as an antiemetic are few. Due to barriers to studying the botanical itself, there are only 3 controlled trials of cannabis in chemotherapy-induced nausea and vomiting in the medical literature and, in 2, cannabis was only used after dronabinol (synthetic THC) had failed; hence, cannabis was only used for severe, refractory symptoms. The third is a randomized, double-blind crossover trial in 20 cancer patients, the results of which are difficult to interpret (58).

Nabiximols, a whole-plant cannabis extract with a 1:1 ratio of THC to CBD delivered as an oromucosal spray, was studied in addition to standard antiemetics in 16 patients with cancer. Compared with placebo, nabiximols was more effective as an antiemetic augmentation strategy (64). A recently published Australian study found that more patients preferred a 1:1 THC to CBD capsule added to a standard antiemetic, which proved more effective than placebo in reducing refractory chemotherapy-induced nausea and vomiting (65).

A study in the gastrointestinal literature not involving cancer patients asked 153 outpatients presenting for evaluation to rate 29 antiemetics on effectiveness. Cannabis scored higher than ondansetron and all other currently available antiemetics (66). The American Society of Clinical Oncology Expert Panel on Antiemetics recommended the FDA-approved cannabinoids be used only to treat nausea and vomiting resistant to standard antiemetic therapies. The panel concluded that "evidence remains insufficient to recommend marijuana in this setting" (67).

Appetite Stimulation

Regarding appetite, the endocannabinoid anandamide leads to a potent enhancement of appetite in low concentrations in mice. Cannabinoid receptors are implicated in food intake control. Knockout mice, genetically programmed not to have a CB1 receptor, tend to eat less than their wild-type littermates, suggesting that cannabinoid receptors are involved in the motivational aspects of eating.

The best available data regarding the effects of cannabinoids on appetite in patients with cancer comes from a trial of the THC derivative dronabinol 2.5 mg twice daily, compared with megestrol 800 mg daily or a combination of the 2 in 469 adults with cancer-associated anorexia. Dronabinol was inferior to the megestrol in increasing appetite and weight, and, when added in combination, dronabinol seemed to decrease the effect of megestrol (68). Although the investigators did not find strong evidence of appetite stimulation of the isolated cannabinoid, the whole-plant botanical may have a different effect. A smaller randomized controlled trial of dronabinol alone in cancer patients demonstrated enhanced chemosensory perception in the treatment group. Enrolled patients found that food looked better, appetite improved, and calories increased, but the patients did not increase weight during the study (69).

There have been 2 additional recent studies. The first was a randomized placebo-controlled trial in 47 patients with non-small cell lung cancer randomly assigned to receive nabilone or placebo. After 8 weeks, the nabilone patients increased their caloric intake; had a higher intake of carbohydrates compared with placebo; and reported statistically significant improvements in quality of life, emotional, and social functioning as well as improvements in pain and insomnia but no statistically significant increase in weight (70). Researchers in a small Israeli study also investigated capsules containing 9.5 mg of THC and 0.5 mg of CBD in patients with cancer over 6 months of treatment. Of the 17 patients who began the trial, only 11 remained on study at 6 weeks, and only 6 completed the 6 months. Of those 6 patients, 3 gained greater than 10% of their weight from baseline and 3 maintained stable weights. Study participants also reported improved appetite, mood, quality of life, and less pain and fatigue (71). In summary, cannabis-based medicines have not been demonstrated to be particularly effective in enhancing appetite in cancer patients. No studies have investigated whole-plant cannabis in this setting, however.

