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Exploring the Use of Medical Marijuana for Supportive Care of Oncology Patients

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Abstract

Medical marijuana, also known as cannabis, is being sought by patients and survivors to alleviate common symptoms of cancer and its treatments that affect their quality of life. The National Academy of Sciences (2017) reports conclusive or substantial evidence that cannabis is successful in treating chronic cancer pain and chemotherapy-induced nausea and vomiting, moderate evidence that cannabinoids are beneficial for sleep disorders that accompany chronic illnesses, and limited evidence supporting use for appetite stimulation and anxiety. However, due to the fact that cannabis is classified as a Schedule I controlled substance, there is an absence of rigorous, scientific evidence to guide health-care professionals. In addition, the Schedule I designation makes it illegal for health-care professionals in the United States to prescribe, administer, or directly distribute these drugs. Legislation has outpaced research in this area. Therefore, the National Council of State Boards of Nursing (NCSBN) appointed a medical marijuana guideline committee to create guidelines for the nursing care of patients using medical marijuana, marijuana education in nursing programs, and guidelines for advanced practice registered nurses (APRNs) certifying a patient for the use of medical marijuana (The NCSBN Medical Marijuana Guidelines Committee, 2018). Six states/districts authorize APRNs to recommend the use of medical marijuana to patients with qualifying conditions (Kaplan, 2015). As of March 2021, 35 states plus the District of Columbia have authorized the use of medical marijuana (DISA Global Solutions, 2021). Therefore, APRNs will be caring for these patients and need to know the medical, pharmacological, and legal issues surrounding medical cannabis use.

CASE STUDY

MR is a pleasant 74-year-old gentleman who comes to the office complaining of increased pain in his spine. He also reports loss of appetite and a 12-lb weight loss over the past 2 weeks. MR has a history of pros-

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tate cancer metastatic to the bone diagnosed in 2018. He is status post treatment with docetaxel and intensity-modulated radiation therapy. He was started on radium-223 dichloride and received the fourth of 6 doses 1 month ago. He is currently on leuprolide and denosumab. His pain was previously controlled on a 100 µg fentanyl patch with 15 mg oxycodone orally for breakthrough pain.

In his support group, he heard anecdotal stories of patients using cannabis to relieve pain, as well as insomnia, nausea, anxiety, and loss of appetite, and wants to know if this is an option for him. He lives in one of the six states that allow advanced practice registered nurses (APRNs) to certify patients for use of medical marijuana. A review is performed of MR's current and past treatments for chronic cancer pain and anorexia, which are qualifying conditions in this state. MR does not want more opioids due to the adverse effects of sedation and constipation. He previously tried a course of gabapentin with no relief. He is unable to take nonsteroidal anti-inflammatory drugs due to renal insufficiency. Acupuncture and meditation provide only momentary relief.

A clinical assessment reveals no conditions that would prevent the use of medical marijuana. MR has no history of alcohol or substance abuse, psychosis, schizophrenia, or bipolar manic disorder. A review of his medications is conducted to assess for any potential drug interactions. It is known that medical marijuana is metabolized by cytochrome P450 (CYP) enzymes, in particular, CYP3A4, CYP2C19, and CYP2C9 (see Table 1 for drug interactions). Serum drug levels may increase with concomitant administration of enzyme inhibiters and decrease with concomitant administration of enzyme inducers (MacCallum & Russo, 2018). None of his cancer drugs are metabolized by the CYP system. However, cannabis does work synergistically with opioids to decrease pain (Abrams et al., 2011). A dose reduction may be possible in the future (The NCSBN Medical Marijuana Guidelines Committee, 2018). Also, medical marijuana has an added central nervous system depressant effect with benzodiazepines, so his alprazolam dose may need to be decreased. Following a thorough review, MR is then registered in the state medical marijuana program for treatment of the chronic pain of cancer and anorexia.

Table 1. Drug Interactions

- It is possible that THC may decrease serum concentrations and pharmacologic effect of CYP1A2 substrates such as clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, or chlorpromazine.
- Substrates that are CYP2C9, 2C19, and 3A4 inhibitors may increase the effects of THC.
- CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, and other PDE5 inhibitors, antihistamines, haloperidol, antiretroviral, and some statins (atorvastatin and simvastatin).
- CYP2D6 metabolizes many antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers, and opioids.
- THC and CBD increase warfarin levels.
- Cannabis-infused tea has no effect on docetaxel or irinotecan.
- Alcohol may increase THC levels.
- Smoked cannabis can decrease theophylline levels.
- Smoked cannabis had no effect on indinavir or nelfinavir.
- CBD increased clobazam levels in children treated for epilepsy.
- Cannabis during treatment with immunotherapy (nivolumab) decreased response rate but not progression-free or overall survival in one small retrospective study.

Note. CYP enzyme interactions occur mostly in the liver with oral cannabis administration. Smoking or topical administration of cannabis bypass the liver. Patients with liver cancer have a greatly reduced ability to metabolize cannabis. THC = tetrahydrocannabinol; CBD = cannabidiol; PDE5 = phosphodiesterase type 5; SSRI = selective serotonin reuptake inhibitors. Information from Alsherbiny & Li (2019); Government of District of Columbia Department of Health (2015); Kleckner et al. (2019); LeClair et al. (2019); Taha et al. (2019).

