REVIEW ARTICLE

Cannabis Use, Lung Cancer, and Related Issues

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ABSTRACT

The cannabis plant and its derivatives have been exploited for centuries for recreational and medicinal purposes, with millions of regular users around the world. The recreational use of cannabis is reflective of its neuropsychiatric effects, such as anxiolysis and euphoria. However, cannabis appears to have an emerging therapeutic role, especially in chronic disease and as an adjunct to cancer treatment. Increasing evidence supports cannabis in the management of chemotherapy-induced nausea and vomiting (CINV) and for pain management; however, studies are limited, particularly by difficulties associated with standardized dosing estimates and inability to accurately assess biologic activities of compounds in cannabis and derivative products. Smoking cannabis has not been proved to be a risk factor in the development of lung cancer, but the data are limited by small studies, misclassification due to self-reporting of use, small numbers of heavy cannabis smokers, and confounding of the risk associated with known causative agents for lung cancer (such as parallel chronic tobacco use). Cannabis and its biologically effective derivatives warrant additional research, ideally, controlled trials in which the cannabidiol and the delta-9-tetrahydrocabinol strength and use are controlled and documented.

Introduction

The terms *cannabis* and *marijuana* are frequently used interchangeably, but cannabis is a generic term that includes cannabinoids, marijuana, and hemp derived from the plant *Cannabis sativa*. The documented use of cannabis dates to several centuries BC.[1] Cannabis is currently the most commonly inhaled drug after tobacco in the United States.[2] An estimated 178 million people age 15 years or older used cannabis at least once in 2012.[3,4] Globally, cannabis dependence affects at least 13 million people, most prominently, young adults, males, and those in high-income countries.[5] Cannabis dependence may severely affect qualify of life, and it is responsible for approximately 2 million disability-adjusted life years worldwide, again most prominently in high-income countries and, on a global scale, in young adults[5] (Fig. 1). Interestingly, data from the National Survey on Drug Use and Health 2006–2013 show an increase in cannabis use among older adults in the United States[6] between 2006–2007 and 2012–2013. In this study, data from the National Survey on Drug Use and Health 2006–2013 indicated increased cannabis use by 57.8% in adults age 50 to 54 and by 250% in adults older than 64 years over that time period, possibly reflecting particular generational demographics.[6] Australia too has relatively high rates of cannabis dependence[5] and rates of cannabis use disorders similar to those in the United States.[7] Legislation around cannabis and its derivatives is being increasingly considered for both recreational and medical use by local, regional, and national governments. This report will review some of the current trends in prevalence of cannabis use and focus on epidemiologic, clinical, biologic, and legislative aspects of cannabis as related to

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lung cancer. In many areas where extensive reviews exist, brief discussions as related to cannabis are presented with reviews highlighted for further information.

Cannabis: Effects, Methods of Utilization, and Dosage Manipulation

More than 100 different cannabinoids have been identified, but delta-9-tetrahydrocabinol (THC) is the most responsible for the psychoactive effects of euphoria and relaxation.[8] Cannabanoid 1 (CB1) receptors in the brain correlate with the psychoactive effects.[3] THC is present in the flowers, leaves, and bracts and is associated with the euphoric effects of cannabis. Cannabidiol (CBD) is the main cannabinoid in hemp and is commonly associated with anxiolysis. CBD lacks the intoxicating properties of THC, is considered nonpsychoactive, and has very low affinity for the cannabinoid (CB) receptors in the brain (CB1 and cannabanoid 2). Activation of CB receptors has the potential to affect cancer-related pathways such as adenylate cyclase.[9]

Cannabis products can be smoked, vaporized, ingested (by eating or drinking), or absorbed through the skin and mucosal surfaces through creams, patches, or sprays. Cannabis is primarily smoked, although there are a number of methods of inhalation,[10] which are summarized in Table 1. Smoked or vaporized cannabis can reach the brain within 30 seconds to a few minutes, and their effect subsides over 1 to 3.5 hours. The psychoactive effects of oral products, such as cannabis in cookies, brownies, or other food products, are more difficult to titrate because the effects occur 30 minutes to 2 hours after ingestion and may last 5 to 8 hours.[3]

Genetic manipulation, cultivation, and breeding of cannabis to titrate a more potent form of THC has increased the potency and level of THC in marijuana over the past several years. The average THC levels in marijuana were 4% in 1995 and increased to 12% by 2012.[11,12] Recent literature reports methods to produce highly reliable marijuana yields.[13] Sinsemilla results from a special technique of growing high-potency marijuana from female plants by preventing pollination and facilitating high resin concentration. Plants produced in this manner do not produce seeds. Cannabis products confiscated by the U.S. Drug Enforcement Administration from 1995 through 2014 have shown a decrease in the percentage of regular marijuana and an increase in the percentage of sinsemilla, with a resulting increase in the percentage of THC (Fig. 2). Though designed to increase potency and euphoric effects, high levels of THC in the blood can result in panic attacks, hallucination, or paranoid thoughts.