CBD has become a highly desired cannabinoid for the treatment of a wide variety of medical conditions and symptoms, often coupled with THC in products with varying ratios of the two. Because much available clinical data suggest that high dosages of CBD are required to achieve therapeutic effects, much commercially available CBD represents an underdosage. Patients with access to medicinal cannabis products often ask about the best ratio of THC to CBD to improve nausea and poor appetite. The answer remains unknown because there is little research investigating any other combination of THC to CBD other than 1:1 as in nabiximols, the whole-plant extract oromucosal spray. In the Netherlands, cannabis accessed from pharmacies is available in 2 high THC to CBD ratios and a third that is 6% THC and 7.5% CBD. Individuals using the lower THC preparation reported less appetite stimulation than those using higher THC preparations. Apparently, THC is most involved in modulating appetite (72). A large ReleafApp-based survey collected information from more than 3300 cannabis users, asking them to rate improvements across 27 measured symptoms on a 0-10 scale. The majority of the patients participating used the dried botanical flower, which was associated with greater symptom relief. Only higher THC levels were associated with greater symptom relief as well as the prevalence of positive and negative side effects. CBD potency levels were generally not associated with either symptom change or side effects (73). Hence, it would appear that THC may offer more therapeutic benefit for cancer-associated anorexia-cachexia, although no isolated cannabinoid has shown effectiveness. However, once again, it is important to emphasize that whole-plant cannabis has not been investigated.

Pain

Elevated levels of the CB1 receptor, like opioid receptors, are found in areas of the brain that modulate processing of noxious stimuli. CB1 and CB2 agonists also have peripheral analgesic actions, and cannabinoids may have antiinflammatory effects. Opioid antagonists do not block the analgesic effects of cannabinoids. The largest body of evidence supporting cannabis as an analgesic has been generated in patients with neuropathic pain, particularly HIV-related peripheral neuropathy (74). A small study in diabetic neuropathy was also positive.

Preclinical data suggest that cannabinoids are effective in treating and possibly preventing chemotherapy-induced peripheral neuropathy in rodents. There is only 1 chemotherapy-induced peripheral neuropathy study of a cannabis-based medication in the medical literature. Sixteen patients with chemotherapy-induced peripheral neuropathy were randomly assigned to nabiximols or placebo in a pilot crossover trial. There was no difference overall between nabiximols and placebo; however, the investigators completed a responder analysis of 5 patients who did report an average 2.6-point drop in pain on the 0-10 scale. The resulting number needed to treat (ie, 5) suggests further study is warranted (75). Two ongoing studies evaluating cannabinoids in patients with chemotherapy-induced peripheral neuropathy are currently listed in ClinicalTrials.gov.

Nabiximols, which is not licensed or approved in the United States, did not fare well in clinical trials of patients with non-neuropathic cancer pain. Six randomized controlled trials of nabiximols in cancer pain were identified for systematic review and 5 for meta-analysis. No difference between nabiximols and placebo for the difference in the change of average pain score

was appreciated. This finding remained when only the 3 phase 3 clinical trials were included in the analysis (76).

Preclinical models suggest cannabinoids may be synergistic with opioids in pain relief. Pharmacokinetic cannabinoid-opioid interactions were investigated in 11 patients on sustained-release morphine and 10 on sustained-release oxycodone. Twelve-hour plasma concentration curves of the opioids were collected before and after exposing participants to vaporized cannabis thrice daily. Morphine plasma concentration decreased a bit after exposure to the vaporized cannabis, but the change was not statistically significant. The oxycodone curves were superimposable. If the level of the opioid either decreased or stayed the same, one would expect the pain to stay the same or increase. Overall, in the 21 participants, the average initial pain score was 40 on a 0-100 numeric rating scale and dropped to 29 on day 5, a statistically significant 27% reduction in pain. The study, however, was not powered for pain as an endpoint (77).

In the Israeli medicinal cannabis program, patients receiving botanical cannabis licenses are asked to complete questionnaires during follow-up. In a report including 2000 patients with cancer, 53% had baseline pain in the 8-10/10 range. At 6-month follow-up, only 5% had pain at that level. Most other symptoms monitored (eg, nausea and vomiting, sleep disorders, restlessness, anxiety, headaches) were greatly improved at 6 months as well (78). It remains unclear, though, whether the improvement was related to the cannabis or to the fact that the cancer may have responded to treatment.

