

# Medical Marijuana (Cannabinoid-Derived Products) for Cancer Patients



Cannabis, also known as marijuana, or called a vast number of other slang terms like weed, herb, pot, grass, bud, ganja, and Mary Jane originated in Central Asia but is grown worldwide today. Cannabis use for medicinal purposes dates back at least 5,000 years, with the earliest reported use being in China around 2700 BC for the relief of pain and cramps.<sup>1</sup>

In the United States, cannabis is still a controlled substance and is classified as a Schedule I agent (a drug with a high potential for abuse and currently no accepted medical use). The U.S. Food and Drug Administration (FDA) has not approved cannabis as a treatment for cancer or any other medical condition. By federal law, the possession of cannabis is illegal, except within approved research settings. However, a growing number of states, territories, and the District of Columbia have enacted laws that decriminalized the recreational and/or medicinal use of marijuana in that specific area.

Cannabis is the fastest growing industry in the world. According to Arcview's market research, regulated marijuana sales in North America totaled \$6.9 billion in 2016. Sales are projected to increase to \$21.6 billion by the year 2021.<sup>2</sup> Over the last few decades, there has been significant interest in the potential use of marijuana for a variety of medical conditions. There are more than 60 U.S. and international health organizations that support granting patients immediate legal access to medicinal marijuana under a physician's supervision.<sup>3</sup>

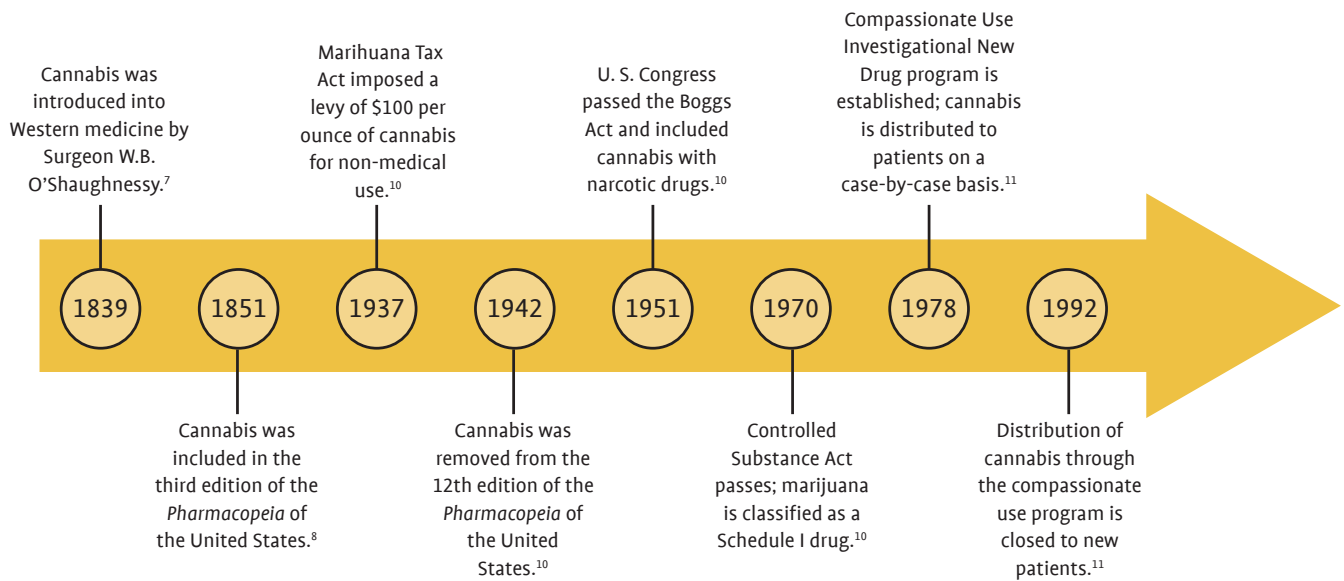
This article is intended to provide a general introduction and overview regarding some of the important aspects and contemporary issues encountered when navigating the field of medical marijuana.

Each state has its own list of the qualifying conditions for which it will allow patients to use medical marijuana. These qualifying conditions are different in each state; however, in many states a number of conditions are cancer related—chemotherapy-induced nausea and vomiting, anxiety, hepatitis C, HIV/AIDS, cachexia (wasting syndrome), and inflammatory bowel disease.