Medical and Recreational Legalization and FDA-Approved Drugs

California was the first state in the United States to legalize medical marijuana in 1996. At the time of this manuscript, a total of 29 states and Washington, D.C., have legalized medical marijuana under varying use conditions and routes of administration (Fig. 3). Medical marijuana has been approved in a number of countries, such as Canada, Germany, Israel, Australia and others, and it regulatory status is rapidly changing. Recreational marijuana was approved in Uruguay in 2013 and is likely to be approved in Canada in late 2017. In the United States, eight states and Washington, D.C., have approved recreational marijuana. The landscape for both medical and recreational marijuana is dynamic in the United States.

The Controlled Substance Act of 1970 has classified cannabis as a Schedule I drug, comprising the most

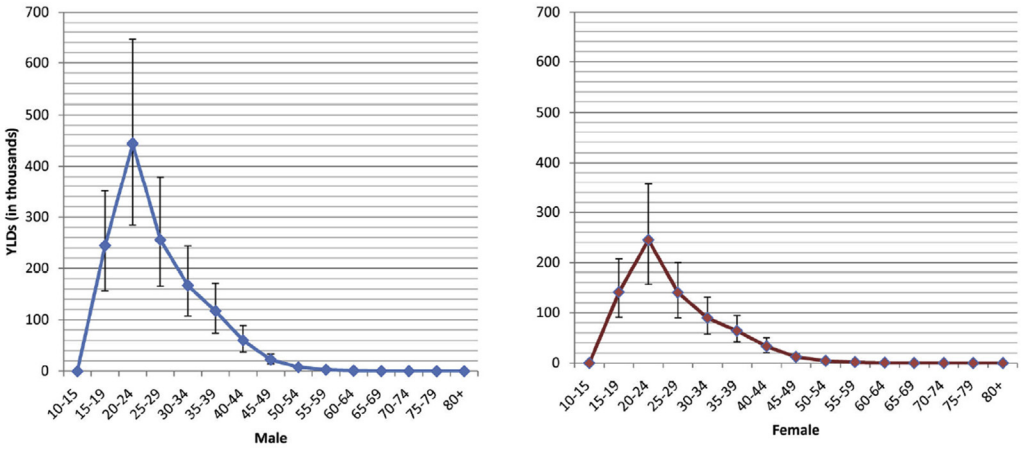

Figure 1. Global cannabis dependence. Disability-adjusted life years (all years of life lived with disability [YLDs]) by age and sex, in thousands, 2010. Reproduced with permission from Degenhardt et al.[5]

Table 1. Methods of inhalation of cannabis

Method of Inhalation	Technique	Advantages	Disadvantages
Blunt	Cannabis rolled into a cigar removed of tobacco	Inexpensive, enhances effect	Harsh smoke, difficult to roll
Bong	Combusted cannabis bubbled through water	Water can trap harmful products	Expensive, less portable
Hookah	Cannabis mixed with flavored tobacco and smoke bubbled through water	Multiple users, higher volume of smoke	Combined with tobacco, potentially more pulmonary damage
Dabbing	Cannabis products chemically dissolved in solvent vapors	Easy to conceal cannabis product, potent effects	Burn injuries are common
G-pen	Cannabis concentrated into wax, oil, or hash and vaporized through e-cigarette	Discreet	Little regulation of ingredients
Joint	Cannabis rolled in paper and smoked	Convenient	Fragile and difficult to roll
Pipe	Cannabis smoked in a glass pipe	Directly inhaled, potent	Breakable, harmful resin can be inhaled
Vaporizer	Cannabis heated to below burning temperature, vapor inhaled	No smoke odor or combustion production	Expensive device, not portable, little regulation of ingredients

Based on summary information presented by Biehl and Burnham.[10]

restrictive substances that "have no medical use." Other Schedule I drugs include heroin and lysergic acid dimethylamide. In 2016, the Drug Enforcement Administration rejected a petition to reclassify cannabis to a Schedule II drug. Pharmaceutical grade cannabinoids are scheduled differently, ranging from Schedule I to Schedule III and include several U.S. Food and Drug Administration (FDA)-approved cannabinoid-based medicines.