Cannabis as an Anticancer Agent

There is much internet attention to the issue of whether cannabis cures cancer. An analysis of hits on social media demonstrated that more people are accessing the false news stories touting that cannabis cures cancer than those viewing the accurate story debunking these claims (79). Proponents identify isolated case reports where cannabis was thought to have cured malignancies. One case report describes 2 young girls with partially resected pilocytic astrocytomas, a malignancy known to resolve spontaneously in some cases. The astrocytomas were only partially resected when the children were 11 and 13 years of age. Throughout the next 3 years, the lesions were stable or slightly progressed. In the subsequent 3 years, both young women achieved complete remission, and the only thing they had in common was that they used cannabis daily (80). It is unclear, however, if remission was actually due to the contribution of cannabis or a reflection of the tendency for these tumors to spontaneously remit in some cases. The remaining isolated case reports all describe patients who died with their cancer so clearly do not provide evidence in support of cannabis as an anticancer agent (81–83).

Several other case studies have been reported. Two 38-year-old men, 1 with a glioblastoma and the other with a grade III oligodendroglioma, were treated with chemoradiation and received CBD 100-450 mg daily with a good clinical response. Both had conventional cancer therapy as well, so the contribution of CBD to their outcomes is unclear (84). Along these same lines, proponents point to a series including 9 consecutive brain tumor patients in Vienna who received pure CBD 400 mg orally daily in addition to standard therapy with resection followed by chemoradiation. Six of the patients had the more aggressive glioblastoma and 3 had lower-grade tumors. The investigator stated the usual median survival with glioblastoma is 14 to 16 months, whereas the mean in their series is 22.3 months, suggesting to them that the CBD had a beneficial effect. However, they also included 3 patients with less aggressive tumors, likely explaining the prolongation of the mean survival (85).

In a second case series, data were collected in a London clinic on 119 patients over a 4-year period who received pharmaceutical-grade synthetic CBD oil at 10 mg twice daily on a 3-days-on-3-days-off schedule. The authors reported a tumor response in 92% of patients, but most patients also received conventional cancer therapy. Only 28 patients received CBD alone, and no data are presented on their outcomes. Although the investigators concluded that CBD is a candidate for treating breast cancer and glioma patients, they did not really provide evidence to support that claim (86). Hence, neither the isolated case reports nor the referenced case series provide any convincing evidence that cannabis has antitumor effects.

Manuel Guzman, PhD, completed the first intervention study, in which he infused THC via a catheter into the tumors of 9 patients with recurrent glioblastomas. He reported that the treatment was well tolerated but there was no difference in survival from patients receiving chemotherapy alone. In vitro, THC inhibited the proliferation and decreased the viability of glioblastoma cells from patient biopsies (87). Later, it was demonstrated that CBD enhanced the inhibitory effects of the THC in the same in vitro model (88).

CB1 and CB2 receptors have been assayed in a variety of tumor specimens (89). The importance of overexpression or underexpression of CB1 and CB2 in different tumors is inconsistent; sometimes it correlates with a good prognosis, and, in other tumor types, it may be associated with a more aggressive tumor. Equally concerning, an Israeli group demonstrated that different cannabis extracts from the whole plant have different effects on the same tumor from different cell lines (90). These observations are consistent with the developing conclusion that cannabis may have no in vivo anticancer effect.

Potential Future Direction

Session 2, "Cannabis and the Cancer Patient," illuminated how legal conundrums surrounding medicinal cannabis complicate clinical care and the conducting of medicinal cannabis research. Partially as a result, risks and benefits of medicinal cannabis have not been well delineated in the cancer patient. Particularly regarding the medicinal benefits of cannabis, much of the research has centered on individual cannabinoids (eg, synthetic THC derivatives) rather than on the full-spectrum, plant-based medicine.

The NCI's Cannabis, Cannabinoids and Cancer Research Workshop has demonstrated the high level of interest among researchers, clinicians, and patient advocates to further evidence-based approaches to and education surrounding oncologic use of medicinal cannabis. The NIH, including the NCI, should consider developing additional research opportunities for basic science, oncologic clinical trials of whole-plant cannabis, and research studies evaluating how best to disseminate clinical knowledge regarding medicinal cannabis to medical professionals, patients and families, and cannabis dispensary personnel. When randomized clinical trials with "trial drug" are not feasible, rigorous pragmatic clinical trials harnessing the widespread use of cannabis among oncology populations in North America and elsewhere should be undertaken (91). The aims of clinical trial research should be to assess the benefits and risks when the botanical is used for indications that oncology patients target, including nausea and vomiting, low appetite, pain, insomnia, mental health symptoms such as depression and anxiety, and as cancer-directed therapy.