An assessment of MR's prior experience with medical marijuana and a discussion of his preferences, needs, and knowledge is conducted. MR reports recreational use of marijuana in the 1970s but has had no exposure since then. He is open to smoking flower, vaping, or edibles. There is no recommended dosage of medical marijuana since it is not a U.S. Food & Drug Administration (FDA)-approved drug. In addition, there is a wide range of medical marijuana concentrations in different products. Based on the assessment and MR's desires, a recommendation is made to start with a low dose and slowly titrate up in order to

reach an optimal dose while avoiding undesirable side effects (see Table 2 for dosing strategies). The recommendation is to start with a 30 mL sublingual tincture of 1:1 cannabinoid (CBD) 300 mg to delta-9-tetrahydrocannabinol (THC) 300 mg. He is instructed to take 1 to 2 drops in the morning and evening for 5 days then increase it to 3 times a day for 5 days. This formulation provides 0.5 mg of THC and 0.5 mg of CBD per drop. A 1:1 formulation was chosen because THC contributes analgesic and anti-inflammatory effects, while CBD can counteract the psychoactive effects of THC and adds anxiolytic effects (LeClair et al., 2019). MR can then increase the dose by 1 to 2 drops every 2 days until he obtains relief or experiences side effects. This may take at least 1 to 2 weeks. For sleep, the recommendation is 1 to 2 puffs of THC medical marijuana vape pen (2 mg per puff) of an indica strain, which can be repeated if necessary after 15 minutes.

MR is requested to keep a diary of doses and effects and to set up a follow-up appointment to monitor his response and any side effects. Documentation of provider assessment, including how the patient qualifies for medical marijuana, goals of treatment, plans to evaluate patient response, and patient education provided must be done (see Table 3 for patient resources). MR is cautioned to only buy medical marijuana at a state-regulated dispensary, as products from other sources may be diluted with toxic substances (such as vitamin E acetate), and flower may be contaminated with fungus or pesticides, which pose a particular risk to immunocompromised patients.

State-regulated dispensaries should be able to provide a Certificate of Analysis (CoA), a document from a third party that lists the product's cannabinoid and terpene profile as well as the presence of any pesticide, heavy metal, or microbial contaminant residue. A review of which dispensaries carry the recommended product is conducted with MR, as each dispensary carries different products. He is also instructed to include medical marijuana on the list of medications he provides his health-care providers so that they can monitor any drug interactions or adverse effects that may occur. In the case of MR's hospitalization, his health-care providers will need to provide substitutes for symptom management, as most hospitals do not allow use on site.

Table 2. Dosing Strategies

- Start low and go slow.
- Determine delivery system(s). Long-acting oral preparations are best for chronic conditions. However, an immediate acting preparation should be available for symptom breakthrough relief.
- Determine if the patient desires a product rich in CBD, THC, or a more equal ratio.
- Caution prior recreational users that THC concentrations in cannabis plants have increased from about 4% in the early 1990s to more than 15% in 2018.
- If a patient is cannabis naive, it is best to start with CBD preparations of 15–20 mg 2 to 3 time a day. If THC is needed, add in 1.5–2.5 mg increments. THC-dominant preparations should first be used at bedtime to limit adverse effects.
- For inhalation, patients should start with 1 puff, wait 10–15 minutes, then increase by 1 puff every 15–30 minutes until symptom relief is obtained.
- If symptom relief is not obtained, adjust the dose up or down in small increments or try a different product.
- With edibles, it is best to wait until the next day to increase dose to avoid overmedicating.
- Cannabis therapeutic doses are individually determined.
- Symptom control can be obtained without euphoric effects if desired with the use of CBD to balance THC side effects, especially for daytime use or the need to drive.
- If THC tolerance develops, this can be annulled with a drug vacation of at least 48 hours.
- Typical oral dose can range from 2–60 mg per day.
- If improvement is not seen after 8–16 weeks, consider stopping treatment or referral to a cannabinoid specialist.
- Example of a THC titration regimen
  - » Days 1–2: 1–2.5 mg once a day at bedtime (consider lower doses in the elderly, children, or those with other concerns).
  - » Days 3–4: If previous dose is well tolerated, increase by 1.25–2.5 mg at bedtime.
  - » Days 5–6: Increase by 1.25–2.5 mg at bedtime and initiate daytime doses.
  - » Increase as needed to a maximum of 15 mg in divided doses every 2 days until relief is obtained or side effects are not tolerated.

Note. Information from Dolce & Chin (2018); Kleckner et al. (2019); MacCallum & Russo (2018); NIDA (2020).

The term medical marijuana refers to the leaves or flowers of the *Cannabis sativa* plant. The words marijuana and cannabis are often used interchangeably. Marijuana was in fact listed in the US Dispensary from 1850 to 1924 (Ryan & Sharts-Harpko, 2017). It was used to treat a variety of illness, including asthma, anorexia, insomnia, seizures, nausea and vomiting, and sexual dysfunction. At the end of alcohol prohibition, the Marihuana Tax Act of 1937 was passed. Under this act, importation, cultivation, possession, or distribution was regulated, and importers were required to pay an annual tax. The act was opposed by the American Medical Association. Marijuana was officially removed from the United States Pharmacopoeia in 1942. The Controlled Substances Act of 1970 classified marijuana as a Schedule I controlled substance (Bridgeman & Abazia, 2017; Ryan & Sharts-Hopko, 2017; The NCSBN Medical Marijuana Guidelines Committee, 2018). The classification not only prevents healthcare providers from prescribing medical marijuana, but it also makes research very challenging. Additionally, many studies are small, retrospective, lack a control group, use a comparator that is no longer a standard treatment, and incorporate a variety of synthetic and plant-based products.

Marijuana was first legalized for medical use by the voters in California in 1996. The federal government opposed this proposition and threatened to revoke the privileges of anyone who prescribed it. In 2000, a group of physicians challenged this policy and the United States District Court made the decision to allow physicians to recommend, but not prescribe, medical marijuana (The NCSBN Medical Marijuana Guidelines Committee, 2018).

