Medical Marijuana
Part 1: Use, Misuse and Addiction

Introduction

Cannabis species and subspecies have been used medicinally for over 5,000 years, though cultivation may reach as far back as 10,000 years.[1] In the United States, the regulation of cannabis as a Schedule I drug has hampered the study of cannabis and its medicinal uses. Since California became the first state to legalize medical marijuana in 1996, almost 30 states and the District of Columbia have followed, and more states are expected to legalize medical marijuana. As a result, there have been recent reviews and studies related to medicinal marijuana. The inquiry made by older and more recent studies is whether cannabis is effective to treat nausea and vomiting due to chemotherapy, stimulating the appetite of patients with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS), chronic pain, seizures, and other conditions or diseases. The results are mixed but in certain instances there is encouraging evidence that cannabis may provide relief for certain conditions. A brief overview of the history of cannabis species and subspecies is covered in the following first sections[1] prior to a more in depth discussion of the botanical chemistry and physiological effects of cannabis in controlled trials and medical studies that focused on its effects related to various human diseases and conditions.

A Brief History Of Hemp

Hemp, a non-psychoactive species of Cannabis sativa, has provided the oldest known fabric, dating to 8000 BCE (before common era). In the 9th

BCE, the Chinese emperor was offered a tribute of hemp-cloth by a tribe of female warriors. The cloth was described as *shining and radiant, infecting men with its sweet-smelling aroma.* Burnt remnants of Cannabis have been found in burial mounds in Siberia and have been dated to 3000 BCE. Imprints of hemp rope are found on pottery in ancient Chinese burial chambers dating to about 10,000 BCE. The hemp nut has been used for bread and cereals, the oil has been used for fuel, lubricants and moisturizers, ink, food and paint. Hemp stalk has been used for its fiber in making fabrics, paper, rope, netting, footwear, biofuel and building materials.

In colonial America, hemp was George Washington's and Thomas Jefferson's main cash crop. The British navy was one of the primary users of hemp, using hemp oil, rope, paper, fiber and cloth for riggings, pennants, sails, oakum, maps, logs, and for any books that sailors brought for their long sea voyages. The term for a British sailor *Jack Tar* came from the fact that the hemp ropes had to be heavily tarred to keep from rotting. Benjamin Franklin started the first paper mill in America; it produced hemp paper and is believed to have provided the hemp paper on which the Declaration of Independence was written.

Hemp is also used as food. Hemp seeds, often referred to as hemp hearts are highly nutritious. Hemp hearts are a complete protein source and contain significant amounts of both the omega-6 essential fatty acid (EFA), linoleic acid, and the omega-3 EFA, linolenic acid in ratios that range from 2 to 3:1, considered the healthiest ratio. In addition, hemp hearts contain gamma-linolenic acid (GLA 18:3 omega-6 and stearidonic acid (SDA 18:4 omega-3).

Hemp seeds are also high in calcium, magnesium, potassium, iron, manganese and zinc. Hemp seeds and roots, while not primarily medicinal, have been used to treat topical inflammation, incontinence and venereal disease.

For a variety of reasons, hemp has often been confused with the psychoactive species of cannabis. In the early 1900s, there was a significant influx of Mexicans into, primarily, the American Southwest. While many Americans were familiar with cannabis, these Mexican migrants referred to cannabis as marijuana. Earlier immigrations had seen the demonization of immigrants and the efforts to restrict immigration had in previous years taken the form of outlawing substances known to be popular in these immigrant groups. For example, opium was restricted to control Chinese immigration and groups associated with the Prohibition and were often associated with various anti-immigrant groups and anti-African-American groups. While the situation is more complicated, historians point to a backlash directed at people of color in many restrictive laws of the era. Physicians and society in general was becoming aware of the addictive properties of opium and morphine. Mexicans, African-Americans, other minority groups or criminals were portrayed as “dope fiends” and laws were passed in part to prevent morphine/opium addicts from using home-grown marijuana as a substitute, but also in an attempt to control crime.

By the end of the 19th century, it is estimated that between 2-5% of the population in the U.S., was addicted, often without knowing it, to opium and morphine derivatives. Popular products containing opium (up to 0.5g/oz.) were sold as treatments for colic, pain, anxiety, sleep disturbances,

migraines and a host of other conditions. Overstressed mothers used popular products like Godfrey's Cordial, Mrs. Winslow's Soothing Syrup and Street's Infants' Quietness to help soothe their colicky baby. Godfrey's Cordial contained 1 gram of opium in every 2 ounces. There were other popular products such as Dr. Fenner's Golden Relief, the People's Healing Liniment for Man or Beast and various other products which contained opium or morphine. The Sears and Roebuck catalog sold a syringe with cocaine for $1.50. At the time, Coca Cola contained approximately 5 ounces of coca leaves for every gallon of syrup. Marijuana was also getting similar attention. The growing understanding of opiate addiction may have met the economic and social anxieties of the era to form a backlash against all cannabis products, whether used as a drug or medicine or for fabric-making and food.

In 1937, the Marijuana Tax Act strictly regulated the cultivation and sale of all cannabis varieties, including hemp. This act made the nonmedical use of marijuana illegal, though its primary purpose was taxation. (The birdseed industry lobbied to be exempt as they argued that hemp seeds gave birds a highly prized shiny gloss). All of this occurred just after prohibition (1920-1933) and the argument has been made that a new source of revenue was needed. Hemp production and cultivation farming in the U.S. was greatly reduced until World War II. In World War II, the film "Hemp for Victory" was made to stress the need for hemp to make war materials. Hemp is used as a "mop crop;" it is used to clean up sewage spills, oil spills and nuclear waste. Hemp is also an attractive rotation crop for many farmers, requires no extra fertilization or pesticides and is heat- and drought-resistant.

Medical Marijuana: A Historical Overview

Cannabis has been used in various forms to treat gout, malaria, rheumatism, glaucoma, nausea, absent-mindedness and other conditions. It was used in ancient China, India, the Middle East, South America and in various regions of Asia and Africa. In China, the emperor Shen-Nung, considered the Father of Chinese Medicine who ruled China during the 28th century BCE, is credited with the earliest known use of medical marijuana. Shen-Nung listed marijuana in the Pen Ts'ao, reported to be one of the earliest herbal medicine texts, though only fragments of the original text have survived. *Ma*, as medical marijuana was known, was highly prized because it contained both Yin and Yang properties. In Traditional Chinese Medicine (TCM), one of the guiding principles to health is the balance of Yin and Yang.

The first written mention of medical marijuana is in the *Ebers Papyrus*, one of the first medical texts written. Other papyri indicated the use of cannabis for cataracts, glaucoma and vomiting. In the ancient Islamic world, cannabis was used to treat pain, as a diuretic, an anti-inflammatory agent, anti-emetic, and as an anti-epileptic. Evidence of the use of marijuana as a medicine exists in ancient Asia, the Middle East, Africa and Europe. The herb was called ganjika in Sanskrit and was reportedly used in sacred rituals. Cannabis is mentioned in the Talmud and is reported to have been found in pipes dug up from Shakespeare's garden; this may have been the "noted weed" from Sonnet 76.

Early American physicians used cannabis to relieve pain from earaches, childbirth, nerves and muscles. They also used it to treat anxiety,

nervousness, diabetes and high blood pressure. In the U.S., *Cannabis indica* was used extensively for some time; a 1934 edition of The Modern Home Physician listed its usefulness for neuralgia, menorrhagia, and pruritus. Other sources listed cannabis as useful in migraines, as a sleep aid and as an anticonvulsant. Between 1840 and 1900, there were well over 100 medical papers published in the U.S., recommending cannabis for disorders ranging from chronic pain, menstrual pain, tetanus, convulsions, the pain of rheumatism and childbirth, asthma, postpartum psychosis, gonorrhea, and chronic bronchitis.

In the early 1900s, medicine itself was undergoing a radical change with Abraham Flexner's 1910 scathing report of the state of medical education in the U.S., and Canada. Part of the response to the large numbers of addicted citizens and the complaints about medical education was the Pure Food and Drug Act in 1906 which created the Food and Drug Administration (FDA), representing a major shift in the role of government in regulating and controlling drugs. In 1914, the Harrison Narcotics Tax Act was enacted, regulating the distribution and taxation of non-medical products containing opium and cocaine. It also made the non-prescription use of drugs a crime; for example, Coca Cola could no longer use the coca in the production of the cola.

Drug use has always been a social and legal problem, and President Nixon signed The Controlled Substances Act of 1970 which classified all forms of cannabis — including hemp — as a Schedule I drug, making it illegal to grow it in the United States (which is why currently the U.S. is forced to import hemp from other countries as long as it contains scant levels of THC; less

0.3% THC is the regulation for hemp cultivation in the European Union and Canada). As a result of this long-term prohibition, most people have forgotten the industrial uses of the plant and continue to misidentify hemp with its cannabis cousin, marijuana. The Controlled Substances Act of 1970 also established the National Commission on Marijuana and Drug Abuse (known as the Shafer Commission). In a March 22, 1972, report, the commission recommended removal of cannabis from Schedule I stating its position that the *possession of marijuana for personal use and the casual distribution of small amounts of marijuana for no remuneration, or insignificant remuneration no longer be an offense*.

With the exception of the World War II era when the government planted huge hemp crops to supply naval rope needs and make up for Asian hemp supplies controlled by the Japanese, cannabis was criminalized and harsher penalties were applied. In the 1950s Congress passed the Boggs Act and the Narcotics Control Act, which laid down mandatory sentences for drug offenders, including marijuana possessors and distributors. In the 1980s, the Reagan Administration's get-tough drug policies continued the policy of treating marijuana as a dangerous, illegal substance. Still, the long-term trend has been toward relaxation of regulation. Since California became the first state to legalize medical marijuana in 1996, almost 30 states and the District of Columbia have followed, with more expected. As anticipated, there are proponents and opponents to both the medical use of marijuana and the decriminalization of marijuana for personal use.

Proponents cite the growing literature indicating marijuana’s usefulness in treating cancer-associated pain and generalized pain, acquired immune

deficiency syndrome (AIDS), epilepsy, glaucoma, multiple sclerosis and a number of other conditions. Opponents claim marijuana is addictive, a gateway drug, decreases fertility, and, depending on the delivery, may impair lung function and cause permanent brain damage. While there is a growing body of literature on the benefits and dangers of marijuana, marijuana is still listed as a Schedule I drug. Importantly, research is still restricted so it may be years before sufficient evidence is available to come to a consensus on legalizing marijuana.

