



National Hospice and Palliative Care Organization  
**Palliative Care Resource Series**

**CANNABIS USE IN PALLIATIVE CARE:  
HISTORY, LEGALITY AND  
IMPLICATIONS FOR PRACTICE**

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## HISTORY AND BACKGROUND

Cannabis, also known as marijuana, has been used for thousands of years for its euphoric effects. It was described in a Chinese medical compendium as a medicinal herb, considered to date from 2737 B.C. Its use spread from China to India and then North Africa, finally reaching Europe at least as early as 500 A.D. Hashish, a cannabis preparation has been found in Egyptian mummies. A major crop in colonial North America, marijuana (hemp) was grown as a fiber. It was extensively cultivated during World War II, when Asian sources were cut off, and was listed in the *United States Pharmacopea* from 1850 to 1942.

## STATE AND FEDERAL LAWS AND REGULATIONS

- 1930s – A campaign instituted by the U.S. Federal Bureau of Narcotics sought to portray marijuana as a powerful, addicting substance that would lead users into narcotic addiction. This philosophy was the beginning of the “gateway” theory that is still believed by some today.
- 1950s – Cannabis was an accessory of the *beat generation*.
- 1960s – It was used by college students and “hippies” and became a symbol of rebellion against authority.
- 1970 – The Controlled Substances Act of 1970 classified marijuana along with heroin and LSD as a Schedule I drug, having the relatively highest abuse potential and no accepted medical usage. Most marijuana came from Mexico at that time.
- 1975 – The Mexican government agreed to eradicate the crop by spraying it with the herbicide paraquat, raising fears of toxic effects. Colombia then became the main supplier.
- 1981-1993 – The “zero tolerance” climate of the Reagan and Bush administrations resulted in passage of strict laws and mandatory sentences for possession of marijuana and heightened vigilance against smuggling at the southern borders. The “war on drugs” thus brought with it a shift from reliance on imported supplies to domestic cultivation, particularly in Hawaii and California.
- In 1982 the Drug Enforcement Administration turned increased attention to marijuana farms in the United States, and there was a shift to the indoor growing of plants specially developed for small size and high yield.
- 1990s – Marijuana smoking began an upward trend once more, especially among teenagers, but by the end of the decade this upswing had leveled off well below former peaks. States started to pass amendments and laws to allow the use of **medicinal marijuana**, defined as “all parts of any plant of the genus *Cannabis* whether growing or not; the seeds thereof; the resin extracted from any part of the plant; and every compound, manufacture, salt, derivative, mixture, or preparation of the plant, resin, or seed [FL statute, Section 892.02(3)]. ”
- 1996 – California was first to pass an amendment to legalize marijuana for medicinal purposes.

Each state has slightly different definitions and limitations on individual growing and the amount that legally can be held or possessed. Please refer to [ProCon.org](http://ProCon.org). Each state also has its own rules on growing, processing, distributing, recommending vs. ordering by physicians; and the types of cannabinoids that can be used.

## THE ENDOCANNABINOID SYSTEM (ECS)

The endocannabinoid system has wide-ranging effects on the body's functioning and even has a documented deficiency syndrome. The phytocannabinoids include tetrahydrocannabinol (THC), tetrahydrocannabivarm (THCV), Cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG). Phytocannabinoids have cognitive effects via receptors but their anti-inflammatory effects may also be affected without receptors.

The ECS is made up of 3 components:

- endocannabinoids are endogenous agents
- receptors, CB1 in the CNS and CB2 in lymph tissue
- regulatory enzymes

The interaction of these components effects mediation of pain, seizure thresholds, appetite and digestion, mood, tumor surveillance, fertility, bone physiology, intraocular pressure, and the hypothalamic-pituitary-adrenal axis.