To this day, the use of medical marijuana, even through authorized state medical marijuana programs (MMPs), conflicts with federal law. The federal government has issued position papers from the Department of Justice (DOJ) on prosecuting people who recommend or use medical marijuana for medical purposes in compliance with state laws. These position papers change with each administration. Under Obama, the Cole Memo (2014) discouraged federal prosecutors from prosecuting those in compliance under local law. However, this guidance was rescinded in 2018 with the Trump administration when the DOJ suggested the prosecution weigh all relevant considerations including impact of the crime on the community when deciding whom to prosecute (Sessions, 2018; The NCSBN Medical Marijuana Guidelines Committee, 2018).

ESSENTIAL KNOWLEDGE FROM THE NATIONAL COUNCIL OF STATE BOARDS OF NURSING

What Are Medical Marijuana Programs?

Medical marijuana programs provide the specifics of each state's medical marijuana legislation. Since all MMPs differ, APRNs need to know exactly what their state laws say. (Links to the legislation of each state can be found at ncsl.org/research/health/state-medical-marijuana-laws.aspx.) However, the state laws share some common features (Kaplan, 2015; The NCSBN Medical Marijuana Guidelines Committee, 2018):

- A definition of which health-care providers may authorize patients to use marijuana as well as specific courses or training required.
- A list of qualifying conditions. Often, the conditions must be deemed terminal, debilitating, and/or not relieved by standard treatments.
- A definition of the required type of provider-patient relationship. Some states require a previous relationship to be up to 6 months.

Table 3. Patient Resources

Name	Link
National Cancer Institute	cancer.gov/about-cancer/treatment/cam/patient/cannabis-pdq
National Center for Complementary and Integrative Health	nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know
Americans for Safe Access	safeaccessnow.org
National Institute on Drug Abuse	drugabuse.gov/drug-topics/marijuana
Neurology of Cannabis	neurologyofcannabis.com

- Forms of marijuana permitted and any limitations on the amount that can distributed.
- How patients with a certified condition can be registered with the MMP.
- Rules regarding designated caregivers.
- Legal protections for patients, designated caregivers, and health-care providers.

The Endocannabinoid System

The endocannabinoid system (ECS) consists of endocannabinoids (eCBs), cannabinoid receptors, endogenous ligands, and enzymes used for their production and degradation. eCBs are also referred to as endogenous cannabinoids. Arachidonoylethanolamide (AEA), also known as anandamide (named after the Sanskrit word for bliss), and 2-arachidonoylglycerol (2-AG) are eCBs produced by both humans and animals (except for insects). They are lipophilic molecules synthesized mainly in the postsynaptic membranes of the brain. They serve as primary messengers across nerve synapses and are synthesized on demand (Bridgeman & Abazia, 2017; Di Marzo et al., 1998; Nahtigal et al., 2016; Pacher et al., 2020; Sarfaraz et al., 2008; see Figure 1).

Two endogenous cannabinoid receptors have been identified: CB1 and CB2. The CB1 receptors are found mostly in the brain (specifically the basal ganglia and limbic system but also the hippocampus and cerebellum), peripheral nervous system, as well as in the liver, stomach, heart, and in male and female reproductive systems. Notably, they do not exist in the brain stem area controlling respiration, so lethal overdoses due to respiratory depression do not occur.

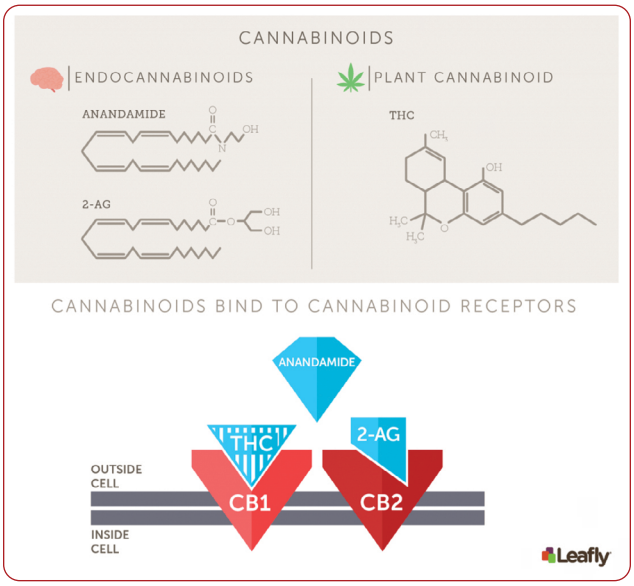

Figure 1. Cannabinoids. Anandamide and 2-AG are the two major endocannabinoids produced endogenously in the body. Reprinted with permission from www.leafly.com/news/science-tech/what-is-the-endocannabinoid-system

The CB2 receptors are found mostly in the immune system, particularly the spleen. Simulation of eCBs is thought to promote homeostasis of five key functions: eating, sleeping, relaxing, forgetting, and protecting (Bridgeman & Abazia, 2017; Di Marzo et al., 1998; Nahtigal et al., 2016; Pacher et al., 2020; Sarfaraz et al., 2008).