Comparative efficacy trials between different routes of administration and concentrations of active ingredients, as well as dose-finding trials, are also warranted. Once these data are available, members of the oncologic community will likely be more confident in guiding cannabis-related clinical care, because they are a clinician group who particularly value evidence-based medical decision making.

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References

1. Braun IM, Nayak MM, Revette A, et al. Cancer patients' experiences with medicinal cannabis-related care. *Cancer*. 2020;127(1):67–73. doi: 10.1002/cncr.33202.
2. Aggarwal SK, Carter GT, Sullivan MD, ZumBrunnen C, Morrill R, Mayer JD. Medicinal use of cannabis in the United States: historical perspectives, current trends, and future directions. *J Opioid Manag*.2009;5(3):153–168. doi: 10.5055/jom.2009.0016.
3. Bridgeman MB, Abazia DT. Medicinal cannabis: history, pharmacology, and implications for the acute care setting. *PT*. 2017;42(3):180–188.
4. Gerber RJ. *Legalizing Marijuana: Drug Policy Reform and Prohibition Politics*. Westport, CT: Praeger; 2004.
5. Procon.org. Historical Timeline: History of Marijuana as Medicine - 2900 BC to Present. https://medicalmarijuana.procon.org/view.timeline.php?timelineID=000026. Accessed February 12, 2021.
6. Miller J. Here's why you shouldn't use the word marijuana anymore. *Ottawa Citizen*. November 3, 2017. https://ottawacitizen.com/news/local-news/word-marijuana-has-racist-past-say-those-who-want- it-banished-from-the-lexicon. Accessed October 18, 2021.
7. The Drug Enforcement Administration. Drug scheduling. https://www.dea.gov/drug- scheduling#:~:text=for%20the%20schedule.)-,Schedule%20I,ecstasy)%2C%20methaqualone%2C%20and%20peyote. Accessed April 8, 2021.
8. Gurman S. Marijuana-research applications go nowhere at Justice Department. *Wall Street Journal*. September 18, 2018.
9. State medical marijuana laws. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed November 28, 2020.
10. US Congress. H.R.3884 - MORE Act of 2020. https://www.congress.gov/bill/116th- congress/house-bill/3884. Accessed February 12, 2021.
11. FindLaw. https://public.findlaw.com/cannabis-law/cannabis-laws-and-regulations/medical-marijuana-laws-by-state.html. Accessed February 12, 2021.
12. National Academies of Sciences, Engineering and Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: National Academies Press; 2017.
13. Marijuana Policy Project. https://www.mpp.org/issues/medical-marijuana/state-by-state- medical-marijuana-laws/medical-marijuana-patient-numbers/. Accessed February 12, 2021.
14. Braun IM, Tulsky JA. Reconciling the discrepancies in medicine's relationship to medical marijuana. *Ann InternMed*.2018; 169(9):646–647. doi: 10.7326/M18-1883.
15. Pergam SA, Woodfield MC, Lee CM, et al. Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. *Cancer*. 2017;123(22):4488–4497. doi:10.1002/cncr.30879.
16. Braun IM, Wright A, Peteet J, Meyer FL, et al. Medical oncologists' beliefs, practices and knowledge regarding marijuana used therapeutically: a nationally-representative survey study. *J Clin Oncol*. 2018;36(19):1957–1962. doi:10.1200/JCO.2017.76.1221.
17. Fann JR, Pergam SA, Woodfield M, et al. Cancer health care provider perceptions and practice patterns regarding patients' cannabis use in a state with legalized medicinal and recreational use. Paper presented at Annual Meeting of the American Psychosocial Oncology Society; February 2018; Tucson, AZ.