The Botany Of Cannabis

Cannabis species are a dioecious (having the male and female reproductive organs in separate individuals) annual with distinct male (staminate) and female (pistillate) plant. Some plants are monoecious or hermaphroditic; the male and female organs are located on the same plant at separate locations. This is commonly believed to be a stress reaction. Cannabis is a flowering herb with serrated leaves that may be palmately compound or digitate. Each serration has a vein branching off from a central vein. Female flowers have a single 5-veined leaf forming a sheath over the ovary. Male flowers have five downy, light yellow or greenish segments. Reproduction in the wild is by wind pollination. Cannabis is considered a short-day plant, flowering when the length of nighttime darkness exceeds a critical photoperiod, and require some period of continuous darkness. Depending on the variety, plants can grow from 3-10 feet high with low numbers of branches.[3]

The plants can be bred for high tetrahydrocannabinol (THC) content and for low THC content. Plants used to produce hemp or hemp seed are bred for low THC content. Hybrids are common and can be bred for higher or lower THC content. Plants bred for low THC tend to produce higher levels of other

cannabinoids, particularly cannabidiol, and to a lesser extent, cannabigerol, cannabinol (a THC degradation product) and others. The plants can also be bred for higher levels of cannabidiol (CBD). The highest content of THC or CBD is found in the trichome glands, which are epidermal outgrowths that resemble fine hairs. These occur most commonly on the floral bracts and calyces of female plants. There are three main species of Cannabis: 1) *Cannabis sativa*, 2) *Cannabis indica*, and 3) *Cannabis ruderalis*. *Cannabis indica* tends to produce plants that have sedating, analgesic, anticonvulsant and muscle relaxing properties while *C. sativa* tends to have analgesic properties, to stimulate appetite and to act as an antiemetic agent. Hybrid breeds have variable effects, depending on the desired effect (*i.e.*, higher or lower levels of THC or CBD).[3-5]

Cannabinoids, Cannabinoid Receptors and Endocannabinoids

Cannabinoids

The cannabis plant produces over 400 unique phytochemicals, about 60 of which can be classified as cannabinoids. Another class of phytochemicals, the aminoalkylindoles, exhibit similar psychotropic activities to THC. Cannabinoids are substituted meroterpenes, a chemical compound formed from units of isoprene (a highly flammable colorless liquid). They are not alkaloids. Cannabinoids can also be classified as phenolics (an aromatic compound) and can be considered bioflavonoids. Cannabinoid receptors and endocannabinoids are explained in the following sections.[2-5]

Cannabinoid Receptors

Cannabinoids act by binding to G-protein-coupled receptors (GPCR) found on the cell surfaces of neurons and widely dispersed on cells of the immune system, vascular endothelium, intestine, liver, the synapses of the peripheral nervous system and in reproductive tissues. These receptors function primarily via the inhibition of adenylate cyclase (AC) and voltage-activated calcium channels (VACC). In the central nervous system, cannabinoid receptors (CB1) are found at high levels in the cortex, hippocampus, basal ganglia and cerebellum, in agreement with the psychotropic, sensory and motor effects seen, particularly with THC. The CB2 receptor is predominantly expressed in peripheral immune cells, particularly on B cells and NK cells. CB2 receptors have also been located in the cerebellum and brainstem, primarily on the microglial cells. CB1 and CB2 receptors are described further below.

While the physiological functions of the cannabinoid receptors are largely unclear, the receptors appear to play a central role in homeostasis and neuromodulation by preventing excitotoxic activity and by reducing the inflammatory response. Other functions appear to include mediating excitatory transmitters such as glutamate, aspartate, Substance P and dopamine. Inhibitory transmitters such as serotonin, glycine, GABA and met-encephalin can also be modulated. Acetylcholine and norepinephrine actions may be either inhibited or increased, depending on the specific site of action.

CB1 and CB2 Receptors

The CB1 and CB2 receptors are explained here. The *CB1 receptor* has the following characteristics:[2-6]

- CB1 receptors located primarily on neurons play a role in the regulation of neurotransmitter release. The CB1 receptors are intimately involved in the endocannabinoid (see below) mediated depolarization-induced suppression of inhibition (de-inhibition), reducing GABA-mediated neurotransmission by inhibiting GABA release.
- CB1 is the most abundant G-protein coupled receptor in brain and is associated with glutamatergic and γ-aminobutyric acid (GABA)ergic terminals.
- The CB1 receptor can function independently of GPCR and can lead also to the activation of phosphatidylinositol 3-kinase/Akt- or phospholipase Cβ-mediated cascades.
- CB1 can also couple to Gs and stimulate the AC/protein kinase cascade.
- CB1 can associate with β-arrestin leading to the regulation of GPCRs.
- The formation of homo/heterodimers leads to differential effects of CB1 agonists in various tissues.
- CB1 can inhibits adenylate cyclase (via Gi/o).
- CB1 can also inhibit voltage activated calcium channels (VACC), inwardly rectifying K+ channels and mitogen-activated protein kinases.
- Peripherally, the CB1 receptor plays a role in increasing lipogenesis
- CB1 is physically associated with lipid rafts, and the levels of CB1 can be significantly affected by cholesterol levels.
- CB1 receptors are found at highest levels at glutaminergic and GABAnergic terminals and are also found in the pituitary, thyroid and adrenal glands.
- CB1 binds primarily to the endocannabinoids arachidonoylethanolamide (AEA) and include 2-Arachidonoylglycerol (2-AG).
- Physiological actions of CB1 include: 1) Decrease in gut motility, 2) Nociception via interneurons in the spinal cord, 3) Hypotension, 4) Bradycardia, and 5) Can increase drug-seeking behavior

CB2 Receptor

The CB2 receptor is expressed in immune cells and tissues. In addition to B and NK cells, the CB2 receptor is found on T cells, macrophages and hematopoietic stem cells. The CB2 receptor also exhibits the following characteristics:

- CB2 receptors are associated with anti-nociception.
- CB2 is coupled to Gi/o proteins and adenyl cyclase (AC) inhibition and mitogen-activated protein kinase stimulation, but it is not coupled to VACC inhibition.
- CB2 in the glia and the microglia are over-expressed in neurological disorders including Alzheimer's Disease, Multiple Sclerosis, Amyotropic Lateral Sclerosis, Parkinson's Disease and Huntington's chorea; CB2 receptors are induced in the CNS, particularly during an inflammatory response. Activation of these receptors decreases the in vitro production of pro-inflammatory cytokines in astrocytes, mast, glial and microglial cells.
- CB2, in general, modulates the immune system via cytokine release.
- CB2 binds primarily to the endocannabinoid 2-Arachidonoylglycerol (2-AG) and is a partial arachidonoylethanolamide (AEA) agonist.
- Physiologic actions of the CB2 receptor includes: 1) Decrease bowel inflammation, 2) Increases the anti-inflammatory activity of mast cells in the spinal cord, 3) Decreases hepatic steatosis, increases hepatic fibrosis, 4) Pro-inflammatory with atherosclerotic plaques, and 5) Reduces drug-seeking behaviors.

Endocannabinoids

Endocannabinoids were first described in 1992 and are the endogenous cannabinoid-like ligand for the CB1 and CB2 receptors. This class of neurotransmitters are fatty acid (arachidonic acid) derivatives. The first endocannabinoid described was anandamide, or arachidonoylethanolamide (AEA). Physiological characteristics of the endocannabinoids include analgesia, motor depression, hypothermia and inductions of a cataleptic state. Other endocannabinoids described include 2-Arachidonoylglycerol (2-AG), noladin ether, N-arachidonoyl-dopamin and virodhamine. 2-AG is a partial AEA agonist. The endocannabinoids are lipophilic and are involved in paracrine and autocrine signaling. The endocannabinoids are not stored but synthesized as needed with a short half-life.

Endocannabinoids have a potential role in controlling inflammation, insulin resistance and sensitivity, lipid synthesis and energy regulation. They also play a critical role in memory, mood, reward systems and therefore neurological systems of drug addiction. The characteristics of endocannabinoids are highlighted in this section in terms of synthesis and physiological effects.[5-10]

Endocannabinoids, endogenous signaling molecules, are typically synthesized in the post-synaptic neurons, beginning with the activation of N-acetyltransferase which transfers an acyl group to phosphatidylethanolamine, a membrane phospholipid, producing N-acyl-phosphatidylethanolamine (NAPE). NAPE is cleaved to form arachidonoylethanolamide (AEA). AEA then diffuses to the pre-synaptic

neuron and activates the CB1 receptor, allowing a method of post-synaptic control of pre-synaptic neurons. Endocannabinoids have the following characteristics:

- N-arachidonoylethanolamine (anandamide) - appears to function to modulate memory, patterns of hunger, appetite and sleep as well as anxiety and pain, and moderates reward functions.
- 2-AG can act as a "retrograde" inhibitor of both excitatory and inhibitory neurotransmitter release.
- Endocannabinoids may stimulate neurogenesis and oligodendrocyte formation via CB1.
- Acting via CB2, endocannabinoids can regulate reactivity of glial/microglial cells; CB2 is over-expressed in neuroinflammatory disease.
- Endocannabinoids stimulate cell migration.
- Endocannabinoids promotes the release of pro-inflammatory cytokines (IL6, TNF).
- 2-AG is secreted in breast milk.

The major psychoactive compound found in cannabis is Δ-9-tetrahydrocannabinol (Δ^9-THC or THC), which is an anandamide agonist. Tetrahydrocannabinol binds both CB1 and CB2 receptors with approximately equal affinity. On the other hand, cannabidiol (CBD) is *not* psychoactive and has relatively low affinity for both CB1 and CB2 receptors. Tetrahydrocannabinol has significant affinity for both cannabinoid receptors.

Endocannabinoids are mediators of the stress response.[10] In addition, cannabidiol, tetrahydrocannabinol, other phytocannabinoids and

endocannabinoids have all been shown to bind to Peroxisome Proliferator-Activated Receptors (PPARs).[11] There are three PPAR isoforms: α, δ, and γ. The PPARs are a family of nuclear receptors which heterodimerise with the retinoid X receptor (RXR), and bind to DNA sequences called PPAR response elements (PPRE). Binding to PPARs results in changes in the transcription of target genes. When cannabinoids bind to PPARs, this causes the recruitment of regulator proteins which then bind to a third site on PPARs, resulting in a modulation of transactivation. The PPAR target genes function for the most part primarily as metabolic regulation, energy homeostasis, cell differentiation and in inflammation.

Not all phytocannabinoids bind to all PPAR isoforms. To date, there is no evidence that the phytocannabinoids bind to PPARα, but most endocannabinoids bind to PPARα.[11] Currently, there is little evidence on PPARδ, but studies have shown that silencing PPARδ can significantly increase CB1 expression and in cell lines where PPARδ is overexpressed, CB1 expression is significantly reduced. Phytocannabinoids (CBS and THC) all bind to PPARγ and are inhibited by PPARγ antagonists. The endocannabinoid AEA has also been shown to bind to both PPARα and PPARγ. The physiological effects (elaborated on below)[11-16] of binding include some of the well-known effects of both phyto- and endocannabinoids.

Anti-inflammatory Effects

The anti-inflammatory effects of endocannabinoids appear to be associated with PPARγ in the gut. The following are chemical characteristics:

- Ajulemic acid (AJA) is a synthetic analogue of a tetrahydrocannabinol metabolite. AJA inhibits the promoter activity of Interleukin-8, a pro-inflammatory cytokine.
- AEA inhibits the secretion if Interleukin-2, a pro-inflammatory cytokine independently of CB1 and CB2
- 2AG also inhibits IL-2 secretion and has also been found to decrease the expression of COX-2 in the response to either IL-1β or LPS.

Neuroprotective Effects

Oleoylethanolamine (OEA) and palmitoylethanolamide (PEA) are endocannabinoid-like compounds. Oleoylethanolamine has been shown to decrease the volume of infarcts following cerebral artery occlusion in PPARα knock-out mice. In addition, OEA can improve neurological function, reduce cerebral edema and infarct size after cerebral artery occlusion. This effect is inhibited by PPARα antagonists and is particularly significant if given within 1 hour of reperfusion.

Palmitoylethanolamide has been shown to protect against excitotoxicity in vitro. This effect is blocked by a PPARα but not PPARγ antagonists. Palmitoylethanolamide also modifies the expression of pro-inflammatory cytokines in response to β-amyloid. This is a PPARα-dependent effect.

Cannabidiol has also been shown to protect against β-amyloid neurotoxicity in rats. This is, however, via activation of PPARγ. In vitro, THC has neuroprotective effects in a cell culture model of Parkinson's disease. This

effect was not inhibited by CB1, and was inhibited by a PPARγ antagonist. In a model of multiple sclerosis, neuroprotective effects of endocannabinoids were shown by specifically inhibiting endocannabinoid uptake using CB1, CB2 and PPARγ antagonists. Activation of both PPARγ (via PEA) and PPARα (via PEA and theupregulation of local endocannabinoids) is associated with the analgesic effects of cannabinoids. This effect may be concomitant with the activation of CB1 and CB2.