Dronabinol capsules (Marinol [AbbVie, North Chicago, IL] or tetrahydrocannabinol) are approved for use in CINV and have been approved for stimulation of appetite on the basis of studies in patients with diagnosed human immunodeficiency virus who have anorexia. Dronabinol is a synthetic compound that binds both CB1 and cannabanoid 2 receptors with a higher affinity for CB1. A liquid preparation of dronabinol (Syndros [Insys Therapeutics, Phoenix, AZ]) was approved for use in 2016 to treat the same conditions and facilitates dose titration associated with liquid formulation as compared with fixed dosing in capsules.

Nabilone (Cesamet [Meda Pharmaceuticals, Solna, Sweden]) is another FDA-approved cannabinoid for CINV. Nabiximol is a mixture of THC and CBD in a 1:1 ratio that is used as an oral spray for analgesic effects and spasticity due to multiple sclerosis. It is approved in 15 different countries, including Canada and Germany, and is currently under FDA review in the United States.[3]

Levonantradol is another synthetic cannabinoid derived from dronabinol, but it is up to 100 times more potent. Developed in the 1980s by Pfizer (New York, NY), the drug is not approved for use by patients but has been used in preclinical studies to evaluate agonist effects of CB1 receptors. As with any potential drugs of abuse, cannabis and cannabinoids have increasingly been vetted through the "designer drug"' process, with many synthetic variants proving to be highly potent, addictive, and of concern for significant abuse while simultaneously having intriguing potential utility as therapeutic agents.[14]

Physiologic Effects Associated with Cannabis

Physiologic effects associated with cannabis use include drowsiness, impaired driving ability, addiction, psychotic episodes, and hyperemesis. In the National Epidemiologic Survey on Alcohol and Related Conditions III (2012–2013), 30.6% of marijuana users exhibited a marijuana use disorder (abuse or dependency),[15] which was a decrease from 35.6% in the 2001–2002 survey; however, the prevalence of marijuana use had doubled in that time. The risk of dependence in long-term users is approximately 9%, which is significantly lower than rates of addiction to heroin, cocaine, alcohol, and nicotine.[3,11] Cannabis use has been associated with increased vehicle crashes. Hallucination, panic attacks, and psychotic episodes have been associated with very high THC levels. The hyperemesis syndrome is more commonly observed in long-term and frequent users of cannabis.[3,16] Death related to overdose from cannabis alone, without other polysubstances, is rare.[17]

Histologic and Airway Effects of Inhaled Cannabis

Smoked cannabis contains many of the same toxins and carcinogens as tobacco smoke.[18,19] These substances

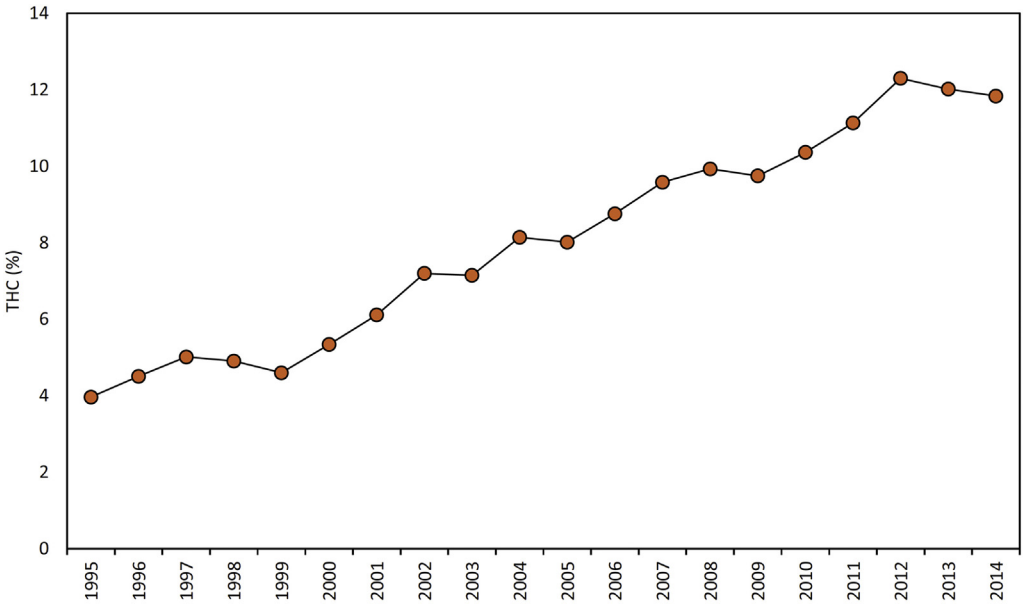

Figure 2. Average delta-9-tetrahydrocannabinol (THC) concentration of Drug Enforcement Administration specimens by year, 1995–2014. Reproduced with permission from ElSohly MA et al.[12]