Phytocannabinoids are plant-derived cannabinoids such as THC and CBD and are found in the marijuana plant *Cannabis sativa L*. More than 140 cannabinoids have been isolated, and there are thousands of medical marijuana strains referred to as "chemovars." Each chemovar has varying concentrations of cannabinoids and other components. THC is the primary cannabinoid responsible for the psychotropic and intoxicating effects of medical marijuana. THC-dominant sativa strains produce uplifting, energizing cerebral effects; THC-dominant indica strains have sedating, relaxing cerebral effects; and hybrid chemovars fall in between. CBD has mild mood-altering psychotropic activity but does not cause intoxication. CBD binds to receptors adjacent to THC, thus modulating its effects. To take advantage of this, medicinal preparation with specific CBD to THC ratios are produced by licensed companies and medical marijuana growers. Other phytocannabinoids, including cannabinol (CBN), cannabigerol (CBG), and cannabichromene (CBC), also appear to have biological effects and are being investigated for therapeutic use. Additionally, more than 200 terpenoids or terpenes have been found in specialized structures called trichomes, which are epidermal projections on the medical marijuana plant. Terpenes are the main component of the essential oils of plants and flowers. They work synergistically with cannabinoids, creating what is referred to as the "entourage effect." This refers to the idea that plants as a whole can be better drugs than individual compounds derived from them. Some terpenes found in many medi-

cal marijuana plants are (The NCSBN Medical Marijuana Guidelines Committee, 2018; Pacher et al., 2020; Sarfaraz et al., 2008):

- Limonene, which has anxiolytic and antidepressant effects.
- Myrcene, which has anti-inflammatory, analgesic, and sedative effects.
- α-pinene, which has anti-inflammatory, antibacterial and bronchodilator effects, as well as the ability to counteract short-term memory defects induced by too much THC.
- Linalool, which has anxiolytic effects.
- β-caryophyllene, which has gastroprotective and anti-inflammatory effects.
- Ocimene, which has possibilities as an antibiotic.
- Terpinolene which, in preclinical studies, has potential as an antibiotic and may have antitumor activity.

Patients who want medical marijuana to treat a particular condition can utilize the terpene profile in the CoA to aid in finding the right product.

Synthetic cannabinoids are those developed in the laboratory. Dronabinol (used to treat chemotherapy-induced nausea and vomiting [CINV] and decreased appetite) and nabilone (used to treat severe CINV) are synthetic preparations of THC.

The cannabidiol oral solution, Epidiolex, is a purified plant-derived preparation of CBD used to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients who are 1 year old or older. THC and cannabidiol (Sativex), also a plant-derived preparation, is a CBD to THC 1:1 ratio oral mucosal spray used for muscle spasms associated with multiple sclerosis. It is not approved in the United States (Kleckner et al., 2019).

Pharmacokinetics

The pharmacokinetics (PK) of medical marijuana vary with the method of administration (see Table 4 for a quick guide to PK). The PK of THC in humans has been evaluated after inhalation (smoking or vaporization) and ingestion. The onset, rate of absorption, and bioavailability are increased after inhalation. THC has been detected in the plasma after the first inhalation, and peak plasma concentrations are achieved after 5 to 10 minutes. Bioavailability of inhaled THC ranges from 2% to 56%. It is thought that up to 50% of the inhaled dose is lost due to pyrolysis and side stream smoke. Factors affecting PK of inhaled THC are the volume of each puff, the duration of time that the puff is held, and the temperature of the vaporizer. Recommended temperatures for vaporizers range from 350°F to 400°F. Temperatures above 400°F may cause the release of the carcinogenic agent benzene and other toxins. Duration of action of inhaled THC is 2 to 4 hours. The rapid action of inhaled medical marijuana makes it ideal for acute or episodic symptoms. Chronic use is associated with respiratory symptoms such as cough, phlegm, and bronchitis, but not lung cancer or chronic obstructive pulmonary disease (COPD) unless patients also use tobacco (Tashkin, 2013). It is felt that vaporization produces less harmful byproducts than smoking and produces decreased pulmonary symptoms (Bridgeman & Abazia, 2017; MacCallum & Russo, 2018; Nahtigal et al., 2016; National Academy of Sciences, 2017). Patients should wait 10 to 15 minutes between puffs to avoid overconsumption and unwanted effects.

Oral consumption and metabolism of medical marijuana "edibles" is much slower and less predictable. The onset of action may be 30 to 90 minutes, with peak levels between 1 to 6 hours and

Table 4. Quick Guide to Pharmacokinetics

	Inhalation: smoke or vapor	Tinctures: drops or sprays	Capsules/edibles	Transdermals	Suppositories
Onset	5 sec–10 min	15–45 min	30–90 min	1–15 min	10–15 min
Peak effect	5–10 min	1–2 hr	1–6 hr	90 min	2–8 hr
Duration	2–4 hr	6–8 hr	4–8 hr	Up to 48 hr	Up to 8 hr
Note	Good for acute symptoms; can cause bronchial irritation	Good for acute symptoms; easy to titrate dose	Good for chronic conditions; difficult to titrate dose	–	Must be placed 1–1.5 in from anal verge

a duration of 4 to 10 hours. Bioavailability after ingestion is 4% to 20%. Oral medical marijuana undergoes significant first-pass hepatic metabolism by the CYP450 gene where delta-9-THC is converted to 11-hydroxy-THC, which is a longer-lasting and more potent cannabinoid. Cannabinoids are lipophilic so are best absorbed in the presence of fats, oils, or polar solvents. Therefore, recent meals may affect absorption. Oral routes are popular due to convenience, more accurate dosing, and are good for chronic symptoms; however, they are more difficult to titrate (Bridgeman & Abazia, 2017; Dolce & Chin, 2018; MacCallum & Russo, 2018; Nahtigal et al., 2016).