Analgesia Effects

- Memory: OEA has central memory enhancing effects which is absent in PPARα knock-out mice; chronic PEA administration has been shown to protect against β-amyloid induced memory deficits in and Alzheimer's disease model. This effect was absent in PPARα knock-out mice.
- Reward: An increase in local endocannabinoids or the administration of either OEA or PEA can inhibit the response to nicotine (but not cocaine or morphine) in the reward centers of the brain. The effect was sensitive to CB1, CB2 and PPARα antagonists.

Cardiovascular Effects

Tetrahydrocannabinol, CBD, AEA and other endocannabinoids can induce time- and NO-dependent vasorelaxation in isolated rat arteries. The effect is also dependent on hydrogen peroxide, superoxide dismutase and PPARγ. OPA, AEA and PEA act on PPARα in vascular endothelium to induce vasodilation.

Metabolic Effects

Appetite suppression, lipolysis and weight loss appear to be PPARα dependent. Administration of OEA was shown to reduce serum cholesterol levels in both mouse and rat models of obesity. Energy homeostasis involves:

- Hypothalamic anorexigenic and orexigenic pathways, which are modulated by the endocannabinoid system and can be affected by complex neurohormonal and environmental factors.
- CB1 receptors in the hypothalamus, which are relatively low in number, but highly efficient, leading to profound crosstalk effects. Endocannabinoids function as "gatekeepers" of the hypothalamic–pituitary–adrenal axis (HPA), particularly during stress. Glucocorticoid synthesis and stress trigger endocannabinoid synthesis and CB1 signaling, which acts to constrain activity under conditions of acute stress and functionally down-regulated HPA activity during conditions of chronic stress. Peripherally, endocannabinoid over-activity results in: 1) Adipose tissue, 2) Pancreas effects of increased insulin release and increased β-cell mass, 3) Liver effects of increased lipogenesis, frequency of steatosis, and decreased insulin sensitivity, 4) Gastrointestinal tract effects of slowing of gastric emptying and decreased gastric motility, 5) Skeletal muscle effects of decreased glucose utilization and O_2 consumption, 6) Central effects of increased appetite, "cravings" for sweet and fatty foods and decreased satiety, and 7) Sleep effects.

The endocannabinoids appear to be involved in regulating the sleep-awake cycle and are under circadian control. Oleoylethanolamine and PEA promote wakefulness, and endocannabinoids promote both non-rapid and rapid eye

movement. CB1 antagonists reduce sleep and increase wakefulness. It has been shown that endocannabinoids can restore sleep cycles in a rat model of insomnia.

Cannabinoids As Therapeutic Agents

As is made clear throughout earlier sections, there is a lack of high-quality studies on the use of phytocannabinoids as therapeutic agents. There has been, however, a recent systematic review and meta-analysis of a total of 79 trials that combined had 6,462 participants. Only 4 of these studies were deemed at low risk of bias. The main outcomes considered were patient-relevant/disease-specific outcomes, activities of daily living, quality of life, global impression of change, and adverse side effects.[14-16,18] The trials were selected to include the following indications:

- Nausea and vomiting due to chemotherapy
- Appetite stimulation in HIV/AIDS
- Chronic pain
- Spasticity due to multiple sclerosis or paraplegia
- Depression
- Anxiety disorder
- Sleep disorder
- Psychosis
- Glaucoma
- Tourette syndrome

Studies showed that the evidence to support use of cannabinoids for the treatment chronic pain and spasticity was *moderate-quality.*

Δ (9)-tetrahydrocannabinol

Tetrahydrocannabinol is an aromatic terpenoid with low water solubility. The function of THC in the cannabis plant may be to act to protect the plant from various herbivores. There is little structural similarity to the endocannabinoids, while, as mentioned, THC does have significant affinity for both CB1 and CB2.

There have been some limited studies with THC but since marijuana or cannabis is still listed federally as a Schedule I drug, much of the information regarding THC activity comes from information on the whole plant. Some species of which may contain higher levels of THC than others. This has led to some contradictory and confusing data.

Research has begun to focus more specifically on the pharmacologically active constituents of cannabis but the continued legal obstacles indicate that more complete pharmacological information is many years away. There are also extrapolations that may be made from synthetic THC—dronabinal. There are however, several known effects of THC. THC administration results in increased dopamine release. Long-term use is associated with a decreased dopamine response. The effects of THC include:

- Analgesia
- Anxiolytic/Sedative effects
- Anti-emetic
- Stimulates appetite
- Antioxidant

- Hallucinogen
- Anti-proliferative
- Protects against effects of methamphetamine
- Reduces over-expression of nitric oxide synthase and production of peroxynitrites via CB1 dependent and independent mechanisms
- In capsule form (as opposed to inhalation), THC produces a significant decrease in airway resistance

Adverse effects include an increased heart rate, reddening of the eyes, dry mouth and throat, increased appetite, and vasodilatation. There may also be cognitive defects, memory defects, distorted perception. There have been reports of psychosis in some individuals. It is unknown if cannabis use actually causes psychotic symptoms or if cannabis precipitates psychosis in predisposed individuals.

Tolerance to THC develops and decreases relatively rapidly. The addictive potential of THC is somewhat controversial. Most safety information is derived from studies of recreational use. According to the National Institute on Drug Abuse, marijuana use can lead to dependence and, in severe cases, addiction: *Marijuana use can lead to the development of problem use, known as a marijuana use disorder, which takes the form of addiction in severe cases... Marijuana use disorder becomes addiction when the person cannot stop using the drug even though it interferes with many aspects of his or her life.*[19,]

Cannabidiol

Cannabidiol (CBD) has significant differences to THC and may provide significant advantages for a wide range of medical applications, particularly in the area of the control of seizure disorders, as discussed in the remainder of this section.[21-27] As mentioned, CBD has low affinity for CB1 and CB2 receptors and, under some conditions at least, acts as an indirect (inverse) antagonist. In this way, CBD may resemble the first generation CB1 inverse agonists.

Cannabidiol has been shown to have anxiolytic properties. In a study using functional neuroimaging to examine the effects of CBD on individuals diagnosed with social anxiety disorder, 400mg doses of CBD was compared to placebo. This dose was associated with significantly decreased subjective anxiety that was correlated with effects on the limbic and paralimbic areas of the brain. Another study, using a simulated public speaking test, indicated that pretreatment with CBD was associated with significantly reduced anxiety, discomfort and cognitive impairment.

A recent clinical trial comparing the effects of a standard antipsychotic (amisulpride) to CBD in patients with schizophrenia indicated that CBD provided equivalent symptom relief. In addition, the study showed that CBD had fewer adverse effects than the amisulpride treatment. However, some studies have indicated that CBD in the presence of THC may exacerbate psychotic symptoms.

Charlotte's Story

Cannabis species high in CBD were developed in large part in response to a young girl, Charlotte, with Dravet syndrome (myoclonic epilepsy of infancy or SMEI). Charlotte had her first dose of medical marijuana at the age of 5 using the original strain "Hippies Disappointment," a cannabis strain low in THC and high in CBD. Prior to the medical marijuana, Charlotte had been taking up to 7 drugs including barbiturates and benzodiazepines and had a trial of a ketogenic diet. The ketogenic diet was relatively successful in controlling seizures, but was accompanied by significant behavioral and cognitive effects. In 2002, when Colorado approved a medical marijuana program, Charlotte's parents decided to try cannabis high in CBD — at the time, Charlotte was experiencing approximately 300 seizures a week. The child was started on low dose CBD oil (orally) and experienced a drastic decrease in seizures. Because of the scarcity and cost of high CBD oil, the parents contacted one of the largest marijuana growers and dispensaries in Colorado. These growers were producing a strain of marijuana that was high in CBD and low in THC after crossbreeding with industrial hemp. At the time, this high CBD oil was not considered desirable.

After seeing the effect of the high CBD oil on Charlotte and researching the potential therapeutic potential for CBD, the growers started a non-profit organization, the "Realm of Caring Foundation" to provide high CBD cannabis to patients with epilepsy, cancer, multiple sclerosis and Parkinson's disease, especially those with financial need.

Cannabidiol and Epilepsy

Research into the potential therapeutics of CBD for epilepsy has indicated good tolerance and significant anticonvulsant effect. A recent review on the use of CBD in intractable epilepsy indicated that this area is stymied by a dearth of pure compound and the legal restrictions. However, it is also clear that there is strong evidence for the safety and efficacy of CBD in the treatment of epilepsy, especially in the pediatric population. While the mechanism by which CBD exerts antiepileptic effects is not clear, it is likely that the mechanism includes the *modulation of equilibrative nucleoside transporter, the orphan G-protein-coupled protein receptor, and the transient receptor potential of melastatin type 8 channel.* Tetrahydrocannabinol also has some anticonvulsant properties but may be proconvulsant under some conditions whereas CBD is consistently anticonvulsant.

A recent U.S. survey of parents with children with Dravet syndrome examined the use of CBD-enriched cannabis in pediatric treatment-resistant epilepsy. The survey was completed by 19 parents, 12 of whom had children with Dravet syndrome. The remainder of the patients had various forms of epilepsy; 53% of parents reported a greater than 80% reduction in the frequency of seizures, and 11% of the children were completely seizure free during a 3-month trial. Of the 12 pediatric patients with Dravet syndrome, 42% of these reported a greater than 80% reduction in seizures. The parents reported improved cognition and alertness. No severe side effects were reported.[21]

The most significant side effect reported was drowsiness and fatigue. The survey did not request information on the form, dose, percentages of CBD

versus THC or dosage, making an accurate assessment difficult. In another survey on infantile spasms and Lennox-Gastaut syndrome, 85% of parents reported a reduction in seizure frequency with 14% reporting a complete elimination of seizures. The most commonly reported side effect was an increased appetite.[21] Researchers have suggested that "*cannabidiol might reduce seizure frequency and might have an adequate safety profile in children and young adults with highly treatment-resistant epilepsy. Randomized controlled trials are warranted to characterize the safety profile and true efficacy of this compound*."[21]

Synthetic/Semi-synthetic Cannabinoids

There have been a number of synthetic cannabinoids developed.[17,27,28] *Sativex* contains both THC and CBD. It is an oral spray for the treatment of neuropathic pain and spasticity and is used primarily in patients with multiple sclerosis. Sativex was launched in the United Kingdom in 2010 and rescheduled to Schedule 4 in the U.S. in 2013. In the U.S., there are currently Phase III clinical trials for the treatment of cancer pain. Sativex achieved FDA "fast track" status in 2014. The FDA defines fast track as: *a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need*.

Dronabinol/Mariol is a synthetic THC and is recommended for use to treat chemotherapy-induced nausea and vomiting, as an appetite stimulant for AIDS patients and as an analgesic for MS neuropathic pain. Dronabinol was moved to Schedule III in 1999.

Nabilone/Cesamet is a synthetic THC and is recommended for use to treat chemotherapy-induced nausea and vomiting. Nabilone was originally approved in 1985 but removed from market. In 2006, Nabilone was re-approved by the FDA, but with advice of precautions and warnings regarding its potential to affect the mental state of the patient.

Dexanabinol is a synthetic non-psychotropic cannabinoid. Dexanabinol blocks NMDA receptors and COX-2 cytokines and chemokines. The recommended use is as a neuroprotective for use after cardiac surgery. Additional recommended uses include treatment of Traumatic Brain Injury (TBI). Dexanabinol has not been approved for use. A Phase I clinical trial for the use of dexanabinol to treat brain cancer is ongoing.

Ajulemic acid (CT-3) is a synthetic analog of a THC metabolite. It is thought to be useful for the treatment of neuropathic pain and spasticity in MS. CT-3 also has anti-inflammatory properties. Synthetic Cannabinoids that are not approved for human use but may be used in laboratory studies include Cannabinor, HU308 and HU331.