### History and Overview

*Cannabis* is a genus of the family Cannabaceae and has generally been recognized to contain three main species: *sativa*, *indica*, and *ruderalis*. *Cannabis sativa* and *Cannabis indica* are both prevalent in the United States and other parts of the world. *Cannabis sativa* has been employed for thousands of years, primarily as a source of a stem fiber (both the plant and the fiber, termed *hemp*) and a resinous intoxicant (the plant and its drug preparations, commonly termed *marijuana*).<sup>4</sup>

Figure 1. A Timeline of Cannabis History in the United States



Traditionally, *Cannabis sativa* plants are tall, reaching heights of up to 20 feet, loosely branched, and have long, narrow leaves. On the other hand, *Cannabis indica* plants are short and densely branched and have wider leaves.

The cannabis plant produces a resin containing compounds called cannabinoids. Cannabinoids, also known as phytocannabinoids, are chemicals in cannabis that cause drug-like effects in the body, including the central nervous system and the immune system. To date, more than 100 different cannabinoids have been identified. Among these, 9-tetrahydrocannabinol (THC) has received the most attention for being responsible for the intoxicated state (psychoactive) sought by recreational cannabis users. Another active cannabinoid is cannabidiol (CBD), which may relieve pain and lower inflammation without causing a “high” from the THC.<sup>6</sup> The highest concentration of cannabinoids is found in the female flowers of the plant.

In general, marijuana refers only to the parts of the plant or derivative products that contain substantial levels of THC. Under U.S. law, cannabis plants with very low levels of THC (no more than 0.3 percent) are not considered marijuana but instead are industrial hemp.

Cannabis use for medicinal purposes dates back thousands of years ago. It was introduced into Western medicine in 1839 by W.B. O'Shaughnessy, a surgeon who learned of its medicinal properties while working in India for the British East India Company. Its use was credited with reported analgesic, sedative, anti-inflammatory, antispasmodic, and anticonvulsant effects.<sup>7</sup>

In 1851, cannabis was included in the third edition of the

*Pharmacopoeia of the United States* (USP). Subsequent revisions of the *Pharmacopoeia* described in detail how to prepare extracts and tinctures of dried cannabis flowers to be used as an analgesic, hypnotic, and anticonvulsant.<sup>8</sup>

Cannabis was included in marketed products sold in the United States by Eli Lilly and Company and other pharmaceutical companies for the treatment of a variety of conditions and/or disorders, including insomnia, migraines, and rheumatism.<sup>9</sup>

Growing concerns about cannabis in the early 1900s resulted in it being outlawed in several states, and the U.S. Treasury Department introduced the Marihuana Tax Act in 1937. This Act imposed a levy of \$1.00 per ounce for the medicinal use of cannabis and \$100 per ounce for non-medical use.<sup>10</sup> In 1942, the American Medical Association removed cannabis from the 12th edition of the *Pharmacopeia of the United States*.<sup>10</sup> In 1951, Congress passed the Boggs Act, which for the first time classified cannabis with narcotic drugs.<sup>10</sup> With the passage of the Controlled Substances Act in 1970, cannabis was classified by Congress as a Schedule I drug. Drugs that are Schedule I are distinguished as having no currently accepted medicinal use in the United States. Other Schedule I substances include heroin, lysergic acid diethylamide, mescaline, and methaqualone.<sup>10</sup> Despite its designation as having no medicinal use, cannabis was distributed by the U.S. government to patients on a case-by-case basis under the Compassionate Use Investigational New Drug program established in 1978. Distribution of cannabis through this program was closed to new patients in 1992.<sup>11</sup> Figure 1, above, shows a timeline of cannabis's history in the United States.

## Legal Status: Federal and State Laws

Although federal law prohibits the use of cannabis, some states have enacted laws that legalized the recreational and/or medicinal use of marijuana in that specific state.<sup>6</sup> In 1996, California voters passed Proposition 215, making California the first state in the United States to permit the use of medical marijuana.<sup>12</sup> Colorado and Washington became the first two states to legalize the recreational use of cannabis in 2012.

### States with Medical and Recreational Marijuana Laws

As of November 30, 2019, 33 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands have passed medical marijuana laws (see Figure 2, page 42).<sup>13</sup> Among them, 10 states, the District of Columbia, and Guam also have legalized marijuana for recreational use. Those 10 states are Alaska, California, Colorado, Maine, Massachusetts, Colorado, Nevada, Oregon, Vermont, and Washington.<sup>13</sup>

### States with Medical Cannabidiol (CBD) Laws

There are an additional 14 states—Alabama, Georgia, Indiana, Iowa, Kansas, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee, Texas, Virginia, Wyoming, and Wisconsin—where the use of medical marijuana has not been legalized but a medical CBD law allowing for the use of cannabis extracts that are high in CBD but minimum in THC has been passed.<sup>13</sup> This is only in instances where a patient with a state-qualifying condition is recommended CBD by his or her provider.<sup>13</sup>

