Medical Cannabis Use Among Individuals With Cancer: An Unresolved and Timely Issue

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The role of cannabis in cancer care is a complex and challenging issue. Cancer and its treatments currently are designated as qualifying conditions in the majority of the 33 states that now have legalized medical cannabis.[1] Consequently, cannabis use in patients with cancer is common: nearly one-quarter of individuals with cancer report current cannabis use[2,3] and >90% of cancer survivors view cannabis as potentially beneficial for symptom management and support its legalization.[4] Recent studies have suggested that physicians may be more likely to recommend cannabis to patients with cancer compared with patients with other serious illnesses,[5] and that oncologists are becoming increasingly accepting of patients using cannabis, despite their continued concerns regarding its safety and efficacy.[6,7] For example, approximately 46% of oncologists reported recommending medical cannabis clinically and approximately 80% discussed it with their patients, despite the fact that approximately 70% acknowledged that they were insufficiently educated regarding medical cannabis.[8] Thus, there appears to be a disconnect between medical cannabis's legal status and high acceptance by patients, recommendations from clinicians, and a poor evidence base concerning its safety and efficacy.

A more complete and nuanced understanding of the relevant issues is imperative in this current climate of growing cannabis availability and acceptance. In this commentary, we have discussed key clinical issues related to the efficacy and safety of cannabis in patients with cancer and noted important lingering questions for clinical practice and research in this area.

Cannabis: Indications, Use Versus Evidence Base

Approximately 75% of individuals with cancer use cannabis for symptom management, most commonly pain, nausea, and sleep disruption[9,10]; however, to the best of our knowledge, the evidence base supporting this has been limited. It is important to note at the outset that the majority of the cannabis research conducted in oncology patients lacks the rigor that would be required of most other oncology treatments in practice. Even the limited number of randomized controlled trials that exist for comparing the efficacy of cannabis with that of placebo or other drugs in oncologic patients are homogeneously low or very low in quality.[11] A recent systematic review characterized the available evidence regarding cannabis for cancer symptom management as low quality and found no benefit for its common indications of pain, sleep, or a reduction of opioid dose.[12] In addition, to our knowledge, evidence for the antiemetic properties of plant-based preparations is seriously lacking. In effect, the best evidence exists for oral, pharmaceutically prepared, synthetic tetrahydrocannabinols (THCs) such as nabilone and dronabinol, which have been found to be superior to placebo and equivalent to other antiemetic medications.[13-15] For example, one observational prospective study found at least a 30% reduction in symptoms such as vomiting and fatigue within the first 4 months after initiating state-sanctioned medical cannabis, whereas a smaller percentage maintain these effects over longer-term follow up.[16]

Similarly, for pain, the few existing cancer pain trials to our knowledge are fraught with methodologic limitations, including small sample size, a short follow-up duration on the order of days to weeks, high attrition, and the exclusion of those patients with variable pain scores.[14] Some observational evidence has suggested that the majority of those who use cannabis report a short-term benefit.[3] In addition, to our knowledge, there are no head-to-head trials comparing

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cannabis with opioids or other analgesics that have been conducted to establish the relative efficacy of cannabis compared with other opioid and nonopioid analgesics. It is important to consider the type of pain (neuropathic vs nociceptive). For example, some data have supported the use of cannabis for neuropathic pain that is not chemotherapy induced.[17] In a very small (16 participants) and arguably underpowered trial of nabiximols (a pharmaceutically prepared oromucosal spray containing a standard ratio of 2.7 mg of THC to 2.5 mg of cannabidiol [CBD] per spray), 5 participants experienced a clinically significant decrease in chemotherapy-induced neuropathic pain,[18] which provided support for designing larger, more rigorous trials of nabiximols.

Cancer itself is a qualifying condition for medical cannabis,[1] opening the door to treating not only cancer-associated pain and symptoms, but also cancer itself. Although there is a body of in vivo and in vitro laboratory evidence to suggest possible mechanisms for the antitumor properties of cannabis such as the induction of apoptosis and prevention of tumor cell proliferation, to our knowledge these findings have not been translated into humans.[19-21] We assert that endorsement of the use of medical cannabis for its purported antineoplastic properties or in lieu of US Food and Drug Administration (FDA)–approved cancer treatments is potentially dangerous.