The Pharmacology Of Medical Marijuana

In this context, medical marijuana refers to the use of the *whole plant*. The whole marijuana plant contains a large number of phytocompounds with at least 60 characterized as cannabinoids. The most well-known and studied of these cannabinoids are THC and CBD. Content of THC and CBD varies based on species of origin, with cross-breeding and hybridization making available both high-THC and high-CBD varieties. Tetrahydrocannabinol is generally

considered the source of psychoactive effects while CBD is minimally psychoactive and has largely anticonvulsant, anxiolytic and antipsychotic properties. A third cannabinoid, cannabinol (CBN), is largely unstudied.[5]

Cannabinoids are lipophilic with a half-life (distribution phase) of approximately 30 minutes. The half-life of the terminal phase is approximately 30 hours, though CBD has a shorter terminal half-life of approximately 9 hours. When smoked, approximately half of the THC is found in the smoke, with about half of that amount exhaled. The bioavailability of THC in smoked cannabis has been estimated to be between 0.10 and 0.25 and approximates the half-life of THC administered by IV. The bioavailability of orally administered THC is estimated to be 5-20%. Cannabidiol bioavailability is slightly lower at 13-19%. Oral forms of cannabis tend to reach peak concentrations later than smoked forms.

Tolerance may develop within a few days and is believed to be due to the downregulation of CB1 (primarily) receptors and G-protein. Acute effects of THC include increased heart rate, decreased alertness and a decrease in motor stability. Chronic effects are relatively unknown, but a slight majority of available studies have indicated decreased neuropsychological performance, without estimating a real-life impact.

The chronic effects of cannabis, particularly on developing brains, is a controversial subject with most studies indicating a decline in IQ and executive function. These studies have been challenged for methodological weakness. Clearly, this is an important area for future research.

There have been some studies on the use of medical marijuana. In fact, there has been a relative explosion of studies, but many have been observational in nature. It should be mentioned in this context that there are even fewer studies using the whole plant, which is likely the most common situation. In addition, there are a number of different delivery systems utilized by patients using medical marijuana and only a few studies, for example, address using a vaporizing apparatus or *vaping*. Other studies have examined the safety and efficacy of medical marijuana in several clinical situations.

Chronic Pain

Non-cancer Pain

A recent systematic review of the use of cannabinoids for the treatment of chronic non-cancer related pain was recently published. The review found 11 high-quality trials, 7 of which demonstrated a significant analgesic effect. A number of the trials also demonstrated improvement in secondary outcomes (*i.e.*, sleep, muscle stiffness and spasticity). Adverse effects most frequently reported induce mild to moderate fatigue and dizziness. The cannabinoids were well tolerated. Devinsky, O., *et al*., stated:[26]

> "*The relative scarcity of proven cannabis-based therapies is not due to data that show that cannabinoids are ineffective or unsafe, but rather reflects a poverty of medical interest and by pharmaceutical companies arising from regulatory restrictions compounded by limits for patent rights on plant cannabinoid - containing preparations that*

have been used medicinally for millennia, as is the case for most natural products. In some Western countries, funding to study, establish, and prevent adverse effects of recreational cannabis use, such as addiction and cognitive and behavioral disorders, has far outpaced basic or clinical scientific research in this area."

Cancer-related Pain and Other Causes of Chronic Pain

Female patients tend to be more sensitive to the analgesic properties of cannabis. Higher oral doses of THC are associated with sedation and decreased alertness. Tetrahydrocannabinol 10 mg oral has been described as having analgesic potential.

The THC/CBD combination treatment has been found to be a useful adjunct for cancer patients with opioid-tolerance. A number of studies have examined potential benefits of inhaled cannabis (vaporized or smoked) in pain relief. Smoked cannabis was effective in relieving pain as compared to placebo (34% vs. 17%) with over 50% of patients reporting a greater than 30% reduction in pain. Adverse effects included increased heart rate, difficulties in concentration, increased sleep and thirst.

Neurological Conditions

In movement disorders, *i.e.*, Parkinson's disease, there has been a recent review of the therapeutic potential of cannabinoids, indicating that in preclinical research variable benefits existed in animal models of Parkinson's disease and Huntington's disease. Clinical trials also suggest benefits for conditions such as tics, but little benefit for tremor in multiple sclerosis or

dyskinesias or motor symptoms in Parkinson's disease. Further research has been recommended.

Epilepsy is another neurological condition studied relative to the benefit of cannabis. There has been a strong case made for the use of CBD for intractable epilepsy, particularly in the pediatric population. Cilio, Thiele and Devinsky (2014)[33], provided a rationale for continued study, but also careful use of CBD in these patients. They stated that "*Pure CBD appears to be an ideal candidate among phytocannabinoids as a therapy for treatment-resistant epilepsy. A first step in this direction is to systematically investigate the safety, pharmacokinetics, and interactions of CBD with other antiepileptic drugs and obtain an initial signal regarding efficacy at different dosages. These data can then be used to plan double-blinded placebo-controlled efficacy trials*."[33]

In a summary of the uses of complementary and alternative medicine by Stephen Wright, *et al*., the following recommendations were approved for multiple sclerosis:[34]

> *Clinicians might offer oral cannabis extract for spasticity symptoms and pain (excluding central neuropathic pain) (Level A). Clinicians might offer tetrahydrocannabinol for spasticity symptoms and pain (excluding central neuropathic pain) (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity (short-term)/tremor (Level B) and possibly effective for spasticity and pain (long-term) (Level C). Clinicians might offer Sativex oromucosal cannabinoid spray (nabiximols) for spasticity*

symptoms, pain, and urinary frequency (Level B). Clinicians should counsel patients that these agents are probably ineffective for objective spasticity/urinary incontinence (Level B). Clinicians might choose not to offer these agents for tremor (Level C). Clinicians might counsel patients that magnetic therapy is probably effective for fatigue and probably ineffective for depression (Level B); fish oil is probably ineffective for relapses, disability, fatigue, MRI lesions, and quality of life (QOL) (Level B); ginkgo biloba is ineffective for cognition (Level A) and possibly effective for fatigue (Level C); reflexology is possibly effective for paresthesia (Level C); Cari Loder regimen is possibly ineffective for disability, symptoms, depression, and fatigue (Level C); and bee sting therapy is possibly ineffective for relapses, disability, fatigue, lesion burden/volume, and health-related QOL (Level C). Cannabinoids may cause adverse effects. Clinicians should exercise caution regarding standardized vs nonstandardized cannabis extracts and overall CAM quality control/nonregulation. Safety/efficacy of other CAM/CAM interaction with MS disease-modifying therapies is unknown.

Neurodegenerative disorders such as Alzheimer's disease have been included in recent studies showing that THC may directly interact with Aβ peptide, inhibiting aggregation, and decreasing both total GSK-3β levels and phosphorylated GSK-3β in a dose-dependent manner.[35] In a recent pilot study, the efficacy and safety of the use of cannabis oil as an add-on to pharmacotherarpy in Alzheimer's disease showed that "*Significant reduction in CGI severity score (6.5 to 5.7; $p < 0.01$) and NPI score were recorded (44.4 to 12.8; $p < 0.01$). NPI domains of significant decrease were:*

Delusions, agitation/aggression, irritability, apathy, sleep and caregiver distress."[36]

Amyotrophic Lateral Sclerosis or ALS is another neurological disease with symptoms including weakness, spasticity, and respiratory difficulties.[37] It is believed that cannabinoids act in the regions affected by ALS. It is further believed that cannabinoids could effectively be used for the management of symptoms such as pain, spasticity, wasting, respiratory failure, dysphagia, negative mood, and dysautonomia. The anti-salivatory components of cannabis may reduce the risk of aspiration pneumonia. Studies have indicated that dronabinol 5 mg was well-tolerated. However, there was no effect on number or intensity of cramps, quality of life, appetite, sleep, or mood.

While the following is an abbreviated list, these are the neurological conditions for which the American Academy of Neurology have a systematic review of the data for the use of medical marijuana in selected neurological disorders. Their conclusions were as shown below.[38]

- In MS, oral cannabis extract is effective while THC is probably effective
- For central pain, or for painful spasms, including spasticity-related pain but excluding neuropathic pain: oral cannabis extract is effective while THC is probably effective
- For urinary dysfunction, oral cannabis extract and THC is ineffective
- For tremor neither, oral cannabis extract or THC is ineffective
- Oral cannabis extract is probably ineffective for the treatment of levodopa-induced dyskinesias in patients with Parkinson disease.

- Oral cannabis extracts have unknown effectiveness for non–chorea-related symptoms of Huntington disease, Tourette syndrome, cervical dystonia, and epilepsy

Other Medical Conditions

The use of cannabis has also been studied for patients suffering from a variety of other conditions.[39-53]

Cachexia

Studies have indicated that in patients, particularly with HIV/AIDS and cancer, who smoked marijuana and used the synthetic cannabinoid dronabinol, had increased food intake and gained weight.

Nausea

Cannabinoids may improve symptoms of nausea in cancer, HIV/AIDS and post-surgically. An oral THC preparation has been shown to be more effective than placebo and traditional anti-emetics in reducing chemotherapy-induced nausea and vomiting (CINV), though conflicting results have been obtained. Dronabinol, a synthetic cannabinoid, has been approved for CINV by the FDA for those who have not shown a treatment response to traditional anti-emetics. However, cannabinoids are not recommended by either the American Society of Clinical Oncology or the European Society for Medical Oncology.

HIV/AIDS

Medical marijuana is usually recommended for HIV/AIDS patients for the treatment of nausea, weight-loss and HIV-associated neuropathies. Cannabis has also been recommended for symptoms of depression and anxiety. It is not intended to treat viral load. A recent Cochrane Systematic Review indicated that evidence for efficacy in treating the symptoms of nausea and weight loss are currently lacking.

Cancer

The use of cannabis in cancer patients has been primarily for the relief of CINV and for chronic cancer pain. Cannabinoids may have a lower addictive potential than opioids and have proved highly beneficial in ameliorating pain in some individuals. In addition, a recent study examining mortality rates and opioid overdoses concluded that "*Medical cannabis laws are associated with significantly lower state-level opioid overdose mortality rates. Further investigation is required to determine how medical cannabis laws may interact with policies aimed at preventing opioid analgesic overdose*."[41]

Crohn's disease

Crohn's disease in an inflammatory bowel disease. It has been estimated that between 16-50% of Crohn's disease patients use self-administered cannabis to relieve symptoms. One study has indicated that cannabis use was better than placebo in reducing steroid use, and improving sleep and

appetite. However, cannabis use for longer than 6 months was also associated with a five-fold higher risk of the necessity of surgical intervention.

Glaucoma

Glaucoma is a neurodegenerative eye disease that can cause blindness. Increased intraocular pressure (IOP) has been reported to be reduced with cannabis use but these studies are small and somewhat dated. In addition, the decrease in IOP is of short duration and is associated with adverse effects because significant reduction in IOP requires frequent use throughout the day. Further studies to determine effective alternate and more focused routes of delivery are needed.

Psychiatric/Behavioral Disorders

Schizophrenia

Schizophrenia typically present in late adolescence or early adulthood and is characterized by disturbances of thought, perception, volition, and cognition. CB1 receptors and cannabinoids, particularly CBD are promising therapeutic approaches for the treatment of schizophrenia. However, THC may be pro-psychotic, possibly in pre-disposed individuals — therefore, the ratio of CBD/THC may be critical. In a study of individuals after a single psychotic episode, those individuals exposed to high THC levels were over-represented as compared to those exposed to hashish (approximately equal amounts of THC/CBD) and high CBD cannabis. Five studies have been reported concerning CBD administration to individuals with psychotic symptoms. All studies showed varying responses but indicated that CBD held significant promise in the treatment of psychotic disorders.