Individual state laws are all different. Under Florida's medical CBD law, state-qualified patients (patients with cancer or experiencing muscle spasms or seizures) may possess cannabis strains containing 10 percent or more of CBD and no more than 0.8 percent of THC.<sup>13</sup> In Texas, the THC limit is set at no more than 0.5 percent and CBD no less than 10 percent in oil preparations.<sup>13</sup> Currently, there are only three states in the United States that do not allow the use of any form of medical marijuana—Idaho, Nebraska, and South Dakota.<sup>13</sup>

It is important to have an understanding of the laws in your state. Regardless of what state you live in, you should not buy or send cannabis through the mail because the drug is still federally illegal. The U.S. Post Office, a federal government agency, will confiscate the marijuana, and the sender may be arrested and prosecuted.

### State Legislature Conditions for Medical Use

Each state has its own list of the qualifying conditions for which it will allow patients to use medical marijuana. These qualifying conditions are different in each state; however, in many states a number of conditions are cancer related—chemotherapy-induced nausea and vomiting, anxiety, hepatitis C, HIV/AIDS, cachexia (wasting syndrome), and inflammatory bowel disease. Other conditions include glaucoma, Tourette's syndrome, multiple sclerosis, Alzheimer's disease, and chronic pain.

To purchase and use either medical marijuana or medical CBD in states where it is legal, patients are usually required to register and apply for a card with the state's Department of Health. There

is a fee for applications, and each state has different limits on the amounts patients are permitted to purchase. In most cases, the purchasing cost of medical marijuana or medical CBD is not covered by insurance.

To become a certified marijuana physician, a physician must hold an active license, take a required course, and pass an exam. This process varies by state. After completion of the state requirements, physicians may apply for certification.

### Dispensing of Medical Marijuana or CBD

Thirty-three states and the District of Columbia have passed legislation legalizing marijuana for medical use. Of those, five have established a role for pharmacists in the dispensing process:<sup>14</sup>

- Arkansas requires every marijuana dispensary to appoint a pharmacist consultant.
- Connecticut permits only pharmacists to apply for and obtain a marijuana dispensary license.
- Minnesota permits only pharmacists to give final approval for the distribution of medical marijuana to a patient.
- New York requires a pharmacist to be on the premises and supervise the activities within a marijuana dispensing facility whenever the facility is open or in operation.
- Pennsylvania requires primary marijuana dispensing facilities to have a physician or pharmacist on site when the facility is open to receive patients and caregivers.

Under federal law, no individual, including pharmacists, can legally dispense medical marijuana, even in states that have passed medical marijuana legislation. Absent a change to federal law, pharmacists involved in the current dispensing process may ask themselves whether their license is at risk for dispensing a federally prohibited drug or, if the medical marijuana is seized, whether they will be prosecuted. Unfortunately, there are no answers at this point.

### Cannabinoid-Derived Pharmaceutical Products

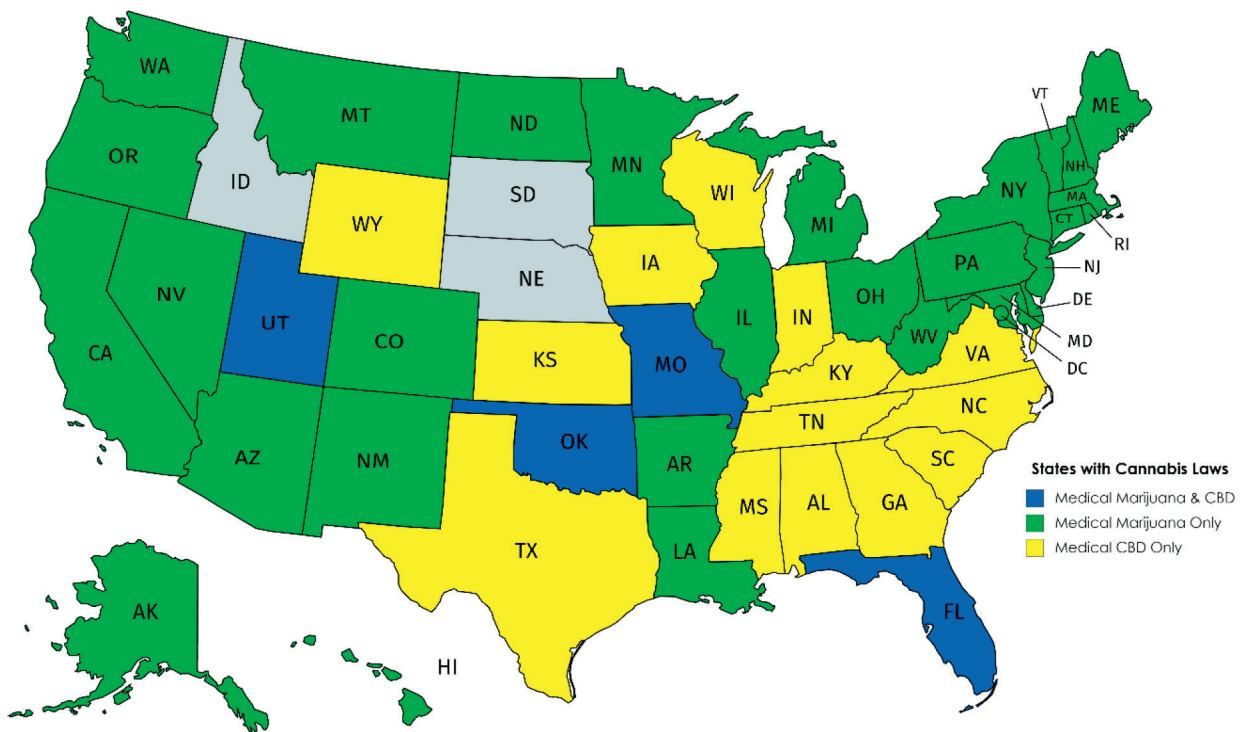
The FDA has approved four drugs that are based on natural cannabinoids (see Table 1, page 43); one is currently under investigation.<sup>7</sup>