The Clinician Response

Within the setting of this limited evidence base, the literature has suggested that cancer clinicians have come to their own conclusions. For example, in one study, up to two-thirds of oncology providers reported believing that cannabis can be an effective treatment for common symptoms such as poor appetite, nausea and vomiting, and anxiety at the end of life. In contrast, approximately one-half of providers perceived that cannabis was never or rarely beneficial for those with early-stage cancer.[6] The authors hypothesized that this distinction was due to the benefits outweighing the risks of cannabis within the context of end-of-life care.[6] Unfortunately, to our knowledge, studies of medical cannabis in individuals at the end of life, including in the hospice setting, are sorely lacking. Thus, efficacy data have lagged behind the recommendations of providers and the legalization of medical cannabis, and more studies are needed to more definitively determine which symptoms and which patients will benefit from medical cannabis.

Within the context of the well-recognized adverse consequences of opioid prescribing, including opioid use disorder, there is hope among providers that cannabis could offer an alternative to opioids; a recent survey found that approximately 50% of the oncology providers sampled viewed cannabis as less addictive than opioid medications.[6] However, it remains unclear whether medical cannabis can reduce opioid dependence in this population, and one study found no association between cannabis use and opioid dose.[12] Although some lessons may be drawn from the chronic noncancer pain literature, these data also are inconsistent. Among those who are prescribed long-term opioid therapy for chronic noncancer pain, one single-arm trial[22] and 2 ecological studies[23,24] have suggested that opioid use may decrease when initiating medical cannabis, yet these studies had notable limitations that did not allow us to conclude causality. Three additional, more methodologically rigorous, studies suggested no association between cannabis use and opioid use or discontinuation.[25-27] In fact, in what to the best of our knowledge is the largest prospective cohort study to examine this relationship, it was found that, among patients receiving long-term opioid medications, concurrent cannabis use negatively affected pain and functional and mental health outcomes and did not lead to a reduction or discontinuation of opioids.[25] Further complicating matters, cross-sectional research has suggested that individuals who concurrently use opioids and cannabis may be more likely to engage in opioid misuse behaviors such as early refills or taking a higher than prescribed dose.[28,29] This is concerning because studies already are reporting a low rate of screening for opioid misuse, the sporadic use of urine drug tests, and infrequent reporting to the state prescription drug monitoring program among oncology providers.[30]

Uncertain Short-Term and Long-Term Consequences

There are several potential short-term and long-term adverse consequences of cannabis use. Balancing these risks with the potential benefits is paramount. One review aptly noted that the number needed to treat with cannabis to observe benefit is 24 whereas the number needed to treat to note a harm is 6.[31]

Cannabis use disorder was the second most frequently diagnosed substance use disorder in 2010 (behind alcohol), representing approximately 15% of substance use disorder diagnoses in a large integrated health care system in California.[32] Emerging literature has supported the association between cannabis legalization and an increased prevalence of cannabis use disorder.[33] This is particularly true for patients with other underlying mental

health disorders.[34] Cannabis use also is associated with the use of other substances.[35] Using national survey data, one study found that prescription opioid use was significantly associated with prior cannabis use in both men and women aged 18 to 25 years.[36] However, more rigorous research is needed to fully characterize whether this relationship is causal.[34]

There also are significant concerns regarding drug-drug interactions with the use of medical cannabis.[37] For example, in patients with cancer, one study found that cannabis was the only factor significantly associated with a decreased response rate to nivolumab immunotherapy, with a decrease in the response rate from 38% to 16% when patients were taking cannabis during immunotherapy.[38] Another review recommended caution when combining cannabis with specific agents given the potential effects of cannabis on membrane transporters and cytochrome P450 metabolism.[39] These impacts are potentially more deleterious among the elderly and patients with concomitant renal and hepatic disease.[39] Cannabinoids interact with other cytochrome P450 3A4 substrates, and many chemotherapeutics fall into this category (eg, tamoxifen and bosutinib).[40] Therefore, for these medications, there is an increased risk of side effects.[40] Furthermore, cannabinoids can inhibit phase 2 hepatic metabolism (eg, glucuronidation), thereby decreasing excretion of chemotherapeutics that are metabolized through these enzymes (eg, sorafenib, regorafenib, methotrexate, and imatinib).[40] One cannabinoid metabolite, 7-COOH-CBD, inhibits the breast cancer resistance protein and bile salt export pump, leading to increased tissue distribution and decreased excretion of the chemotherapeutics that use these pathways (eg, paclitaxel).[40] The coadministration of cannabinoids and chemotherapeutics with the potential for drug-drug interactions via any of these pathways is discouraged. If such medications and cannabinoids must be administered together, increased monitoring for side effects is recommended and/or a dose reduction of chemotherapeutics should be considered. Cannabidiol itself has an overlapping side effect profile with chemotherapeutics, and can in itself cause worsening of nausea, somnolence, appetite suppression, infection risk, weight loss, sleep disturbance, and diarrhea.[40]