Oral mucosal preparations have on onset of 15 to 45 minutes if held sublingually and last 3 to 4 hours; the onset is 90 minutes if swallowed and lasts 6 to 8 hours. Topical preparations such as salves are used for local pain such as that from dermatologic or arthritic conditions and have a variable onset of action and duration. Newer transdermals using nanoparticles or ionized particles may have enhanced and time-released absorption. Their onset is usually within 15 minutes and may last up to 48 hours depending on dose.

A less popular form of medical marijuana is suppositories. THC-hemisuccinate is the form of THC that has the best rectal absorption. Suppositories could be helpful for palliative care, patients who cannot swallow, gastrointestinal illnesses, and for healing skin damaged by rectal radiation. Onset of action is about 15 minutes and the effect may last up to 12 hours (Backes, 2017; Dolce & Chin, 2018; MacCallum & Russo, 2018; see Table 2 for dosing strategies and Table 4 for a guide to PK).

Adverse Effects of Medical Marijuana

In general, medical marijuana is considered safe and well tolerated (Bar-Lev Schleider et al., 2018; Kleckner et al., 2019; MacCallum & Russo, 2018; Ware al., 2015). An Israeli study of 2,970 cancer patients found that 30% of patients reported at least one side effect from medical marijuana at 6 months, but that the side effects were relatively minor: dizziness, dry mouth, increased appetite, sleepiness, and psychoactive effects. Most patients reported fewer side effects as well as less severe side effects than with their prescription medications (Bar-Lev Schleider et al., 2018). Ware and colleagues (2015) prospectively studied safety issues using a standardized medical marijuana product (12.5% THC) in patients who did not have cancer but were being managed in chronic pain clinics. Patients could choose the route of administration. The patients were compared with patients in the same clinics who did not use medical marijuana and were followed for 1 year. They found no significant difference in the occurrence of serious adverse effects.

Adverse effects are related primarily to THC and are dose dependent. THC administered with CBD reduces psychoactive side effects. Side effects of THC such as fatigue, tachycardia, and dizziness are often avoidable when the starting dose is low and titration is slow. Slow titration also decreases the incidence of psychoactive side effects. There have been no reported deaths due to overdose due to the lack of CB1 receptors in the cardiorespiratory centers of the brainstem (MacCallum & Russo, 2018).

The most common adverse effects reported are drowsiness and fatigue, dizziness, dry mouth, anxiety, nausea, cognitive effects (alteration in perception, time distortion, memory and attention), and cough or bronchitis if smoked. Euphoria, blurred vision, and headache are also common. Rare side effects are orthostatic hypotension, paranoia, toxic psychosis, depression, ataxia, tachycardia, diarrhea, and medical marijuana hyperemesis syndrome (Kleckner et al., 2019; MacCallum & Russo, 2018). Medical marijuana hyperemesis syndrome is most often seen in patients under 50 years old with a long history of marijuana use. These patients present with severe, cyclic nausea and vomiting. Cessation of marijuana, long, hot showers or baths, and capsaicin applied to the abdomen are recommended to relieve the symptoms (Lapoint, 2014; The NCSBN Medical Marijuana Guidelines Committee, 2018). Allergies to cannabis have also been reported. They are immunoglobulin E (IgE) mediated and vary depending on the route of administration (Kleckner et al., 2019).

Cannabis use disorder (CUD) is a term used when medical marijuana use leads to significant impairment or distress. Long-term medical marijuana use can lead to addiction; 9% of users are at risk (The NCSBN Medical Marijuana Guidelines Committee, 2018). Adolescents are at greater risk, as are persons with persistent negative emotions

and psychological distress (The NCSBN Medical Marijuana Guidelines Committee, 2018). Medical marijuana withdrawal syndrome is usually seen in patients with heavy, prolonged use. Symptoms may include insomnia, lack of appetite, restlessness, anxiety, irritability, anger, depression, physical discomfort, and unpleasant dreams (The NCSBN Medical Marijuana Guidelines Committee, 2018).

Contraindications

Pregnancy, lactation, and psychosis are considered to be contraindications for cannabis use. Care should be taken in patients with unstable cardiac conditions due to tachycardia and possible hypotension. There is no evidence of QTc prolongation. Medical marijuana use in children and teens is controversial. There is felt to be an increased risk of schizophrenia and psychosis-related disorders in those with a predisposition to these disorders. According to the National Institute on Drug Abuse (NIDA, 2020), people who use marijuana, especially during adolescence, and carry the AKT serine/threonine kinase 1 (*AKT1*) C/C gene variant or the Val variant of the catechol-O-methyltransferase (*COMT*) gene have an increased risk of developing psychosis. Marijuana use also seems to worsen the course of the illness in those who already have schizophrenia. Additionally, regular use of medical marijuana under the age of 18 has been associated with lower IQ and changes in brain regions critical to memory and learning. In one study of 1,037 persons from birth to age 38, the frequent use of marijuana starting in adolescents was associated with a loss of an average of 6 to 8 IQ points. There was no decline seen when use started as an adult (Bridgeman & Abazia, 2017; Government of District of Columbia Department of Health, 2015; Meier et al., 2012; The NCSBN Medical Marijuan Guidelines Committee, 2018).

Smoking as a route of administration should be avoided in patients with COPD or chronic bronchitis. Medical marijuana may increase symptoms of poor balance in patients with dyskinetic disorders and thus increase the risk of falls. Patients should be cautioned not to drive or operate heavy machinery when using medical marijuana, as impaired attention and psychomotor performance may occur (Bridgeman & Abazia, 2017; Government of District of Columbia Department of Health, 2015; National Academy of Sciences, 2017; The NCSBN Medical Marijuan Guidelines Committee, 2018).