Posttraumatic Stress Disorder

Posttraumatic Stress Disorder or PTSD is a common problem. Cannabis is a common self-medicating tool in individuals with PTSD but there are increasing reports of associated comorbidities such as depression, anxiety, psychosis, and substance misuse/addiction. As is the case with other conditions, research in this area is hampered by the wide range of cannabinoids used (*i.e.*, whole plant, tincture, oil, *etc.*, and synthetic cannabinoids), delivery system, dose and dosages. One small (and uncontrolled) study from the New Mexico Medical Cannabis program indicated that individuals asked to retrospectively rate their PTSD symptoms, rated cannabis (whole plant) highly, with a 75% reduction of PTSD symptoms.[48]

Another small study examined safety and tolerability of THC on PTSD. All patients were concurrently on benzodiazepines, complicating interpretation. Participants reported improvement in self-reported nightmares and sleep quality as well as interviewer-assessed arousal. There was no significant improvement in intrusion or avoidance symptoms.[49]

Depression and Anxiety

There have been several recent reviews concerning the association of depression and anxiety with cannabis use. A recent meta-analysis of longitudinal studies indicated that there may be an increased risk of depressive disorders associated with cannabis use, though the analysis was complicated by the large degree of heterogeneity in the various studies.[50] Another prospective study from Sweden indicated that there were no

associations between depression, anxiety and cannabis use.[51] Other studies report cross-sectional association with anxiety but not longitudinal associations.[52] Finally, another meta-analysis or 31 studies did find an association between anxiety and cannabis use, but the association was relatively small.[53]

On the one hand, there is a myriad of studies related to cannabis use in various medical and mental health conditions but the Drug Enforcement Administration (DEA) recently refused to remove cannabis from the Schedule I list; this may be due to statistics that marijuana users are three times as likely to use heroin. These types of studies, while sorely needed, are very difficult to get permission to do and even harder to get federally funded. The National Institute on Drug Abuse (NIDA) has indicated that as part of its mandate to study drug abuse and addiction and other health effects of both legal and illegal drugs, NIDA funds a wide range of research on marijuana (cannabis). Its main psychotropic ingredient, delta-9-tetrahydrocannabinol (THC); and chemicals related to THC (cannabinoids), including:

- Patterns and trends in marijuana use and attitudes, particularly among adolescents
- Short- and medium-term effects of THC on the brain and behavior; driving under the influence of cannabis; and genetic, epigenetic, and environmental factors that mediate marijuana's effects
- Long-term effects of prenatal and adolescent cannabis exposure on brain development
- Development and impact assessment of prevention programs on marijuana use
- Screening and brief assessment for cannabis use disorder

- Medications, Health, and behavioral treatments for cannabis use disorder
- Function of the brain's endocannabinoid system, including its role in pain, mental illness, and HIV
- Potential therapeutic uses of THC and other cannabinoids in treatment of pain, HIV, addiction, and other health conditions
- Social, behavioral, and public health and safety impacts of policy changes related to marijuana (*i.e.*, "medical marijuana" and recreational legalization")

During the period of 2008 to 2014, the National Institutes of Health granted $1.4 billion for cannabis research.[19] Of that amount, $1.1 billion was for the study of cannabis use and addiction with $297 billion spent on the physiological actions of cannabis and the potential therapeutic benefits. In 2015, the NIH supported "*81 projects totaling over $111 million on cannabinoid research. Within this investment, 49 projects ($21 million) examined therapeutic properties of cannabinoids, and 15 projects ($9 million) focused on CBD. Cannabinoid research is supported broadly across NIH Institutes and Centers (ICs), with each IC supporting research specifically focused on the impact of cannabinoids on health effects within their scientific mission*." The bulk of the projects (173) was through NIDA, the institute responsible for investigating addiction,[19] which also received the bulk of therapeutic cannabinoid research monies ($10 923 472 of a total of $21,214,163) and CBD research ($6,854,092 of a total of $9,035,446).

Summary

The central problem with cannabis has been and remains that much of the evidence currently available is based on anecdotes, case presentations,

prospective surveys and that while cannabis remains a Schedule I drug, it is extraordinarily difficult to conduct gold-standard randomized controlled testing on the myriad effects of the whole plant, the most commonly used form of cannabis. Research has begun to focus more specifically on the pharmacologically active constituents of cannabis but the continued legal obstacles indicate that more complete pharmacological information is many years away.

Medical Marijuana:
Part 2: Legalization And Medicinal Use

Introduction

Since passage of The Controlled Substances Act of 1970, all forms of cannabis, including hemp, were, and today are, classified as a Schedule I drug, making it illegal to grow or use cannabis in the United States under federal law. Currently, however, the District of Columbia and 28 states have legalized medical cannabis in some form. This creates a tension between federal and state law since cannabis use that is legal under a state's law is still illegal under federal law. In addition, in 2016, Florida, Georgia, Indiana, Iowa, Kansas, Kentucky, Mississippi, Missouri, Nebraska, South Carolina, Tennessee, West Virginia, Wisconsin and Utah failed to pass medical cannabis legislation. In the states that have legalized cannabis, the legal use is not unfettered. There are limitations for prescribing cannabis and its personal use. The limits for personal use, the responsibilities of physicians and the diseases and conditions covered by state law varies from state to

state, as do the rules for positive defense if an individual is arrested under that state's laws.

Medical Marijuana Laws by State

It is important to realize that the status of the legal use of medical or recreational marijuana under state law is fluid and constantly changing. Therefore, the information given in this article and Table I below summarizing these factors is meant only as a guide for clinicians and not as legal advice. A specific person's ability to use medical or recreational marijuana under a specific state's laws should be determined by the individual through local department of health, local medical associations, and/or with the advice of an attorney to determine the status of medical marijuana for the individual in his/her community.

Some professional guidance has been developed for physicians by legal experts and state medical associations.[65] For example, the California Medical Association provided the following statement:[65] "*Any physician who recommends the use of marijuana by a patient should have arrived at that decision in accordance with accepted standards of medical responsibility, i.e., history and physical examination of the patient; development of a treatment plan with objectives; provision of informed consent, including discussion of side effects; periodic review of the treatment's efficacy, and, of critical importance, proper record keeping that supports the decision to recommend the use of marijuana. However, the Board recognizes that these principles may require further elaboration to take into account the factors that may affect the physician-patient relationship in this context*."

General Requirements

In general, patients being considered for medical marijuana (sometimes referred to as 'medical cannabis') should have a current source of primary care, a Primary Care Provider (PCP) that they see regularly. The patient should be seen routinely for scheduled visits with a PCP overseeing a serious illness or symptoms for which medical cannabis is used, either by the PCP or by another specialist, chiropractor, or other health clinician of the patient's choice. These requirements accomplish two important objectives of 1) affirming that the patient has access to primary care, and 2) clarifying the clinician's role when consulting to prescribe medical cannabis, which is distinct from that of the PCP (a common misunderstanding).

It is helpful to screen patients[66] by phone who call in for a medical cannabis evaluation to make sure they understand the requirements of the consulting clinician prior to being given an initial appointment. Those who would not be willing to comply with requirements would not qualify for medical cannabis and should be eliminated as potential patients.

Prior to the appointment of a new patient, a medical questionnaire and release forms or consents should be provided to the patient. The medical cannabis evaluation can then be conducted during an office visit, which includes the collection of relevant history, problem-specific physical exam, and review of the completed questionnaire and outside medical records. Pros and cons of medical cannabis use are discussed with the patient, and informed consent documents are reviewed and signed. Based on all of the above, a decision is reached on whether or not to recommend cannabis to the patient.

In cases where there exists some documentation or physical evidence of a serious illness for which cannabis might be beneficial, recent health records should be required for review. There should be appropriate follow-up appointments arranged for patients receiving cannabis recommendations. A yearly re-evaluation is minimum for patients approved to receive medical cannabis.

It is highly recommended that clinicians contact their local department of health and/or their local medical association to determine the status of medical cannabis in their own areas.[67,68] The following table outlines the laws state by state regulating medical and recreational cannabis use.

Table 1: Medical Marijuana Laws by State

State	Approved Conditions	Legal Limits for Personal Use	Current Status/Additional Information
Alaska	Cachexia, cancer, chronic pain, epilepsy and other disorders characterized by seizures, glaucoma, HIV/AIDS, MS and other disorders characterized by muscle spasticity, and nausea; other conditions are subject to approval by the Alaska Department of Health and Social Services	*1 oz usable; 6 plants (3 mature, 3 immature)* Patients or caregivers may legally possess no more than one ounce of usable marijuana, and may cultivate no more than six marijuana plants, of which no more than three may be mature. The law establishes a confidential state-	Alaska Bureau of Vital Statistics Marijuana Registry P.O. Box 110699 Juneau, AK 99811-0699 Phone: 907-465-5423 BVSSpecialServices@health.state.ak.us Website: AK Marijuana Registry Online

		run patient registry to issue identification cards to qualifying patients.	
Arizona	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Alzheimer disease, cachexia, severe and chronic pain, severe nausea, seizures (including epilepsy), severe or persistent muscle spasms	*2.5 oz usable; 0-12 plants* Qualified patients or their registered caregivers may obtain up to 2.5 ounces of marijuana in a 14-day period from a registered nonprofit medical marijuana dispensary. If the patient lives more than 25 miles from the nearest dispensary, the patient or caregiver may cultivate up to 12 marijuana plants in an enclosed, locked facility.	Arizona Department of Health Services (ADHS) Medical Marijuana Program 150 North 18th Avenue Phoenix, Arizona 85007 Phone: 602-364-1793 M2programsupport@azdhs.gov Website: Arizona Medical Marijuana Program
Arkansas	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Tourette's syndrome, Crohn's disease, ulcerative colitis, PTSD, severe arthritis, fibromyalgia, Alzheimer's disease; chronic/debilitating disease or medical condition or its treatment that produces one or more of the following: cachexia (wasting syndrome); peripheral	*2.5 ounces of usable marijuana per 14-day period*	Arkansas Department of Health Phone: 501-661-2367 adhquestions@arkansas.gov Website: Medical Marijuana Program

	neuropathy; intractable pain, which is pain that has not responded to ordinary medications, treatment, or surgical measures for more than six months; severe nausea; seizures, including without limitation those characteristic of epilepsy; or severe and persistent muscle spasms, including without limitation those characteristic of multiple sclerosis; Other medical condition or DOH approved treatment.		
California	AIDS, anorexia, arthritis, cachexia, cancer, chronic pain, glaucoma, migraine, persistent muscle spasms (including spasms associated with MS), seizures (including seizures associated with epilepsy), severe nausea, other chronic or persistent medical symptoms	*8 oz usable; 6 mature or 12 immature plants* Qualified patients and their primary caregivers may possess no more than eight ounces of dried marijuana and/or six mature (or 12 immature) marijuana plants. However, S.B. 420 allows patients to possess larger amounts of marijuana when recommended by a physician. The	California Department of Public Health Public Health Policy and Research Branch Attention: Medical Marijuana Identification Card Program MS 5202 P.O. Box 997377 Sacramento, CA 95899-7377 Phone: 916-552-8600 Fax: 916-440-5591 mmpinfo@cdph.ca.gov Website: CA Medical Marijuana Program Guidelines for the Security and Non-diversion of Marijuana Grown for Medical Use Information provided by the state on sources for medical marijuana:

		legislation also allows counties and municipalities to approve and/or maintain local ordinances permitting patients to possess larger quantities of medicinal pot than allowed under the new state guidelines. *"Qualified patients… with valid identification cards, and the designated primary caregivers of qualified patients ... shall not solely on the basis of that fact be subject to state criminal sanctions."*	"The MMP is not authorized to provide information on acquiring marijuana or other related products." "Medical Marijuana Program Frequently Asked Questions," cdph.ca.gov (accessed Mar. 1, 2016) "The California Department of Public Health's MMP does not have jurisdiction over medical marijuana cooperatives, dispensaries, or collectives. For questions related to these areas, please contact your local city or county business licensing office." "Medical Marijuana Identification Card Program," cdph.ca.gov
Colorado	Cancer, glaucoma, HIV/AIDS, cachexia, severe pain, severe nausea, seizures (including those characteristic of epilepsy), persistent muscle spasms (including those characteristic of MS); other conditions are subject to approval by the Colorado Board of Health	*2 oz usable; 6 plants (3 mature, 3 immature)* A patient or a primary caregiver who has been issued a Medical Marijuana Registry identification card may possess no more than two ounces of a usable form of marijuana and not more than six marijuana plants, with three or fewer being mature, flowering	Medical Marijuana Registry Colorado Department of Public Health and Environment HSV-8630 4300 Cherry Creek Drive South Denver, CO 80246 Phone: 303-692-2184 medical.marijuana@state.co.us Website: CO Medical Marijuana Registry