## PHYSIOLOGIC AND COGNITIVE EFFECTS OF CANNABIS

The effects of cannabis are dependent on many factors:

- the dose of cannabis
- ratio of various cannabinoids used
- route of administration
- the timing (immediately after ingestion vs. long-term)
- the health status of the patient
- the age of the patient
- the co-administration of other drugs
- recreational use before using medicinal marijuana vs. naïve users

THC is responsible for most psychoactive effects as compared to cannabidiol (CBD). Although cannabis is generally a CNS depressant causing drowsiness, it can have reverse effects of anxiety, panic, and psychosis especially in first time users.

- Smoking can cause acute cognitive and psychomotor changes, decreasing the ability to perform tasks requiring coordinated actions such as driving or machinery use.
- Reasoning becomes impaired and non-cohesive, with decreased concentration on tasks requiring motor skills. There have been studies showing poor performance with working memory, executive functioning, and speed of processing. Acutely after smoking there can be hallucinations, time distortion, and intensification of tactile, auditory, and visual experiences.
- Initially there is increased motor activity followed by decreased activity, coordination, ataxia, dysarthria, and weakness.
- Cannabis stimulates the appetite by interaction in the CNS with CB1 receptors that are associated with satiety and appetite regulation. This effect can be a benefit in patients on opioids, anti-virals, or patients with AIDS or cancer cachexia.

- Similarly, cannabis has anti-emetic properties. It can effectively decrease or eliminate nausea and vomiting in patients receiving chemotherapy or radiation therapy. Interestingly, it seems to be more effective in preventing nausea than vomiting unlike most other anti-emetics, making it the drug of choice for anticipatory nausea.
- The NIDA has shown that immediately after smoking there can be a 20%-100% increase in heart rate, lasting up to 3 hours. However, long-term users may experience bradycardia. Tachycardia is rare with highest heart rates of 125 bpm.
- THC/CBD alter hypothalamic/pituitary function decreasing testosterone, progesterone, LH, FSH, and prolactin. It can inhibit spermatogenesis and decrease sperm mobility, and lengthen menstrual cycles. This can suppress ovulation and female fertility. It is listed as Pregnancy Category C with no adequate studies on human fetuses.
- Cannabis lowers intraocular pressure helping glaucoma patients although the effects last only 4-6 hours after smoking, suggesting sedation if it is the sole drug used for glaucoma. It can also cause injected conjunctiva.

There have been studies to suggest that cannabis intoxication can increase the odds ratio of motor vehicle accidents to 1.92. The effects dissipate in several hours. The presence of some cannabinoids can be detected in plasma for many hours, and even days after single administration and may be excreted in the urine for even longer.

A meta-analysis of long-term users is consistent with substantial negative neuro-cognitive testing, but the data remain inconclusive about permanent changes in the brain. Thus, long-term neuro-cognitive effects of cannabis are likely to be minimal or non-existent in adults but might be more substantial in youth who begin regular use during a period of brain development and maturation.

A study of *The Academic Consequences of Marijuana Use During College* showed that "marijuana use adversely affected college academic performance, both direct and indirect, with users having poor class attendance. However, in another widely publicized longitudinal study, *Chronic Adolescent Marijuana Use as a Risk Factor for Physical and Mental Health Problems in Young Adults* revealed "no difference in any of the mental or physical health outcomes that were measured regardless of the amount or frequency of marijuana use during adolescence."

## THE ADMINISTRATION AND DOSING OF CANNABIS PRODUCTS

There are multiple forms of cannabinoids allowing for different routes of administration:

1. Unprocessed plant material for smoking or vaporization
2. Liquid or oil preparations for vaporization
3. Liquid or oil preparation for oromucosal, sublingual, or tube administration
4. Liquid or oil preparation for IV or SC administration
5. Patch matrix for transdermal administration
6. Capsules for oral administration
7. Edible products
8. Rectal suppositories
9. Ointment, creams, and lotions

The route of administration determines the pharmacokinetics and effects of the cannabinoids.