18. Pergam SA. Fungal pneumonias in patients with hematologic malignancies and those undergoing hematopoietic cell transplantation. *Clin Chest Med*. 2017;38(2):279–294. doi:10.1016/j.ccm.2016.12.006.
19. Yong MK, Slavin MA, Kontoyiannis DP. Invasive fungal disease and cytomegalovirus infection: is there an association? *Curr Opin Infect Dis*. 2018;31(6):481–489.
20. Zarakas MA, Desai JV, Chamilos G, Lionakis MS. Fungal infections with ibrutinib and other small- molecule kinase inhibitors. *Curr Fungal Infect Rep*. 2019;13(3):86–98.
21. Verweij PE, Kerremans JJ, Voss A, Meis JF. Fungal contamination of tobacco and marijuana. *JAMA*. 2000;284(22):2875.
22. Kagen SL. Aspergillus: an inhalable contaminant of marihuana. *N Engl J Med*. 1981;304(8):483- 484.
23. Moody MM, Wharton RC, Schnaper N, Schimpff SC. Do water pipes prevent transmission of fungi from contaminated marijuana? *N Engl J Med*. 1982;306(24):1492–1493.
24. Stone T, Henkle J, Prakash V. Pulmonary mucormycosis associated with medical marijuana use. *Respir Med Case Rep*. 2019;26:176–179.
25. Benedict K, Thompson GR, Jackson BR. Cannabis use and fungal infections in a commercially insured population, United States, 2016. *Emerg Infect Dis*. 2020;26(6):1308–1310. doi:10.3201/eid2606.191570.
26. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole resistance in Aspergillus fumigatus: can we retain the clinical use of mold-active antifungal azoles? *Clin Infect Dis*. 2016;62(3):362–368.
27. Wei X, Zhang Y, Lu L. The molecular mechanism of azole resistance in Aspergillus fumigatus: from bedside to bench and back. *J Microbiol*. 2015;53(2):91–99
28. Kidd SE, Goeman E, Meis JF, Slavin MA, Verweij PE. Multi-triazole-resistant Aspergillus fumigatus infections in Australia. *Mycoses*. 2015;58(6):350–355.
29. Verweij PE, Snelders E, Kema GH, Mellado E, Melchers WJ. Azole resistance in Aspergillus fumigatus: a side-effect of environmental fungicide use? *Lancet Infect Dis*. 2009;9(12):789–795.
30. Schneider S, Bebing R, Dauberschmidt C. Detection of pesticides in seized illegal cannabis plants. *Anal Methods*. 2014;6:515–520
31. Cuypers E, Vanhove W, Gotink J, Bonneure A, Van Damme P, Tytgat J. The use of pesticides in Belgian illicit indoor cannabis plantations. *Forensic Sci Int*. 2017;277:59–65.
32. Ungerleider JT, Andrysiak T, Tashkin DP, Gale RP. Contamination of marihuana cigarettes with pathogenic bacteria–possible source of infection in cancer patients. *Cancer Treat Rep*. 1982;66(3):589- 591.
33. Taylor DN, Wachsmuth IK, Shangkuan YH, et al. Salmonellosis associated with marijuana: a multistate outbreak traced by plasmid fingerprinting. *N Engl J Med*. 1982;306(21):1249–1253.
34. Baldwin GC, Tashkin DP, Buckley DM, Park AN, Dubinett SM, Roth MD. Marijuana and cocaine impair alveolar macrophage function and cytokine production. *Am J Respir Crit Care Med*. 1997;156(5):1606–1613.
35. Tashkin DP. Marijuana and lung disease. *Chest*. 2018;154(3):653–663.
36. Caiaffa WT, Vlahov D, Graham NM, et al. Drug smoking, Pneumocystis carinii pneumonia, and immunosuppression increase risk of bacterial pneumonia in human immunodeficiency virus-seropositive injection drug users. *Am J Respir Crit Care Med*. 1994;150(6 Pt 1):1493–1498.
37. Winhusen T, Theobald J, Kaelber DC, Lewis D. The association between regular cannabis use, with and without tobacco co-use, and adverse cardiovascular outcomes: cannabis may have a greater impact in non-tobacco smokers. *Am J Drug Alcohol Abuse*. 2020;46(4):454–461. doi:10.1080/00952990.2019.1676433.