		plants that are producing a usable form of marijuana. Patients who do not join the registry or possess greater amounts of marijuana than allowed by law may argue the "*affirmative defense of medical necessity*" if they are arrested on marijuana charges.	
Connecticut	Cancer, glaucoma, HIV/AIDS, Parkinson disease, MS, nervous tissue of the spinal cord damage with objective neurological indication of intractable spasticity, epilepsy, cachexia, Crohn disease, PTSD … any medical condition, treatment, or disease approved by the Department of Consumer Protection	*1-mo supply*: "The maximum allowable monthly amount is 2.5 ounces unless your physician indicates a lesser amount is appropriate."	Medical Marijuana Program Department of Consumer Protection (DCP) 165 Capitol Avenue, Room 145 Hartford, CT 06106 Phone: 860-713-6066 Toll-Free: 800-842-2649 dcp.mmp@ct.gov Website: CT Medical Marijuana Program
Delaware	Adult Patient Qualifying Conditions - terminal illness, cancer, HIV/AIDS, decompensated cirrhosis, ALS, agitation of Alzheimer's disease, Post-	*6 oz usable* Patients 18 and older with a Delaware registry identification card may possess up to six ounces of marijuana. A registered	Delaware Department of Health and Social Services Office of Medical Marijuana 417 Federal Street Suite 130 Dover, Delaware 19901 Phone: 302-744-4749 Fax: 302-739-3071 MedicalMarijuanaDPH@state.de.us

	traumatic Stress Disorder (PTSD), intractable epilepsy, autism with self-injurious or aggressive behavior; Chronic/debilitating disease or medical condition or its treatment that produces cachexia or wasting syndrome, severe, debilitating pain not responding to previously prescribed medication/surgical measure for >3 mo., or for which other treatment options produced serious side effects, intractable nausea, seizures, or severe and persistent muscle spasms, including but not limited to those characteristic of Multiple Sclerosis *Pediatric Patient:* intractable epilepsy, chronic or debilitating disease/ medical condition with failed treatment involving cachexia or wasting syndrome, intractable nausea, or severe, painful, and persistent muscle spasms	compassion center may not dispense more than three ounces of marijuana to a registered qualifying patient in any fourteen-day period, and a patient may register with only one compassion center. Home cultivation is not allowed. Senate Bill 17 contains a provision that allows for an affirmative defense for individuals "in possession of no more than six ounces of usable marijuana." Rylie's Law allows the use of non-smoked cannabis oil that is no more than 7% THC for minors with intractable epilepsy or dystonia.	Website: DE Medical Marijuana Program
Florida	Cancer, epilepsy, glaucoma, HIV/AIDS, PTSD, ALS, Crohn's	To be determined during the rulemaking	Medical Marijuana Legalization Initiative (Amendment 2) – Approved Nov. 8, 2016 by 71.3% of voters. Amends the Florida

	disease, Parkinson's disease, multiple sclerosis, or other debilitating medical conditions of the same kind or class as or comparable to those enumerated, and for which a physician believes that the medical use of marijuana would likely outweigh the potential health risks for a patient.	process	Constitution. Effective: Jan. 3, 2017 Florida Department of Health 850-245-4444 Website: http://www.floridahealth.gov/ The law gives the Florida Department of Health six months to establish regulations and set a possession limit, and nine months to begin issuing identification cards. After nine months, a valid physician certification will serve as a qualifying patient identification card until the Department begins issuing cards.
Hawaii	Cancer, glaucoma, HIV/AIDS, a chronic or debilitating disease or medical condition or its treatment that produces cachexia, severe pain, severe nausea, seizures including those characteristic of epilepsy, or severe and persistent muscle spasms including those characteristic of MS or Crohn disease; other conditions are subject to approval by the Hawaii Department of Health	*3 oz usable; 7 plants (3 mature, 4 immature)* The amount of marijuana that may be possessed jointly between the qualifying patient and the primary caregiver is an "adequate supply," not to exceed seven plants, and no more than four ounces of usable marijuana jointly between a registered patient and caregiver. A qualifying patient or primary caregiver... shall be allowed to purchase no more than four ounces of marijuana within a consecutive	Department of Health Medical Marijuana Program 4348 Waialae Avenue #648 Honolulu, Hawaii 96816 Phone: 808-733-2177 medicalmarijuana@doh.hawaii.gov Website: HI Medical Marijuana Registry Program

		period of fifteen days.	
Illinois	Debilitating medical conditions include 40 chronic diseases and conditions: cancer, glaucoma, positive status for human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS), hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, agitation of Alzheimer's disease, cachexia/wasting syndrome, muscular dystrophy, severe fibromyalgia, spinal cord disease (including but not limited to arachnoiditis), Tarlov cysts, hydromyelia syringomyelia, Rheumatoid arthritis, fibrous dysplasia, spinal cord injury, traumatic brain injury and post-concussion syndrome, Multiple Sclerosis, Arnold-Chiari malformation and Syringomelia, Spinocerebellar Ataxia (SCA), Parkinson's Disease, Tourette Syndrome, Myoclonus, Dystonia, Reflex	*2.5 ounces usable cannabis during 14-day period*	Illinois Department of Public Health Division of Medical Cannabis Illinois Department of Public Health 535 W. Jefferson Street Springfield, IL 62761-0001 Attn: Rulemaking DPH.MedicalCannabis@illinois.gov Website: Medical Cannabis Program

	Sympathetic Dystrophy, RSD (Complex Regional Pain Syndromes Type I), Causalgia, CRPS (Complex Regional Pain Syndrome Type II), Neurofibromatosis, Chronic inflammatory Demyelinating Polyneuropathy, Chronic Inflammatory Demyelinating Polyneuropathy, Sjogren's Syndrome, Lupus, Interstitial Cystitis, Myasthenia Gravis, Hydrocephalus, nail-patella syndrome or residual limb pain; or the treatment of these conditions.		
Maine	Cancer, glaucoma, HIV, acquired immune deficiency syndrome, hepatitis C, amyotrophic lateral sclerosis, Crohn's disease, Alzheimer's, nail-patella syndrome, chronic intractable pain, cachexia or wasting syndrome, severe nausea, seizures (epilepsy), severe and persistent muscle spasms, and multiple sclerosis.	*2.5 oz usable; 6 plants* Patients (or their primary caregivers) may legally possess no more than one and one-quarter (1.25) ounces of usable marijuana, and may cultivate no more than six marijuana plants, of which no more than three may be mature. Patients possessing greater amounts of marijuana than allowed by law are afforded a	Maine Medical Use of Marijuana Program (MMMP) Division of Licensing and Regulatory Services Department of Health and Human Services 11 State House Station Augusta, ME 04333 Phone: 207-287-4325 dhhs@maine.gov Website: Maine Medical Marijuana Program

		"simple defense" to a charge of marijuana possession.	
Maryland	Cachexia, anorexia, or wasting syndrome, severe or chronic pain, severe nausea, seizures, severe or persistent muscle spasms, or other conditions approved by the commission	*30-d supply, amount to be determined*	Maryland Department of Health and Mental Hygiene 201 West Preston Street Baltimore, MD 21201 dhmh.medicalcannabis@maryland.gov Website: Natalie M. LaPrade Medical Marijuana Commission
Massachusetts	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, Parkinson disease, MS, and other conditions as determined in writing by a qualifying patient's physician	*60-d supply (10 oz) for personal medical use*	Department of Public Health of the Commonwealth of Massachusetts One Ashburton Place 11th Floor Boston, MA 02108 Phone: 617-624-5062 medicalmarijuana@state.ma.us Website: www.mass.gov/medicalmarijuana
Michigan	Cancer, glaucoma, HIV/AIDS, hepatitis C, ALS, Crohn disease, agitation of Alzheimer disease, nail patella syndrome, cachexia or wasting syndrome, severe and chronic pain, severe nausea, seizures, epilepsy, muscle spasms, MS, PTSD	*2.5 oz usable; 12 plants* Patients may possess up to two and one-half (2.5) ounces of usable marijuana and twelve marijuana plants kept in an enclosed, locked facility. The twelve plants may be kept by the patient only if he or she has not specified a primary caregiver to cultivate the marijuana for him or her.	Michigan Medical Marihuana Program Department of Licensing and Regulatory Affairs Bureau of Professional Licensing Michigan Medical Marihuana Program PO Box 30083 Lansing, MI 48909 Phone: 517-284-6400 BHP-MMMPINFO@michigan.gov Website: MI Medical Marihuana Program

Minnesota	Cancer (if the underlying condition or treatment produces severe or chronic pain, nausea, severe vomiting, or cachexia or severe wasting), glaucoma, HIV/AIDS, Tourette syndrome, ALS, seizures/epilepsy, severe and persistent muscle spasms/MS, Crohn disease, terminal illness with a life expectancy of	*30-d supply of nonsmokable marijuana* Commissioner of Health will register 2 in-state manufacturers for the production of all medical cannabis within the state. Manufacturers are required to ensure that the medical cannabis distributed contains a maximum of a 30-day supply of the dosage determined for that patient. "Medical cannabis" is defined as any species of the genus cannabis plant delivered in the form of (1) liquid, including, but not limited to, oil; (2) pill; (3) vaporized delivery method that does not require the use of dried leaves or plant form.	Minnesota Department of Health Office of Medical Cannabis 651-201-5598 844-879-3381 (toll-free) health.cannabis@state.mn.us Website: Medical Cannabis Program
Montana	Cancer, glaucoma, HIV/AIDS; cachexia/ wasting syndrome, severe or chronic pain, severe nausea, seizures including those caused by epilepsy, severe or persistent muscle spasms including	*1 oz usable; 4 plants (mature); 12 seedlings* Registered cardholders are limited to 12 seedlings (<12"), 4 mature flowering plants, and 1 ounce of	Medical Marijuana Program Montana Department of Health and Human Services Licensure Bureau 2401 Colonial Drive, 2nd Floor P.O. Box 202953 Helena, MT 59620-2953 Phone: 406-444-0596 jbuska@mt.gov

	those caused by MS or Crohn disease, or any other medical condition/treatment adopted by the department by rule Added: Pain, PTSD	usable marijuana. If a registered cardholder assigns a provider, they cannot grow for themselves. A second physician is required to confirm a chronic pain diagnosis.	Website: MT Medical Marijuana Program Medical Marijuana Program FAQs
Nevada	AIDS, cancer, glaucoma, and any medical condition or treatment for a medical condition that produces cachexia, persistent muscle spasms or seizures, severe nausea or pain, PTSD; other conditions are subject to approval by the state health division of the state department of human resources	Patients (or their primary caregivers) may legally possess no more than two and a half ounces of usable marijuana in a 14-day period and 12 plants. The medical marijuana program website has a list of 15 open dispensaries. Nevada law allows home cultivation only in specific circumstances. "*The Nevada MM Program is not a resource for the growing process and does not have information to give to patients.* *It is advised that you talk to an attorney to learn about your rights and protections*."	Nevada State Health Division 4150 Technology Way, Suite 106 Carson City, NV, 89706 Phone: 775-684-3487 Fax: 775-684-4156 medicalmarijuana@health.nv.gov Website: NV Medical Marijuana Program
New Hampshire	(1) Cancer, glaucoma, positive status for human	Two oz of usable cannabis during a 10-d period	New Hampshire Department of Health and Human Services Therapeutic Cannabis Program