include carbon monoxide, ammonia, acetaldehyde, formaldehyde, acrolein, phenols, nitrosamines, polycyclic aromatic hydrocarbons, and others. In a systematic comparison of smoke from marijuana and tobacco cigarettes consumed under two sets of smoking conditions, there were qualitative similarities and quantitative differences. Ammonia level was 20-fold higher in marijuana. Nitric oxide, hydrogen cyanide, and some aromatic amines were three to five times more concentrated than in tobacco smoke. Some polycyclic aromatic hydrocarbons were present in lower concentration in marijuana.[18,19] Many of these compounds are carcinogens and damaging to the respiratory epithelium.

Regular smoking of marijuana alone is associated with airway inflammation similar to that with cigarette smoking. Bronchoscopic biopsies of smokers of marijuana alone or in combination with tobacco have demonstrated more frequent histologic changes in smokers of both. However, marijuana use alone did cause basal cell and goblet cell hyperplasia, inflammation, and squamous metaplasia in a large percentage of the 40 subjects examined.[20]

Regular cannabis use, in a general practice population of established adult cannabis and tobacco users, was associated with more prominent reporting of respiratory symptoms.[21] Smoking cannabis alone does cause

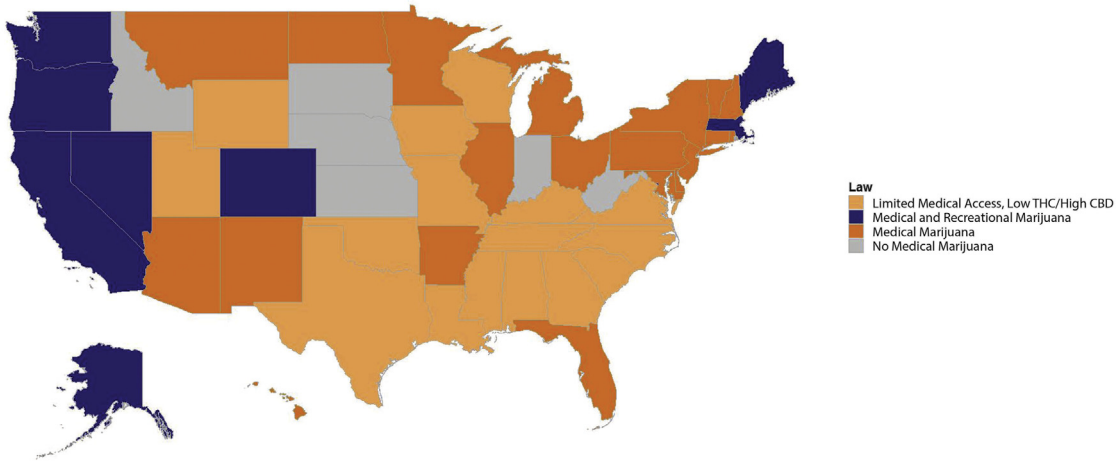

Figure 3. Cannabis laws by state, November 2016. THC, delta-9-tetrahydrocannabinol; CBD, cannabidiol. Reproduced with permission from National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on the Health Effects of Marijuana.[3]

symptoms of chronic bronchitis (cough, wheeze, and sputum), with no additive effects observed in combined marijuana and tobacco smoking.[22] A large cross-sectional study of adults did not demonstrate any adverse spirometric changes with cumulative lifetime marijuana use of up to 20 joint-years; however, greater than 20 joint-years was associated with a twofold increase in the odds of a ratio of forced expiratory volume in 1 second to forced vital capacity less than 70%. This was a result of increase in forced vital capacity rather than a decline in forced expiratory volume in 1 second, as is typical with obstructive airway disease.[23] The American Thoracic Society Marijuana Workgroup opined that there appears to be a modest association between marijuana smoking and the development of chronic obstructive pulmonary disease chronic obstructive pulmonary disease, particularly in heavy smokers; "however, this epidemiological association requires significant further study."[22(p.1703)]