- Smoking or vaporizing cannabis reaches the lung alveoli and bloodstream and crosses the blood-brain barrier. The psychoactive effects occur within 90 seconds, reach a maximum in 15-30 minutes and taper off in 2-3 hours. Use of a water pipe removes gas-phase toxins but not particulate materials. Vaporization causes more rapid delivery and higher concentrations over the same time period and with convection vaporization more accurate temperature, and, therefore, less risk of combustion byproducts inhaled.
- Oral administration allows psychoactive effects at 90 minutes, with a maximum of 2-3 hours, lasting 4-12 hours. There is a very heterogeneous response so that some have peak activity at 6 hours. There is first pass elimination by the liver resulting in only 50% of the dose reaching the systemic bloodstream, but the metabolite, 11 hydroxyTHC has a 4-fold greater psychoactivity. Oral administration has drawbacks including delayed onset of action; variable gut availability; first pass metabolism; difficulty in administering to anorexic or vomiting patients; and difficulty in regulating and adjusting doses. In an attempt to avoid unwanted side effects, dosage should be "low and slow." A dose range of 2.5mg to 120mg of THC per day is a starting guideline.

There are no uniform dosing guidelines for several reasons:

1. Significant variation of cannabis types
2. Limited pharmacological data and lack of uniformity of studies in humans
3. Tolerance and adverse effects are variable
4. Personal variation in metabolism
5. Physiologic changes in ECS in response to more exposure
6. Different physiologic responses in differing underlying medical conditions
7. Drug-drug interactions through the Cytochrome P450 system (CYP450, CYP2C9, CYP2C19, CYP3A4)

The cannabinoids penetrate highly vascular tissue including the liver, jejunum, spleen, heart, lungs, kidneys, muscle, mammary glands, placenta, adrenal cortex, thyroid and pituitary, then fat storage. There have been some studies that show that doses up to 500mg in humans are non-toxic. The acute toxicity is very low with a median lethal dose (LD50) in animals of oral THC >800mg/kg within 30-60 minutes. They have been unable to determine if all-cause mortality rates are higher in chronic users. Some studies show increased risk of MI and CVA due to the cardiovascular effects. In March 2014 Colorado law enforcement stated a young adult died and was linked to cannabis overconsumption without polysubstance abuse, taking 50mg in 30 minutes.

The **absolute contraindications** to cannabis use include any patient with psychotic (schizophrenia) illness since THC is associated with aggravating or precipitating psychotic episodes. THC is a vasodilator, decreasing blood pressure and increasing cardiac demand. Smoking cannabis raises fourfold the risk of MI in the immediate aftermath of smoking.

The **relative contraindications** include primary liver, renal, and pulmonary diseases or a past history of seizures or drug abuse.

- The liver and kidneys excrete the metabolites so that close monitoring of symptoms is important. In liver disease, in particular, there are reports that cannabis reduces liver inflammation while it has also been reported to worsen fibrosis and steatosis.

- In patients with COPD and asthma, smoking should be avoided and other routes of administration chosen.
- There should be special precautions in pediatric patients and the elderly. In children, most state laws require it as a last alternative. The elderly metabolize cannabis more slowly and are more sensitive to its effects, so “low and slow” is the dogma.
- A 2014 study of 213 patients with treatment-refractory epilepsy showed that the side effects were: Somnolence 21%; Fatigue 17%; Diarrhea 16%; and Decreased Appetite 16%. Care must be taken to minimize drug interactions.
- Most importantly, cannabis reinforces the sedative effects of other sedative-hypnotics, benzodiazepines, and alcohol. Caution also must be taken with sympathomimetic substances, opioids, and tricyclic antidepressants.

## IN SUMMARY

The recent trend in US state legislatures is to pass rules and regulations to allow medicinal marijuana and the trend continues. Its use in Palliative Care and Hospice is evident in treating patients with cancer, neurodegenerative diseases, inflammatory diseases, end-of-life angst, uncontrolled seizures and HIV cachexia. All physicians and especially palliative care physicians and ARNPs need a basic understanding of the history, legality, pharmacokinetics, cannabis products, dosage and administration, and side effects including contraindications. This hopefully will serve as a primer and resource for further study.