### Cannabinoid-Derived Non-Pharmaceutical Products

*Cannabis* is a flowering plant. Once mature, the plant's leaves and flowers are covered with trichomes, tiny glands of resinous oil containing cannabinoids and terpenes, which provide physical and psychoactive effects.<sup>15</sup> Cannabis leaves and flowers are consumed in several forms: dried flower buds or various types of concentrated, loose, or pressed resin extracted from the flowers or leaves through a variety of methods, including:

- **Kief** is a powder made from trichomes removed from the leaves and flowers of cannabis plants that is used for smoking.
- **Hashish** is a paste-like substance, a collection of compressed or concentrated trichomes, that is used for smoking, ingestion by food, or inhalation with a vaporizer.
- **Hash oil** is a mix of essential oils and resins extracted from mature cannabis foliage that is used for smoking or inhalation with a vaporizer.

Figure 2. U.S. States and Territories That Have Approved the Medical Use of Marijuana and CBD



- *Cannabis edibles* are usually ingested or eaten when added to brownies, cookies, dressings, and other foods. They can also be brewed into a tea or other beverage.
- *Cannabis oil* is a cooking oil infused with cannabinoids usually used to help create cannabis edibles.
- *Cannabis tincture* is an extract of cannabinoids with ethanol alcohol for use in droplet amounts that are absorbed through the mucous membranes in the mouth.
- *Sublingual spray* is similar to the tincture (above) but is placed under the tongue for use.
- *Cannabis topicals* are topical creams, lotions, ointments, and patches that have cannabis (THC or CBD) in it.

Unlike most pharmaceutical products, cannabis products are not standardized in composition, formulation, or dose. This means that there is not yet a way to know exactly what and how much THC or CBD is in each pill or spray. It will usually take experimentation with product types and dosages to determine the right dose for individuals and their purpose. Digesting cannabis (not smoking or absorbing it) also metabolizes the cannabinoids somewhat differently, which can produce different subjective effects, depending on the individual.

The effects of THC, the psychoactive effect, are delayed by 30 to 60 minutes after eating or drinking marijuana-infused products compared to just seconds or minutes after inhaling marijuana smoke or vapor.<sup>12,13</sup> The effects from ingestion can last up to 10 hours for some people. One should not drive due to impaired coordination that can lead to unsafe driving.

When oral cannabis is ingested, there is a low (6 percent to 20 percent) and variable oral bioavailability. Peak plasma concentrations of THC occur after 1 to 6 hours and remain elevated with a terminal half-life of 20 to 30 hours. Taken by mouth, 9-THC is initially metabolized in the liver to 11-OH-THC, a potent psychoactive metabolite.<sup>16,17</sup>

Inhaled cannabinoids are rapidly absorbed into the bloodstream with a peak concentration in 2 to 10 minutes, declining rapidly for a period of 30 minutes and with less generation of the psychoactive 11-OH metabolite.<sup>16,17</sup>

In some states where marijuana has been legalized, smokable products are excluded. In New York, the law permits qualified patients to possess a 30-day supply of cannabis-infused, non-smokable products, with only non-smokable preparations allowed.<sup>18</sup>