Marijuana Use and Lung Cancer

There is no conclusive evidence that cannabis smoking is associated with an increased incidence of lung cancer.[3,24,25] The best available data are from a pooled analysis of six case-control studies with a total of 2159 cancers and 2985 controls from the United States, Canada, United Kingdom, and New Zealand within the International Lung Cancer Consortium.[24] Unconditional logistic regression adjustment was performed for sociodemographic factors, tobacco smoking status, and pack-years. The overall pooled OR for habitual versus nonhabitual cannabis users or never-users was 0.96 (95% confidence interval [CI]: 0.66–1.38). The OR for those with consumption of at least 10 joint-years (one joint per day for 10 years) was 0.94 (95 CI: 0.67–1.32). An epidemiologic review of six lung cancer studies, including the study by Zhang et al.[24] and two studies included in that review, concluded that these studies did not support an association of marijuana use and lung cancer.[25] A limitation of these pooled and epidemiologic analyses is the small numbers of cannabis users who were heavy and chronic users.

Additionally, the data are based on self-reporting and are subject to recall bias and unknown variations in cannabis dose related to differences between cannabis plants, differences in processing, and inhalational techniques. The National Academy of Science Expert Panel concluded that there is moderate evidence of no statistical association between cannabis smoking and the incidence of lung cancer.[3]

Potential Benefits

Cancer-Associated Pain

There is moderate to substantial evidence that the use of cannabinoids is of benefit for treatment of chronic pain, including neuropathy.[3,26–28] The National Academy of Science Expert Panel concluded that there is substantial evidence that cannabis is an effective treatment for chronic pain in adults.[3] Chronic pain is the most commonly cited reason for use of medical marijuana in the states of Colorado and Oregon. Whiting et al.[26] performed a meta-analysis of 28 studies in the literature using nabiximol (n = 13), nabilone (n = 5), THC oral mucosal spray (n = 3), smoked THC (n = 4), and one vaporized cannabis. All but one of these studies were placebo controlled. The causes of pain varied but included neuropathy, cancer pain, and others. The average number of patients reporting improvement in pain of 30% or more was greater with cannabinoids (OR = 1.41, 95% CI: 0.99–2.0). Two studies of vaporized cannabis reported pain reductions similar to that in the Whiting meta-analysis.[29,30] There are survey data of patient reported outcomes suggesting that cannabis use may result in reduced use of prescription drugs for pain, anxiety, or depression.[31] Notably, most studies reporting on the benefits of cannabis for the treatment of pain are reporting on non–cancer-associated pain. Benefits as related to cancer pain primarily represent extrapolations from improvements in pain from other diseases. The American Society of Clinical Oncology guidelines stated that there is insufficient evidence to recommend medical cannabis for frontline management of chronic pain in patients with cancer; however, evidence suggests that it is worthy of consideration as an adjunct analgesic for refractory pain (evidence quality, intermediate; strength of recommendation, moderate).[28]

CINV

There is conclusive evidence that oral cannabinoids are effective for treatment of CINV.[26,32] Nabilone and dronabinol are FDA approved for nausea and vomiting due to chemotherapy in patients who fail to respond to standard antiemetics. A meta-analysis of 28 trials (1772 participants) included eight trials that were placebo controlled and 20 that had active comparisons (prochlorperazine most commonly). All the studies suggested a greater benefit of cannabinoids compared with the benefit from both active comparators and placebo. Complete nausea and vomiting response was greater with oral cannabinoids (dronabinol or nabiximols) than with placebo (OR = 3.82; 95% CI: 1.55–9.43). There were no studies of good quality showing benefit of either inhaled or ingested plant-based cannabis.[3,26] Other meta-analyses have confirmed the benefits of dronabinol and nabilone with CINV, whereas levonantradol demonstrated equivalence of the antiemetic effect to that of neuroleptics.[33,34] A patient's preference for cannabis was associated with the greatest magnitude in reduction of nausea and vomiting.[33] However, many studies were

performed several years ago, which was before the advent of other effective antiemetics such as serotonergic 5-hydroxytryptamine receptor antagonists.[32] The American Society of Clinical Oncology guidelines stated that the evidence is insufficient for a recommendation regarding the use of medical marijuana in place of the tested FDA-approved cannabinoids dronabinol and nabilone for the treatment of nausea and vomiting due to chemotherapy or radiation therapy. When a cannabinoid is chosen for rescue and refractory use, the Expert Panel recommends dronabinol or nabilone.[35] The National Academy of Science Expert Panel stated that that there is conclusive evidence that oral cannabinoids are effective antiemetics for treatment of CINV.[3]