Cannabis use also is associated with other acute medical, mental health, and safety risks including an increased risk of motor vehicle accidents,[17] increased risk of manic episodes and psychosis,[17] and small negative effects on cognitive functioning among those who use cannabis frequently.[41] Often those patients with comorbid psychiatric illnesses, cognitive decline, or multiple chronic health conditions are excluded from cannabis trials, and therefore we do not have an adequate understanding of the magnitude of risk of these harms in medically and psychiatrically complex individuals. Moreover, the route of administration has been shown to be differentially associated with harms and should be considered in patients with cancer. Cannabis hyperemesis syndrome, psychosis, and paranoia are common reasons for cannabis-associated emergency department visits and the type of adverse event experienced may be differentially related to the route of administration.[42] There is growing awareness of vaping-associated pulmonary injury and mortality,[43] and up to 40% of medical cannabis users report vaping as a route of administration.[44] Finally, high-potency edible cannabis has been associated with altered mentation.[45]

The Legal and Policy Landscape

After the passing of the 2018 Farm Bill, which removed hemp from the Controlled Substances Act, the availability of CBD products increased exponentially. The sales of CBD products are regulated on a state level, such that some states allow CDB products to be sold in nondispensary settings such as grocery stores, whereas other states allow for CBD specialty shops to sell these products. These products are being marketed as improving aspects of health including immune function, pain, and mental health. Nevertheless, there is limited evidence to support the positive health benefits of CBD. Specifically, the formulations contained in the vast majority of trials have been combinations of THC and CBD, with few low-quality trials examining CBD alone. Much research to date has suggested that CBD products often are mislabeled, containing undocumented THC or no CDB at all.[46] Although CBD may have fewer of the intoxicating effects compared with THC,[47] these products still are associated with harms. The FDA recently released a warning against unknown harms including contaminants, liver injury, and side effects such as drowsiness and irritability and cautioned consumers that of all CBD products (with the exception of Epidiolex, a purified form of CBD used to treat rare seizure disorders), none has been tested or approved by the FDA.[48]

In the setting of limited evidence regarding known benefits and substantial evidence of risk, there is a troubling lack of regulatory oversight among many of the states participating in medical cannabis programs.[49] Some state programs such as that in New York State are highly regulated, offering only a few preparations and limiting dispensary licenses, whereas other states have less regulation regarding the number of licensed dispensaries, the

types of formulations available, and product oversight. Although some states require cannabis products to be tested for solvents, pesticides, and other harmful chemicals, others do not require such testing. The lack of cannabis product screening programs, inaccurate labeling,[46] lack of regulation of high-potency products, and the lack of a centralized database to report adverse events all can lead to harms.[46,50] Specifically, recent anecdotal evidence also raises clinical concerns regarding toxicity stemming from a lack of standardization of the doses of active ingredients in medical cannabis as well as highly variable prescribing practices. There is much regulatory infrastructure needed to ensure consumer safety.

Given this existing evidence base and the increasing availability and widespread use of medical cannabis among patients with cancer, it is clear that more research is needed urgently. Both evidence and policies regulating medical cannabis lag far behind its clinical use. However, there remain significant barriers to examining the therapeutic benefits and safety of cannabis in controlled trials. Currently, its schedule I classification makes obtaining funding and conducting the research administratively burdensome and complex. Investigators who do obtain funding and the necessary approvals to pursue a cannabis trial encounter several issues related to generalizability. It is interesting to note that the limited number of formulations available for research by federal agencies do not represent the breadth of products available for patients to obtain from a recreational or medical dispensary. In September 2019, the Marijuana 1-to-3 Act of 2019, which would reclassify cannabis as a schedule III drug to increase funding and availability for research, was proposed to Congress (H.R. 4323), and this hopefully will mitigate some of the research barriers.[51]

Conclusions

To address the evidence gap, we argue that comparative effectiveness trials comparing cannabis with opioids, commonly used antiemetics, or other common symptom management approaches must be conducted to compare the risk-benefit ratio and clinically meaningful improvements in pain, function, and other patient-reported outcomes. We also recommend the prioritization of research conducted within hospice, palliative care, and end-of-life settings. From a policy perspective, there is an urgent need for the more stringent regulation of dosage concentrations and a national reporting mechanism to monitor medical cannabis–related adverse events and patient and clinical characteristics associated with cannabis-related outcomes and associations among cannabis, addiction, and symptom management. Based on lessons learned from the opioid-related public toll, taking some steps back to generate a more rigorous scientific and policy framework for cannabis use will be a step in the right direction.

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