**Table 1. FDA Approved Cannabinoid-Derived Pharmaceutical Products**

Substance	Route of Administration	Descriptions	Indications
<b>Synthetic compounds</b>			
Dronabinol (Marinol)	Oral capsule	Synthetic THC	For chemotherapy-induced nausea and vomiting or to stimulate appetite in AIDS wasting syndrome
Dronabinol (Syndros)	Oral solution	Synthetic THC	For chemotherapy-induced nausea and vomiting or to stimulate appetite in AIDS wasting syndrome
Nabilone (Cesamet)	Oral capsule	Synthetic THC	For chemotherapy-induced nausea and vomiting or to stimulate appetite in AIDS wasting syndrome
<b>Natural product-derived compound</b>			
Epidiolex	Oral oil	Concentrated CBD oil (98 percent CBD) from <i>Cannabis</i> extract	For the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome
Nabiximol (Sativex) FDA Fast Track (approved in the United Kingdom, Canada, and other countries)	Oromucosal spray	Ethanol <i>Cannabis</i> extract of TCH:CBD (in a 1:1 ratio). Extract from two <i>Cannabis</i> plant varieties	Symptomatic relief of multiple sclerosis and as an adjuvant analgesic for cancer pain

Marijuana smoke irritates the lungs. Frequent marijuana smokers can have many of the same problems as tobacco smokers, such as a daily cough, mucus, more chest colds, and a higher risk of lung infection. Some of the cancer-causing chemicals in tobacco smoke are also in marijuana smoke. Marijuana smokers may also inhale deeper and hold the smoke in their lungs longer. Therefore, marijuana smokers’ lungs may be exposed to more chemicals that can cause cancer. Lung tissue from regular marijuana users shows signs of pre-cancerous changes.<sup>19</sup> However, several studies have failed to show that marijuana smokers have a higher risk of lung cancer. More studies about marijuana smoking and lung cancer are needed.<sup>20</sup>

**Knowledge Gaps**

According to survey results published in the *Journal of Clinical Oncology* in 2018 titled “Medical Oncologists’ Beliefs, Practices, and Knowledge Regarding Marijuana Used Therapeutically: A Nationally Representative Survey Study,”<sup>21</sup> Ilana M. Braun and colleagues concluded that a significant percentage of oncologists who recommend medical marijuana to their patients did not feel knowledgeable enough to do so. This survey was mailed in November 2016 to a nationally representative, random sample

of 400 medical oncologists. Main outcome measures included whether oncologists:<sup>21</sup>

- Reported discussing medical marijuana with patients
- Recommended medical marijuana clinically in the past year
- Felt sufficiently informed to make such recommendations.


The survey also queried oncologists’ views on medical marijuana’s comparative effectiveness for several conditions (including its use as an adjunct to standard pain management strategies) and its risks compared with prescription opioids. The overall response rate was 63 percent. Of all participants who responded, more than half (55 percent) practice in states where medical marijuana is legal. Key findings from the survey include:<sup>21</sup>

- Eighty percent of oncologists conducted discussions about medical marijuana with their patients; 78 percent reported that these conversations were most frequently initiated by patients and their families.
- Forty-six percent of oncologists recommended medical marijuana clinically.
- Seventy percent of oncologists did not feel sufficiently informed to make recommendations regarding medical marijuana.

- Sixty-seven percent viewed it as a helpful adjunct to standard pain management strategies; a majority viewed it as presenting a lower risk than opioids for overdose death (75 percent) and addiction (52 percent).
- Sixty-five percent thought that medical marijuana is equally or more effective than standard treatments for anorexia and cachexia.

This study identified a concerning discrepancy between oncologists' self-reported knowledge base and their beliefs and practices regarding medical marijuana. Those findings are clinically important and suggest critical gaps in research, medical education, and policy regarding medical marijuana.

Important questions concerning medical marijuana must be addressed, especially given that medical marijuana laws are popular on a state level. Cancer is a “qualifying condition” recognized by almost all states that have medical marijuana legislation. Marijuana use has the greatest impact to oncology than any other specialty.

Because cannabis is a Schedule I controlled substance, clinical trials face a huge barrier. Randomized controlled trials of whole-plant medical marijuana have not been done among patients with cancer yet, so oncologists often extrapolate from evidence in clinical trials carried out on other diseases, as well as from clinical trials carried out with pharmaceutical synthetic cannabinoids or cannabinoids-derived products. To advance the field, we need to catch up with science, regulation, and, very important, education for healthcare providers, including physicians, pharmacists, nurses, and others. 

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