Cancer-Associated Anorexia-Cachexia

The FDA approved the use of dronabinol for human immunodeficiency virus–induced anorexia, but there is currently insufficient evidence to support or refute the effectiveness of cannabinoids for cancer-associated anorexia-cachexia. Notably, two phase III trials have evaluated cannabinoids for anorexia-cachexia. Jatoi et al. randomized 469 patients with loss of appetite and weight loss of 5 pounds or more over 2 months.[36] Patients received dronabinol, 2.5 mg twice daily, megestrol acetate, 800 mg daily, or the combination. Megestrol was superior for appetite and weight gain, but the combination was not better than megestrol alone. Weight gain of 10% or greater for megestrol or dronabinol was 11% versus 3% ($p = 0.02$). The Cannabis-In-Cachexia-Study-Group randomized patients with advanced cancer with a weight loss of 5% or greater over 6 months to treatment with 2.5 mg of THC plus 1 mg of CBD, 2.5 mg of THC, or placebo for 6 weeks.[37] They enrolled 243 participants, but only 164 completed treatment. The intent-to-treat analysis showed no significant differences for appetite, quality of life, or toxicity. Increased appetite was reported in 73%, 58%, and 69% of participants, respectively.

Limitations of Current Evidence between Cannabis and Lung Cancer

There are several common limitations to studies relating cannabis to cancer risk and as a potential adjunctive treatment to cancer-related pain and CINV. Psychoactive components of cannabis are highly variable between plant varieties and culturing techniques. There is relatively little understanding of the critical receptor-based pathways for the effects of cannabis on pain, CINV, and potential appetite modulation. There are few data evaluating the complexities of cancer care as related to the efficacy of cannabis during or after cancer treatment. The dynamic metabolic and immunologic effects of chemotherapy and cancer treatment may alter the pharmacodynamics or pharmacokinetic properties of cannabis or its derivatives. For example, activation of CB receptors may alter cancer cell physiology[9] and, theoretically, response to cancer. In parallel, targeted therapeutics that alter adenylate cyclase or other downstream pathways of CB receptors may alter the efficacy of cannabis or its derivatives. There are no data to suggest that cannabis is an effective anticancer treatment for any type of cancer.[3] Effect modification between cannabis and other drugs of abuse confound an accurate estimate of risk and benefits. Though THC can be detected in bodily fluids and urine, a more rapid and cost-effective biologic marker would significantly improve the accurate, repeated assessment of cannabis use and overcome the known misclassification associated with self-report. In the arena of well-structured clinical trials, cancer care provides an opportunity to conduct controlled trials to further evaluate the potential benefits of cannabis to improve cancer-related symptoms. Careful consideration of the regulatory environment can facilitate more accurate prospective risk evaluations. However, the observations to date certainly justify a more structured evaluation of the potential risks and benefits of cannabis.

Conclusion

The available literature confirms the benefit of cannabinoids in pain control for some patients. FDA-approved oral cannabinoids are effective adjunctive treatment for CINV; however, studies comparing these drugs with 5-hydroxytryptamine receptor antagonists are not available. To date, there are no convincing studies showing benefit of ingested or inhaled plant-based cannabis for nausea and vomiting. There is insufficient evidence that cannabinoids are beneficial for cancer-associated anorexia-cachexia. Smoking cannabis is associated with symptoms of chronic bronchitis, and there may be a modest association with the development of chronic obstructive pulmonary disease. Current evidence does not suggest an association with lung cancer. These studies are limited by the relatively small numbers of individuals who were heavy and chronic users and the other limitation of cannabis use as outlined previously. The increasing strength of the THC in currently available cannabis and the increasing use of this substance as it is legalized for either medical or recreational purposes warrants careful observation and future studies. Future studies in the United States are being delayed by the designation of cannabis as a Schedule I drug and the fact that the National Institute of Drug Abuse has only one approved manufacturer for clinical trials, the University of Mississippi.[3] It is hoped that these hurdles will soon be overcome in countries with scientific and visionary leadership.

Cannabis use among patients with cancer is common. A cross-sectional survey of adult patients with cancer at a National Cancer Institute–designated Cancer Center in Washington state reported that 222 of 926 (24%) had used cannabis in the past year and 21% had used cannabis in the past month.[38] Random urine samples for THC found similar percentages. Legalization was reported to be important in the decision to use cannabis. Patients with cancer noted that they are not receiving adequate information from their oncology providers. Cancer caregivers need to become better informed.

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