OVERVIEW OF RESEARCH ASSOCIATED WITH MEDICAL USE IN CANCER PATIENTS

Lack of high-quality data and randomized controlled trials due to government restrictions has impeded the accumulation of high-quality evidence. Evidence thus has been derived mostly from clinical and basic science research. Therefore, the NCSBN recommends that medical cannabis is best used when current first- and second-line medications or therapies have failed or been insufficient and for patients who might benefit from complementary use (The NCSBN Medical Marijuana Guidelines Committee, 2018).

Preclinical research indicates that cannabinoids have more anticancer than procancer effects. Cannabinoids have been shown to inhibit some cancer cell types by modulating signaling pathways that lead to cell death and the inhibition of angiogenesis (Abrams & Guzman, 2014; Ghasemiesfe et al., 2019). Medical marijuana has also demonstrated anti-inflammatory and antioxidant effects. A meta-analysis published in 2019 concluded there is low-strength evidence that regular use of marijuana for 10 years is associated with the development of testicular germ cell tumors but insufficient evidence to associate marijuana use with lung, head and neck, oral squamous cell cancers, and lung cancer (Ghasemiesfe et al., 2019; National Academy of Sciences, 2017). However, the possibility exists that medical marijuana could interact with cancer treatments such as chemotherapy or immunotherapy (see Table 1 on drug interactions). One small, retrospective Israeli study of 140 patients on nivolumab for advanced malignancies showed a reduced response rate to the immunotherapy (although there was no change in progression-free or overall survival) in the 51 patients who used medical marijuana during treatment (Taha et al., 2019).

Chronic Pain

Pain is one of the most common symptoms in patients with cancer and has a negative impact on patients' activities of daily living and quality of

life. Pain is reported in up to 60% of patients being actively treated for cancer and up to 90% of those with advanced disease (Boland et al., 2020). There is evidence that cannabis affects both sensation and perception of pain. CB1 receptors are located on nociceptors, allowing medical marijuana to have a direct effect on nociceptors in the periphery. CB1 and CB2 receptors in the nervous and immune systems allow for additional modulation of pain sensation (Kleckner et al., 2019). Additionally, medical marijuana is known to have a euphoric effect, so it may increase a subjective sense of well-being that may decrease the perception of pain.

Various systematic reviews arrive at conflicting opinions on the helpfulness of medical marijuana in reducing pain. The National Academy of Sciences concluded that there is substantial evidence that medical marijuana is an effective treatment for chronic pain in adults (National Academy of Sciences, 2017). Another systematic review and meta-analysis of 28 studies using various formulations of medical marijuana demonstrated a nonsignificant improvement in pain control (Whiting et al., 2015). Davis (2016) looked at multiple studies of low to moderate quality and reported a modest reduction in cancer pain. Ware and colleagues (2015) compared outcomes for over a year in a study of 215 patients with chronic noncancer pain who used a standardized preparation of medical marijuana administered by whatever route the patient chose. There was a comparison group of 216 patients with chronic noncancer pain who did not use medical marijuana. They found a significant reduction in pain intensity reported on the 0 to 10 numerical rating scale, as well as an improvement in physical function in the medical marijuana group but not in the control group. However, Boland and colleagues (2020) reported in their systematic review and meta-analysis that the addition of medical marijuana to opiates in patients with advanced cancer did not decrease pain.

Two recent studies showed significant relief in pain. Bar-Lev Schleider and colleagues (2018) assessed pain intensity and quality of life in more than 1,000 patients and demonstrated a significant reduction in pain in those using medical marijuana. Prior to use, 52.9% of the patients reported their pain to be between 8 to 10 on a 0 to 10 pain scale where 0 is no pain and 10 is intense pain; after 6 months, only 4.6% of patients reported pain at this intensity. Patients also said their quality of life improved; 18.7% reported a good quality of life before starting medical marijuana, while 69.5% reported a good quality of life 6 months later (Bar-Lev Schleider et al., 2018). Another retrospective study of 244 patients reported a decrease in opioid use of 64%, less drug-related side effects, and an improved quality of life (Kleckner et al., 2019).

The exact pathway in which medical marijuana acts to relieve the symptoms of chemotherapy-induced peripheral neuropathy (CIPN) is not known. However, preclinical studies in rats have presented evidence that CBD plays a role in reducing neuropathic pain. Studies in rats have shown that a CB1/CB2 receptor agonist both reduced paclitaxel-induced thermal hyperalgesia and tactile allodynia by activating CB1 and CB2 receptors. The same agonist also prevented vincristine-induced neuropathy (Kleckner et al., 2019).

Placebo-controlled trials in patients with chronic neuropathic pain from various etiologies other than cancer have been conducted. Patients reported that smoking medical marijuana significantly decreased neuropathic pain when compared with placebo (Kleckner et al., 2019).

Nausea and Vomiting

Chemotherapy-induced nausea and vomiting is highly prevalent. Although modern regimens are effective at preventing vomiting, 40% to 75% of patients still report nausea when highly or moderately emetogenic chemotherapies are administered (Bar-Lev Schleider et al., 2018; Kleckner et al., 2019). Dronabinol and nabilone are FDA-approved for the treatment of CINV in patients who have not responded adequately to conventional antiemetic therapy, and the National Comprehensive Cancer Network (NCCN) Guidelines on antiemesis (2020) list dronabinol and nabilone as agents that can be added for breakthrough treatment of CINV.