38. Wolf CE, Poklis JL, Poklis A. Stability of tetrahydrocannabinol and cannabidiol in prepared quality control edible brownies. *J Anal Toxicol*. 2017;41(2):153–157.
39. Schmitz N, Richert L. Pharmacists and the future of cannabis medicine. *J Am Pharm Assoc*. 2020;60(1):207–211.
40. Andre C, Jaber-Filho JA, Bento RM, Damasceno LM, Aquino-Neto FR. Delirium following ingestion of marijuana present in chocolate cookies. *CNS Spectr*. 2006;11(4):262–264.
41. Mudan A, DeRoos F, Perrone J. Medical marijuana miscalculation. *N Engl J Med*. 2019;381(11):1086–1087.
42. Peters RJ, William M, Ross MW, et al. The use of fry (embalming fluid and PCP-laced cigarettes or marijuana sticks) among crack cocaine smokers. *J Drug Educ*. 2008;38(3):285–295. doi:10.2190/DE.38.3.f.
43. Greger J, Bates V, Mechtler L, Gengo F. A review of cannabis and interactions with anticoagulant and antiplatelet agents. *J Clin Pharmacol*. 2020;60(4): 432–438.
44. Leino AD, Emoto C, Fukuda T, Privitera M, Vinks AA, Alloway RR. Evidence of a clinically significant drug-drug interaction between cannabidiol and tacrolimus. *Am J Transplant*. 2019;19(10):2944–2948.
45. Vierke C, Marxen B, Boettcher M, Hiemke C, Havemann-Reinecke U. Buprenorphine-cannabis interaction in patients undergoing opioid maintenance therapy. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(5):847–856. doi: 10.1007/s00406-019-01091-0.
46. Taha T, Meiri D, Talhamy S, Wollner M, Peer A, Bar-Sela G. Cannabis impacts tumor response rate to nivolumab in patients with advanced malignancies. *Oncologist*. 2019;24(4):549–554.
47. Perisetti A, Gajendran M, Dasari CS, et al. Cannabis hyperemesis syndrome: an update on the pathophysiology and management. *Ann Gastroenterol*. 2020; 33(6):571–578.
48. Schier JG, Meiman JG, Layden J, et al. Severe pulmonary disease was associated with electronic-cigarette product use. *CDC*. 2019;68(36);787–790.
49. Wing C, Bradford AC, Carroll AE, Hollingsworth A. Association of state marijuana legalization policies for medical and recreational use with vaping-associated lung disease. *JAMA Netw Open*. 2020;3(4):e202187.
50. Wang GS, Banerji S, Contreras AE, Hall KE. Marijuana exposures in Colorado, reported to regional poison centre, 2000-2018. *Inj Prev*. 2020;26(2):184–186.
51. Phillips JA, Holland MG, Baldwin DD, et al. Marijuana in the workplace: guidance for occupational health professionals and employers: joint guidance statement of the American Association of Occupational Health Nurses and the American College of Occupational and Environmental Medicine. *Workplace Health Saf*. 2015;63(4):139–164.
52. Bonar EE, Cranford JA, Arterberry BJ, Walton MA, Bohnert KM, Ilgen MA. Driving under the influence of cannabis among medical cannabis patients with chronic pain. *Drug Alcohol Depend*. 2019;195:193–197.
53. Yezefski T, Steelquist J, Watabayashi K, Sherman D, Shankaran V. Impact of trained oncology financial navigators on patient out-of-pocket spending. *Am J Manag Care*. 2018;24(5 Suppl):S74–S79.
54. Hastert TA, Young GS, Pennell ML, et al. Financial burden among older, long-term cancer survivors: results from the LILAC study. *Cancer Med*. 2018;7(9): 4261–4272.
55. Altice CK, Banegas MP, Tucker-Seeley RD, Yabroff KR. Financial hardships experienced by cancer survivors: a systematic review. *J Natl Cancer Inst*. 2017; 109(2):djw205.