	immunodeficiency virus, acquired immune deficiency syndrome, hepatitis C currently receiving antiviral treatment, amyotrophic lateral sclerosis, muscular dystrophy, Crohn's disease, multiple sclerosis, chronic pancreatitis, spinal cord injury or disease, traumatic brain injury, epilepsy, lupus, Parkinson's disease, Alzheimer's disease, or one or more injuries that significantly interferes with daily activities as documented by the patient's provider; AND (2) A severely debilitating or terminal medical condition or its treatment that has produced at least one of the following: elevated intraocular pressure, cachexia, chemotherapy-induced anorexia, wasting syndrome, agitation of Alzheimer's disease, severe pain that has not responded to previously prescribed medication or surgical measures or for which other treatment options		129 Pleasant Street, Brown Building Concord, NH 03301-3857 Phone: 603-271-9234 Email Contact Form Website: Therapeutic Use of Cannabis Program

	produced serious side effects, constant or severe nausea, moderate to severe vomiting, seizures, or severe, persistent muscle spasms."		
New Jersey	Amyotrophic lateral sclerosis (ALS); multiple sclerosis; terminal cancer; muscular dystrophy; inflammatory bowel disease, including Crohn's disease; terminal illness, if the physician has determined a prognosis of less than 12 mo. of life. If conventional therapy is unsuccessful: seizure disorder, including epilepsy, intractable skeletal muscular spasticity, glaucoma. If severe or chronic pain, severe nausea or vomiting, cachexia, or wasting syndrome results from the condition or treatment: Positive status for HIV/AIDS; cancer.	*2 oz usable* Allows edible forms of marijuana only for qualifying minors, who must receive approval from a pediatrician and a psychiatrist.	Department of Health (DOH) P. O. Box 360 Trenton, NJ 08625-0360 Phone: 609-292-0424 Contact form Website: Medicinal Marijuana Program Information provided by the state on sources for medical marijuana: Patients are not allowed to grow their own marijuana. On Mar. 21, 2011, the New Jersey DOH announced the locations of six nonprofit alternative treatment centers (ATCs) from which medical marijuana may be obtained, five of which were operational as of Mar. 1, 2016.
New Mexico	Amyotrophic Lateral Sclerosis (Lou Gehrig's disease); cancer; Crohn's disease; epilepsy; glaucoma; hepatitis C infection	6 oz usable; 16 plants (4 mature, 12 immature) Usable cannabis is defined as dried leaves and flowers; it does not include seeds,	New Mexico Department of Health Medical Cannabis Program 1190 Saint Francis Drive Suite S-3400 Santa Fe, NM 87505 Phone: 505-827-2321 medical.cannabis@state.nm.us

	currently receiving antiviral treatment; HIV/AIDS; Huntington's Disease; hospice care; inclusion body myositis; inflammatory autoimmune mediated arthritis; intractable nausea/vomiting; multiple sclerosis; damage to the nervous tissue of the spinal cord; painful peripheral neuropathy; Parkinson's disease; PTSD; severe chronic pain; severe anorexia/cachexia; spasmodic torticollis; ulcerative colitis	stalks or roots. A primary caregiver may provide services to a maximum of four qualified patients under the Medical Cannabis Program.	Website: NM Medical Cannabis Program
New York	Potentially eligible for medical marijuana if diagnosed with a specific severe, debilitating or life threatening condition that is accompanied by an associated or complicating condition. By law, those conditions are: cancer, HIV infection or AIDS, amyotrophic lateral sclerosis (ALS), Parkinson's disease, multiple sclerosis, spinal cord injury with spasticity, epilepsy, inflammatory bowel disease,	*30-d supply nonsmokable marijuana* Physicians must complete a four-hour New York State Department of Health (Department)-approved course and register with the Department to certify patients.	New York Department of Health 866-811-7957 Email Contact Form Website: New York State Medical Marijuana Program

	neuropathy, and Huntington's disease. The associated or complicating conditions are cachexia or wasting syndrome, severe or chronic pain, severe nausea, seizures, or severe or persistent muscle spasms.		
North Dakota	Cancer, HIV/AIDS, hepatitis C, ALS, PTSD, Alzheimer's disease, dementia, Crohn's disease, fibromyalgia, spinal stenosis or chronic back pain including neuropathy or damage to spinal cord nervous tissue with intractable spasticity, epilepsy, glaucoma; A chronic/debilitating disease medical condition or its treatment that produces one or more of: cachexia or wasting syndrome, severe debilitating pain not responding to prior prescribed medication/surgical measures for more than three months or for which other treatment options produced serious side effects. Intractable nausea, seizures, or severe and persistent muscle spasms, including but not	*3 ounces of usable marijuana per 14-day period* North Dakota Compassionate Care Act" – Approved Nov. 8, 2016 by 63.7% of the voters	North Dakota Department of Health 701-328-2372 Website: www.ndhealth.gov "If the qualifying patient's home is located more than forty miles from the nearest compassionate care center, the qualified patient or designated caregiver may cultivate up to eight marijuana plants in an enclosed, locked facility." Source: North Dakota Compassionate Care Act

	limited to those characteristic of multiple sclerosis; Any other medical condition or its treatment added by the North Dakota Department of Health.		
Ohio	AIDS/HIV, Alzheimer's disease, ALS, cancer, chronic traumatic encephalopathy, Crohn's disease, epilepsy, fibromyalgia, glaucoma, hepatitis C, inflammatory bowel disease, multiple sclerosis, chronic, severe, or intractable pain, Parkinson's disease, PTSD, sickle cell anemia, spinal cord disease or injury, Tourette's syndrome, traumatic brain injury, ulcerative colitis	*The law allows for a maximum of a 90-day supply, to be determined during the rulemaking process.* The Ohio Department of Commerce and the State of Ohio Board of Pharmacy are required by law to take all actions necessary to ensure that Ohio's Medical Marijuana Control Program is fully operational no later than September 2018. At that time, there will be an established structure for Ohioans with a qualifying medical condition to obtain guidance for medical marijuana, and purchase it from a licensed dispensary.	Ohio Medical Marijuana Control Program Effective: Sep. 8, 2016 Website: medicalmarijuana.ohio.gov Contact Form
Oregon	Cancer, glaucoma, HIV/AIDS, or treatment of these conditions; a	*24 oz usable; 24 plants (6 mature, 18 immature)*	Oregon Department of Human Services Medical Marijuana Program PO Box 14116 Portland, OR 97293

	medical condition or treatment for a medical condition that produces cachexia, severe pain, severe nausea, seizures including those caused by epilepsy, or persistent muscle spasms including those caused by MS; other conditions are subject to approval by the Health Division of the Oregon Department of Human Resources PTSD added, 2013	A registry identification cardholder or the designated primary caregiver of the cardholder may possess up to six mature marijuana plants and 24 ounces of usable marijuana. A registry identification cardholder and the designated primary caregiver of the cardholder may possess a combined total of up to 18 marijuana seedlings. The law also redefines "mature plants" to include only those cannabis plants that are more than 12 inches in height and diameter, and establish a state-registry for those authorized to produce medical cannabis to qualified patients. As of 10/1/2015, registered medical marijuana dispensaries may sell limited amounts of recreational marijuana to adults age 21 and older.	Phone: 855-244-9580 (toll-free) medmj.dispensaries@state.or.us Website: healthoregon.org/ommp
Pennsylvania	Cancer, HIV/AIDS, ALS, Parkinson's,	*30-day supply;*	Pennsylvania Department of Health

	multiple sclerosis, damage to the nervous tissue of the spinal cord with objective neurological indication of intractable spasticity, epilepsy, inflammatory bowel disease, neuropathies, Huntington's disease, Crohn's disease, PTSD, intractable seizures, glaucoma, sickle cell anemia, severe chronic or intractable pain of neuropathic origin or severe chronic or intractable pain in which conventional therapeutic intervention and opiate therapy is contraindicated or ineffective, autism.	Medical marijuana may only be dispensed to a patient or caregiver in the following forms: (i) pill; (ii) oil; (iii) topical forms, including gel, creams or ointments; (iv) a form medically appropriate for administration by vaporization or nebulization, excluding dry leaf or plant form... (v) tincture; or (vi) liquid. Unless otherwise provided in regulations adopted by the department under section 1202, medical marijuana may not be dispensed to a patient or a caregiver in dry leaf or plant form.	1-877-PA-HEALTH Website: Medical Marijuana Program In July [2016], parents, legal guardians, caregivers, and spouses will be able to apply to the department for a Safe Harbor Letter that will allow them to administer medical marijuana obtained from outside of Pennsylvania to minors in their care. Once approved, the letter should be carried whenever medical marijuana is being transported outside of an individual's home.
Rhode Island	Cancer, glaucoma, HIV/AIDS, hepatitis C, or treatment of these conditions; a chronic/debilitating disease or medical condition or its treatment that produces cachexia, debilitating chronic pain, nausea, seizures including those characteristic of epilepsy, or severe and persistent muscle spasms including those characteristic	*2.5 oz usable; 12 plants* Primary caregivers may not possess an amount of marijuana in excess of 24 marijuana plants and five ounces of usable marijuana for qualifying patients through the Department's registration process.	Rhode Island Department of Health Office of Health Professions Regulation, Room 104 3 Capitol Hill Providence, RI 02908-5097 Phone: 401-222-2828 doh.mmp@health.ri.gov Website: RI Medical Marijuana Program (MMP)

	of MS or Crohn disease, agitation of Alzheimer disease, or any other medical condition or its treatment approved by the state department of health	Allows the creation of compassion centers, which may acquire, possess, cultivate, manufacture, deliver, transfer, transport, supply, or dispense marijuana, or related supplies and educational materials, to registered qualifying patients and their registered primary caregivers.	
Vermont	Cancer, HIV/AIDS, MS, or the treatment of these conditions if the disease or the treatment results in severe, persistent, and intractable symptoms; a disease, medical condition, or its treatment that is chronic, debilitating, and produces ≥1 severe, persistent, intractable symptoms of cachexia or wasting syndrome, severe pain or nausea, or seizures	*2 oz usable; 9 plants (2 mature, 7 immature)* A marijuana plant shall be considered mature when male or female flower buds are readily observed on the plant by unaided visual examination. Until this sexual differentiation has taken place, a marijuana plant will be considered immature.	Marijuana Registry Department of Public Safety 45 State Drive Waterbury, VT 05671-1300 Phone: 802-241-5115 Fax: 802-241-5230 DPS.MJRegistry@vermont.gov Website: VT Marijuana Registry Program
Washington	Cachexia, cancer, HIV/AIDS, epilepsy, glaucoma, intractable pain (defined as pain unrelieved by standard treatment	Patients and designated providers entered into the database will be able to:	Department of Health PO Box 47866 Olympia, WA 98504-7866 Phone: 360-236-4700 Fax: 360-236-4768 MedicalMarijuana@doh.wa.gov

	or medications), chronic renal failure, MS. Crohn disease, hepatitis C with debilitating nausea or intractable pain, or diseases including anorexia that result in nausea, vomiting, wasting, appetite loss, cramping, seizures, muscle spasms, or spasticity when those conditions are unrelieved by standard treatments or medications	Possess six plants and eight ounces of useable marijuana. Be authorized by their healthcare practitioner for up to fifteen plants and sixteen ounces of usable marijuana. Qualifying patients with terminal or debilitating illnesses who, in the judgment of their physicians, may benefit from the medical use of marijuana, shall not be found guilty of a crime under state law for their possession and limited use of marijuana. Qualifying patients in Washington need a valid Medical Marijuana authorization form from their clinicians. Patients/providers holding valid authorizations (not in the database) will have an affirmative defense to criminal prosecution if they possess no	Website: Medical Marijuana (Cannabis)

		more than four plants and six ounces of usable marijuana. They may purchase only in accordance with the laws and rules for non-patients.	
Washington, DC	HIV/AIDS, cancer, glaucoma, conditions characterized by severe and persistent muscle spasms such as MS, patients undergoing chemotherapy or radiotherapy or using azidothymidine or protease inhibitors	*2 oz dried; limits on other forms to be determined* Patients are permitted to purchase up to 2 oz. of dried medical marijuana/mo. or equivalent of 2 oz. dried medical marijuana when sold in any other form.	Health Regulation and Licensing Administration 899 N. Capitol Street, NE 2nd Floor Washington, DC 20002 Phone: 202-442-5955 doh.mmp@dc.gov Website: Medical Marijuana Program

Medical Cannabis's Potency, Action And Absorption

Using medical cannabis has a number of difficult aspects. This may be one of the relatively few areas where a patient may have more experience with use, dose and dosing than the patient's medical clinician, adding to the complexity and the hesitancy for many clinicians.