It is hypothesized that cannabinoids, specifically CBD, exert their antiemetic effect through modulation of the 5-HT_3 and 5-HT_{1A} receptors. Additionally, cannabinoids modulated the release of substance P in preclinical studies (Kleckner et al., 2019). The National Academy of Sciences (2017)

decided that there is conclusive evidence that oral cannabinoids are effective antiemetics for the treatment of CINV (National Academy of Sciences, 2017). In his systematic review, Davis (2016) concluded that nabilone was a better antiemetic than the older drugs domperidone, chlorperazine, and alizapride, but noted there were no comparisons between medical marijuana and the serotonin receptor antagonists. He also pointed out that there have been no direct comparisons to olanzapine and aprepitant, which are both effective drugs for breakthrough nausea and vomiting. Whiting and colleagues (2015) assessed 28 studies comparing medical marijuana with a variety of antiemetics including ondansetron. They found that the average number of patients showing a complete nausea and vomiting response was greater with medical marijuana than with placebo and that there was a nonsignificant greater benefit of medical marijuana compared with the other active comparators. There is also evidence that nabilone is somewhat effective in managing nausea and vomiting related to radiation therapy and anesthesia after abdominal surgery (Abrams & Guzman, 2014).

More recent clinical evidence supports patient claims that cannabis relieves CINV. Bar-Lev Schleider and colleagues (2018) reported that 1,662 patients in their study used medical marijuana (as an oil or flower, capsules, or cigarettes) for CINV. At 6 months, 36.3% of patients reported no more nausea or vomiting, 54.7% claimed symptom improvement, and 9% reported no change (Bar-Lev Schleider et al., 2018). A study by Reblin and colleagues (2019) looked at medical marijuana use in patients with gliomas treated at a comprehensive cancer center in Florida. Thirteen patients used medical marijuana (smoked or ingested THC, CBD only, or THC and CBD oil) for the treatment of nausea; 12 reported symptom relief and 1 reported no effect (Reblin et al, 2019). A study of patients enrolled in Minnesota's medical marijuana program (which allows vapes, capsules, oral solutions, and topical agents) revealed that 40.5% of patients complaining of nausea achieved 30% or greater improvement in symptoms within 4 months and that 49.8% of patients complaining of vomiting achieved a 30% or greater improvement of symptoms in 4 months (Anderson et al., 2019).

The route of delivery must be considered when using medical marijuana for treating nausea and vomiting. A nonoral route is preferred so that the drug has more opportunity to be retained (not expelled) and to reach the target site.

Anorexia and Decreased Appetite

Anorexia and weight loss in cancer patients lead to a poorer quality of life and decreased survival. Dysgeusia is also a common complaint among patients undergoing chemotherapy as well as those with advanced cancer. It is possible that CB1 receptors in the hypothalamus, hindbrain, limbic system, intestinal system, and adipose tissue modulate peptides involved in appetite regulation (Kleckner et al., 2019). Thus, it is possible that medical cannabis may stimulate the orosensory reward pathway and increase the enjoyment of food.

The National Academy of Sciences (2017) did not find enough evidence to support or refute the use of cannabis as a treatment for decreased appetite or anorexia-cachexia syndrome in cancer patients. However, they did conclude that there is limited evidence supporting its use in increasing appetite and decreasing weight loss in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS; National Academy of Sciences, 2017). Davis (2016) reports two small trials and a small case series with medical marijuana where appetite was improved and weight loss was slowed in patients with cancer. However, a large, randomized trial revealed megestrol as superior to dronabinol in increasing appetite (Davis, 2016). There are also animal studies that show that THC and other cannabinoids stimulate appetite and increase food intake. For example, anandamide enhanced appetite in mice and rats.

However, there is some clinical evidence showing that medical marijuana can help increase appetite and improve dysgeusia in adult cancer patients. In 2011, Brisbois and colleagues reported on a randomized trial comparing oral tetrahydrocannabinol to oral placebo. They found the tetrahydrocannabinol significantly heightened chemosensory perception of food resulting in the perception that food "tasted better." Also, premeal appetite and the number of calories eaten as protein increased. Bar-Lev Schleider and colleagues (2018) reported that 1,453 patients in their study utilized medical

marijuana for lack of appetite. 25.8% said the symptom disappeared at 6 months, 62.1% reported improvement, and 12.1% reported no change (Bar-Lev Schleider et al., 2018). Reblin and colleagues (2017) reported on 12 patients who used medical marijuana as an appetite stimulant, and all reported symptom relief. In the Minnesota study by Anderson and colleagues (2019), 1,000 patients reported a lack of appetite, and 38.8% achieved a 30% or greater improvement in appetite within 4 months of initiating the use of medical marijuana. In addition, a randomized study of 47 patients from the National Cancer Institute of Canada found that, after 8 weeks, patients who were given nabilone had a significantly increased caloric intake compared with those given placebo (Turcot et al., 2018).

Medical marijuana may be a good option for cancer patients to try, because the recommended drugs (megestrol acetate, metoclopramide, and steroids) are only recommended for short-term use due to side effects. Dronabinol use is not limited. It is important to note that although medical marijuana may increase appetite and caloric intake, it may not necessarily reverse the cancer cachexia related to energy wasting (Abrams & Guzman., 2014; Kleckner et al., 2019).

Sleep Disorders and Fatigue

Sleep disorders (insomnia, difficultly falling and staying asleep, or unrestful sleep) are complaints of approximately 80% of patients with cancer. Additionally, patients with cancer-related fatigue have a high incidence of sleep disorders. Animal studies have shown that endogenous cannabinoids regulate the circadian rhythm; for example, there is evidence in rats that 2-AG level is highest during the light phase of the dark-light cycle, while AEA is higher during the dark phase (Kleckner et al., 2019).