56. What is marijuana really worth? AccessedNovember 15, 2020. Schier JG, Meiman JG, Layden J, et al.. Severe pulmonary disease associated with electronic-cigarette- product use - interim guidance. *MMWR Morb Mortal Wkly Rep*. 2019;68(36):787–790.
57. Macari DM, Gbadamosi B, Jaiyesimi I, Gaikazian S. Medical cannabis in cancer patients: a survey of a community hematology oncology population. *Am J Clin Oncol*. 2020;43(9):636–639.
58. Benamar M. Cannabinoids in medicine: a review of their therapeutic potential. *J Ethnopharmacol*. 2006;105(1-2):1–25.
59. Tramèr MR, Carroll D, Campbell FA, Reynolds DJ, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. *BMJ*. 2001;323(7303):16–21.
60. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. *Cochrane Database of Syst Rev*. 2015;11:CD009464.
61. Chow R, Valdez C, Chow N, Zhang D, Im J, Sodhi E, Lock M. Oral cannabinoid for the prophylaxis of chemotherapy-induced nausea and vomiting—a systematic review and meta-analysis. *Support Care Cancer*. 2020;28(5):2095–103.
62. Schussel V, Kenzo L, Santos A, et al. Cannabinoids for nausea and vomiting related to chemotherapy: overview of systematic reviews. *Phyother Res*. 2018; 32(4):567–576. doi:10.1002/ptr.5975.
63. Tafelski S, Häuser, W, Schäfer, M. Efficacy, tolerability, and safety of cannabinoids for chemotherapy-induced nausea and vomiting—a systematic review of systematic reviews. *Schmerz*. 2016;30(1):14–24. doi: 10.1007/s00482-015-0092-3.
64. Duran M, Pérez E, Abanades S, Vidal X, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. *Br J Clin Pharmacol*. 2010;70(5):656–663. doi: 10.1111/j.1365-2125.2010.03743.x.
65. Grimison P, Mersiades A, Kirby A. Begbie S. Simes J, Stockler M. Oral THC:CBD cannabis extract for refractory chemotherapy-induced nausea and vomiting: a randomised, placebo-controlled, phase II crossover trial. *Ann Oncol*. 2020; 31(11):1553–1560. doi:10.1016/j.annonc.2020.07.020.
66. Zikos T, Nguyen L, Kamal A, et al. Ondansetron, and promethazine are perceived as most effective treatments for gastrointestinal nausea. *Digest Dis Sci*. 2020;65(11):3280–3286. doi:10.1007/s10620- 020-06195-5.
67. Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO guideline update. *J Clin Oncol*. 2020;38(24):2782–2797.
68. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol*. 2002;20(2):567–573. doi: 10.1200/JCO.2002.20.2.567.
69. Brisbois TD, de Kock H, Watanabe M, et al. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. *Ann Oncol*. 2011; 22(9):2086–2093
70. Turcott JG, Del Rocío Guillen Núñez M, Flores-Estrada D, Oñate-Ocaña LF, Zatarain-Barrón ZL, Barrón F, Arrieta O. The effect of nabilone on appetite, nutritional status, and quality of life in lung cancer patients: a randomized, double-blind clinical trial. *Support Care Cancer*. 2018;26(9):3029–3038. doi: 10.1007/s00520-018-4154-9.
71. Bar-Sela G, Zalman D, Semenysty V. The effects of dosage-controlled cannabis capsules on cancer-related cachexia and anorexia syndrome in advanced cancer patients: pilot study. *Integr Cancer Thera*. 2019;18:1534735419881498. doi:10.1177/1534735419881498.
72. Brunt TM, van Genugten M, Höner-Snoeken K, van de Velde MJ, Niesink RJM. Therapeutic satisfaction and subjective effects of different strains of pharmaceutical-grade cannabis. *J Clin Psychopharmacol*. 2014;3:1–6.
73. Stith SS, Vigil JM, Brockelman F, et al. The association between cannabis product characteristics and symptom relief. *Sci Rep*. 2019;9(1):2712. doi: 10.1038/s41598-019-39462-1.