There is moderate evidence that medical marijuana helps sleep disorders due to chronic illness (National Academy of Sciences, 2017). The evidence that assesses medical marijuana's effect on sleep and fatigue derives from studies of patients with other chronic disorders: irritable bowel disease, fibromyalgia, Crohn disease, Parkinson disease, multiple sclerosis, and post-traumatic stress syndrome. These patients reported less fatigue and sleep disturbances than patients not using medical marijuana (Kleckner et al., 2019).

Studies in patients with cancer have evaluated the effect on sleep and fatigue as secondary outcomes. Turcott and colleagues (2018) studied the effect of nabilone on appetite in a randomized controlled trial and found that patients using nabilone reported a significant decrease in insomnia. In the Bar-Lev Schleider and colleagues study (2018), 2,329 patients used medical marijuana for sleep problems: The sleep problem went away in only 16.7% of patients, but 70.8% reported improvement, while 12.3% reported no relief. In the same study, 2,160 patients used medical marijuana for weakness and fatigue. Only 10.9% reported the symptoms went away, while 55.9% reported improvement and 33.2% reported no improvement (Bar-Lev Schleider et al., 2018). In a study by Anderson and colleagues (2019) in Minnesota, it was reported that of 1,073 patients with disturbed sleep, 41.8% claimed a 30% or more improvement within the first 4 months. In this same study, of the 1,113 patients reporting fatigue, only 27% had an improvement of 30% or more after 4 months. Reblin and colleagues (2019) had only 2 patients using cannabis as a sleep aid, but both found relief from medical marijuana.

Gastrointestinal Distress

Gastrointestinal (GI) distress (abdominal pain, bloating, cramps, constipation, diarrhea, or flatulence) are common in patients with cancer, particularly in those undergoing chemotherapy and with advanced cancer. However, there is not a lot known about how medical marijuana may modulate GI symptoms or its efficacy in treating them. It is hypothesized that medical marijuana moderates the inflammatory cytokines produced by cancer and chemotherapy or via a direct effect on the endocannabinoid systems that helps regulate gut motility and peristalsis (Kleckner et al., 2019). A study by Bar-Lev Schleider and colleagues (2018) evaluated the 1,918 patients who complained of digestive problems. After 6 months of medical marijuana use, the problems disappeared in 26.7% of the patients, improved in 50.3% of the patients, and did not help 23% of the patients.

Cognitive Impairment

Cognitive impairment is a common complaint in patients with cancer. Kleckner and colleagues (2019) reported that up to 30% of patients report cognitive

impairment before treatment even starts, and that number increases to 75% during treatment. Unfortunately, research is lacking on the effect of medical marijuana and cognitive impairment. Patients have reported that moderate to large doses of medical marijuana cause acute impairment in memory and attention, but it appears these effects are temporary. In fact, the study by Ware and colleagues (2015) on the safety of using medical marijuana as a treatment for pain found that neurocognitive tests showed significant improvement after 6 and 12 months both in the group using medical marijuana and the group that did not. There is also some preclinical evidence that CBD can reverse age-related cognitive impairment in rats; and, in older mice, low dose THC restored learning and improved spatial learning and memory (Kleckner et al., 2019).

Anxiety and Depression

Anxiety and depression are very common emotions in patients with cancer; approximately one third of patients experience severe reactions. Preclinical studies of anxiety and depression are lacking; however, the endocannabinoid system is known to be involved in mood regulation, so there is a possibility medical marijuana could modulate mood disorders by binding with cannabinoid receptors in the brain area that influences pleasure. A decrease in generalized anxiety disorder has been demonstrated in mice (Kleckner et al., 2019).

In a study by Bar-Lev Schleider and colleagues (2018), 1,694 patients used medical marijuana for anxiety and depression. At 6 months, the symptoms disappeared in 10.1% but were improved in 74.1%, and 15.8% reported no change. A study by Anderson and colleagues (2019) in Minnesota found that 990 patients used cannabis for depression and that 44.5% reported a 30% or greater improvement in depression within 4 months. Reblin and colleagues (2019) reported 10 patients used medical marijuana for "ability to cope emotionally" and 9 of the 10 reported symptom relief. Quality of life and emotional functioning demonstrated significant increases in Turcott and colleagues' (2018) study of nabilone use in lung cancer patients.

SUMMARY

In the illustrative case, MR reported pain relief without side effects by using six drops of 1:1 CBD to THC three times a day. For convenience, he switched to 10 mg 1:1 CBD to THC capsules once in the morning and once in the late afternoon. He reported that 1 to 2 puffs of indica THC at bedtime helped him fall asleep but not stay asleep, so a 5 mg indica THC capsule was added at bedtime. He was reminded to make sure to store his medical marijuana in an area out of reach of children and nonregistered individuals and to dispose of any unused products in a collection receptacle indicated by the Drug Enforcement Administration (DEA), which can be located by calling the DEA at 800-882-9539. He was also told that his medical marijuana card was only good in the state in which it was issued and that it is illegal to take the drug over state lines.

Evidence for medical marijuana use is limited by inadequate research and legal availability. However, medical marijuana has a safety profile superior to many other medications and has no reported deaths due to overdoses. Individuals are using medical marijuana and health-care providers will see them in their practices. Health-care providers need to have knowledge of the current legal statutes regarding both medicinal and recreational medical marijuana, as well as the jurisdiction of the MMP where they practice. They also need to have an understanding of the endocannabinoid system, medical marijuana pharmacology, and safety considerations for patient use. In addition, health-care providers need to practice shared decision-making and not judge patients' choices for treatment of chronic pain and other symptoms.

Disclosure

The authors have no conflicts of interest to disclose.

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