74. Andreae MH, Carter GM, Shaparin N, et al. Inhaled cannabis for chronic neuropathic pain: a meta- analysis of individual patient data. *J Pain*. 2015;16(12): 1221–1232. doi:10.1016/j.jpain.2015.07.009.
75. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. *J Pain Symptom Manage*. 2014;47(1):166–73. doi: 10.1016/j.jpainsymman.2013.02.018.
76. Boland EG, Bennett MI, Allgar V, et al. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. *BMJ Support Palliat Care*. 2020; 10(1):14–24.
77. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther*. 2011;90(6):844–851. doi: 10.1038/clpt.2011.188.
78. Bar-Lev Schleider L, Mechoulam R, Lederman V, Hilou M, Lencovsky O, Betzalel O, Shbiro L, Novack V. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. *Eur J Intern Med*. 2018;49:37–43. doi:10.1016/j.ejim.2018.01.023.
79. Shi S, Brant AR, Sabolch A, et al. False news of a cannabis cancer cure. *Cureus*. 2019;11(1): e3918. doi:10.7759/cureus.3918.
80. Foroughi M, Hendson G, Sargent MA, Steinbok P. Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas—possible role of cannabis inhalation. *Childs Nerv Syst*. 2011;27(4):671–679. doi:10.1007/s00381-011-1410-4.
81. Singh Y, Bali C. Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation. *Case Rep Oncol*. 2013;28; 6(3):585–592.doi:10.1159/000356446.
82. Maida V, Corban J. Topical medical cannabis: a new treatment for wound pain—three cases of Pyoderma Gangrenosum. *J Pain Symptom Manage*.2017; 54(5):732–736. doi:10.1016/j.jpainsymman.2017.06.005.
83. Sulé-Suso J, Watson NA, van Pittius DG, Jegannathen A. Striking lung cancer response to self-administration of cannabidiol: a case report and literature review. *SAGE Open Med Case Rep*.2019;7:2050313X19832160. doi: 10.1177/2050313X19832160.
84. Dall'Stella PB, Docema M, Maldaun M, Feher O, Lancellotti, C. Case report: clinical outcome and image response of two patients with secondary high-grade glioma treated with chemoradiation, PCV, and cannabidiol. *Front Oncol*. 2019;8:643. doi:10.3389/fonc.2018.00643.
85. Likar R, Koestenberger M, Stultschnig M, Nhaler G. Concomitant treatment of malignant brain tumours with CBD – a case series and review of the literature. *Anticancer Res*.2019;39 (10) 5797–5801. doi: 10.21873/anticanres.13783.
86. Kenyon J, Liu W, Dalgleish A. Report of objective clinical responses of cancer patients to pharmaceutical-grade synthetic cannabidiol. *Anticancer Res*. 2018; 38(10):5831–5835. doi:10.21873/anticanres.12924.
87. Guzmán, M., Duarte, M., Blázquez, C. et al. A pilot clinical study of Δ9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br J Cancer*. 2006;95(2):197–203. doi:10.1038/sj.bjc.6603236.

88. Marcu JP, Christian RT, Lau D, et al. Cannabidiol enhances the inhibitory effects of delta9- tetrahydrocannabinol on human glioblastoma cell proliferation and survival. *Mol Cancer Ther*. 2010;9(1):180–189. doi:10.1158/1535-7163.MCT-09-040.
89. Ladin DA, Soliman E, Griffin L, Van Dross R. Preclinical and clinical assessment of cannabinoids as anti-cancer agents. *Front Pharmacol*. 2016;7:361. doi: 10.3389/fphar.2016.00361.
90. Baram L, Peled E, Berman P, et al. The heterogeneity and complexity of cannabis extracts as antitumor agents. *Oncotarget*. 2019;10(41):4091–4106. doi: 10.18632/oncotarget.26983.
91. Hutchison KE, Bidwell LC, Ellingson JM, Bryan AD. Cannabis and health research: rapid progress requires innovative research designs. *Value Health*. 2019;22:1289–1294. doi:10.1016/j.jval.2019.05.005.