In a survey of Colorado Family Physicians, only 19% felt that cannabis should be recommended for use, but over 80% believed that the use of cannabis should be taught in a medical school curriculum and should be incorporated into all medical training. A majority also felt that there are

significant health risks, both physical and mental, associated with the use of cannabis.[54]

Potency, Purity and Dose

Potency is generally dependent on THC concentration and is usually expressed as % THC per dry weight of material. In high cannabidiol (CBD) herbs, it is expressed as % CBD per dry weight.

Average THC concentration in high THC cannabis is 1-5%, hashish 5-15%, and hashish oil 20%. The form of marijuana known as sinsemilla is derived from the unpollinated female cannabis plant and is preferred for its high THC content (up to 17% THC). Recreational doses are highly variable and users often titer their own dose. A single intake of smoke from a pipe or joint is called a hit and is approximately 0.20 gram. The lower the potency or THC content the more hits are needed to achieve the desired effects; 1-3 hits of high potency sinsemilla is typically enough to produce the desired effects. In terms of its psychoactive effect, a drop or two of hash oil on a cigarette is equal to a single "marijuana joint".[17-19]

Pharmacodynamics

The major psychoactive compound found in cannabis is Δ-9-tetrahydrocannabinol (Δ9-THC or THC), which is an anandamide agonist. Tetrahydrocannabinol binds both CB1 and CB2 receptors with approximately equal affinity. On the other hand, cannabidiol (CBD) is not psychoactive and has relatively low affinity for both CB1 and CB2 receptors.

Tetrahydrocannabinol has significant affinity for both cannabinoid receptors. When tetrahydrocannabinol and CBD bind to cannabinoid receptors, they often interfere with important endogenous cannabinoid neurotransmitter systems. Tetrahydrocannabinol and CBD are partial agonists of CB1 and CB2. Receptor distribution correlates with brain areas involved in physiological, psychomotor and cognitive effects. Correspondingly, THC produces alterations in motor behavior, perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature. Cannabidiol tends to act on anxiety centers, motor centers, sleep centers and cognition.[17-19]

Pharmacokinetics

Absorption is slower following the oral route of administration with lower, more delayed peak THC levels. Bioavailability is reduced following oral ingestion due to extensive first pass metabolism. Smoking cannabis results in rapid absorption with peak THC plasma concentrations occurring prior to the end of smoking. Concentrations vary depending on the potency of cannabis and the manner in which the drug is smoked, however, peak plasma concentrations of 100-200 ng/mL are routinely encountered. Plasma THC concentrations generally fall below 5 ng/mL less than 3 hours after smoking. Tetrahydrocannabinol is a highly lipid soluble, and plasma and urinary elimination half-lives are best estimated at 3-4 days, where the rate-limiting step is the slow redistribution to plasma of THC sequestered in the tissues. Shorter half-lives are generally reported due to limited collection intervals and less sensitive analytical methods.[55]

Plasma THC concentrations in occasional users rapidly fall below limits of quantitation within 8 to 12 hours. Tetrahydrocannabinol is rapidly and extensively metabolized with very little of it being excreted unchanged from the body. Tetrahydrocannabinol is primarily metabolized to 11-hydroxy-THC which has equipotent psycho-activity. The 11-hydroxy-THC is then rapidly metabolized to the 11-nor-9-carboxy-THC (THC-COOH) which is not psychoactive. The majority of THC is excreted via the feces (~ 65%) with approximately 30% of the THC being eliminated in the urine as conjugated glucuronic acids and free THC hydroxylated metabolites. Less is understood regarding CBD pharmacokinetics in humans.

The pharmacokinetics of cannabinoids delivered by means other than smoking is significantly different. In general, onset of action is slower and the duration of action is longer. The natural cannabinoids cannot necessarily be compared to the synthetic cannabinoids such as dronabinol or Sativex quite simply because the pharmacokinetics of the natural cannabinoids may be effected by the complexity of the mixture.[55]

Interactions with CYP450 Enzymes

The cannabinoids are extensively metabolized by the CYP450 enzymes. Tetrahydrocannabinol and CBD are hydrolyzed via the enzymes CYP2C9, CYP2C19 and CYP3A4 isoenzymes. Cannabidiol is the most potent inhibitor of the CYP450 system with significant activity by THC.[56]

Cannabis Delivery Systems

There are several different routes for delivery of medical cannabis. These may include those outlined below.

Smoking (combustion)

Smoking may be done using a pipe, a water bong or a rolled joint. This is the traditional delivery method for many, but has significant disadvantages and advantages. A typical cannabis cigarette (joint, doob, doobie, blunt, reefer) contains 0.5 to 1 gram of marijuana/cannabis (weed, herb, ganga, pot, bud, flower).

The disadvantages include 1) significant proportion of cannabinoids are lost in side stream smoke, 2) second-hand cannabis smoke is a concern for others in the immediate vicinity, and 3) smoking cannabis can contribute to lung diseases such as COPD and asthma.

The advantages include 1) rapid effect, occurring within 30 to 60 seconds; and full effect is usually within 10-15 minutes, 2) effect is relatively long, and may last for 2-3 hours, 3) vaporization where a vaporizer device that heats the cannabis without combustion is used (the vapor (*vape*) is high in cannabinoids that can be directly inhaled, and primarily provides the volatile oils of cannabis, 4) based on anecdotal experience and data on asthma patients, vaporization is an efficient delivery system, costs for vaporizers vary but range between $200 to $800, and 5) vaporizer pens can range from $50-$200, and vaporizers can be portable or desktop models.

This delivery method is more efficient than combustion. It is less irritating for the lungs, though there is insufficient evidence to state this with certainty. The effect is rapid and can occur within 30 to 60 seconds. Full effect is usually within 10-15 minutes. Also, a typical bowl can hold 0.1 to 0.5 grams of dried herb

Edibles

The delivery system of edibles may often be best for pediatric patients. However, oral dosing can result in higher serum levels, so a general "rule of thumb" is to titrate the dose beginning with 25% of an edible that contains approximately 1 gram of cannabis and waiting for a minimum of 1 hour before repeating the dose. The dose can slowly be titrated (by increments of 25%) until the desired symptom relief is achieved. Edibles are most useful for neuropathic pain, sleep disorders and seizures.

Edibles are commonly made using either cannabis oil or cannabutter. Cannabis oil is a product of cold distillation while cannabutter is a longer process of heating on low heat. The cannabutter is substituted for oil or butter in common recipes. Cannabis oil and cannabutter can be bought in most dispensaries, but are often made at home from scratch.

Cannabis oil should only be used at temperatures below 280^{o}F. Cannabis edibles may be more likely to be used. Cannabis edibles go through first pass metabolism.

Tinctures

Tinctures are a traditional route for delivery. A tincture is composed of the herb soaked in 95% grain or grape alcohol (ethanol) and consumed as a drink. A (plant) glycerin extract can be used if the patient is an alcoholic or prefers non-alcohol based systems, but generally glycerin extracts are less potent because the components generally have better solubility in alcohol. Higher doses are generally required with glycerin extracts. Some herbalists use a vinegar and glycerin mixture. Content will vary from batch to batch and from year to year, necessitating re-titration for dosing in every batch

Typical dosage is 3-5 drops under the tongue as needed. Usually 3-4 times a day. The tincture can also be added to water; 3-5 drops are added to 6-8 ounces of water. This water can be sipped throughout the day, providing a somewhat more constant dose.

Topical Applications

Cannabis oil can be applied directly to the skin or can be mixed with shea butter or glycerin. There are no available studies to guide dosing. General recommendation is to start with small amounts and titer based on symptom relief.

Cannabis Tea

Dried herb or powdered herb will make a weak tea which may be effective. Titer to determine effective dosing, usually ~ 3-4 cups/day. For children or to get a handle on dosage, use 3-5 drops of tincture in boiled water. This approach can also be used with alcoholic patients or any patient sensitive or averse to alcohol

Dosing of Cannabis for Medical Conditions

While there are various dosing approaches, most commonly, titrating a dose upward until symptom relief has been achieved involves observing guidelines of cannabis administration for varying medical conditions. These are highlighted here.

Amyotrophic Lateral Sclerosis

10mg (by mouth) daily for 2 weeks has been used

Chemotherapy-induced Nausea and Vomiting

Dronobinol 5 mg/m^2 by mouth, 1-3 hours before chemotherapy followed by same dose every 2-4 hours after chemotherapy. Alternatively, 2-3 mg nabilone, by mouth, the night before chemotherapy followed by the same dose 1-3 hours before chemotherapy and every 1-3 hours after chemotherapy. Other cannabinoids include:

- 1-8mg nabilone daily
- 24-50 mg/m^2 of dronabinol daily
- 10 mg/m^2 of dronabinol 4-5 times daily
- 12 mg/m^2 of dronabinol twice daily; or 15 mg of dronabinol twice daily.

Poor appetite (in cancer)

- 2.5 mg THC with or without 1mg CBD daily

Poor appetite (other conditions)

- 2.5 mg dronabinol twice daily for 2 weeks

Chronic Pain

- May be taken orally or by oral spray
- Doses of THC, benzopyranoperidine (BPP), cannabidiol (CBD), nabilone, dronabinol range from 2.5 to 20 mg daily.
- Smoked cannabis: (% THC varies): 3-5 joints daily
- In cancer patients, 5-20 mg THC daily (may be divided doses). Alternatively, 1-2 mg nabilone twice daily
- Mouth sprays: 2.5-120 mg daily, divided doses

Dementia

- 2.5mg dronabinol twice daily

Epilepsy

- 2-300 mg CBD daily

Movement Disorders

- 1-2 mg nabilone daily
- MS: 2.5 mg dronabinol daily, increasing to a maximum dose (10 mg) daily

Glaucoma

- 5 mg THC (sublingual) daily
- 20-30 mg CBD daily

If a patient is purchasing from a cannabis dispensary, it would be prudent to determine that the dispensary is assaying levels of THC and CBD. Patients using cannabis may find it useful to try strains with varying ratios of THC and CBD, depending on the desired result. It should be recommended that they *always* start with the lowest dose possible, titrate slowly to get the desired effects, and, to stay aware of tolerance issues and to maintain the lowest dose possible to achieve the desired results. In addition, if possible, cannabis *vacations* should be encouraged (giving the patient a break from using medical cannabis).

Cannabis Administration and Drug Interactions

Based on known pharmacology, use caution when co-administering the following medications with cannabis:

- Amphetamines
- Sympathomimetics
- Anticholinergics
- Tricyclic antidepressants, SSRIs
- Barbiturates, benzodiazepines, antipsychotics, opioids, antihistamines, muscle relaxants, CNS depressants

Cannabidiol is an allosteric modulator of the μ- and the δ-opioid receptor, but effective at relatively high concentrations of greater than 100 μM. In experimentally induced seizures in rats, the anticonvulsant potency of phenytoin was increased by co-administration of CBD or by the co-administration of phenobarbital + CBD. Additionally, CBD reduced the anticonvulsant activity of chlordiazepoxide, clonazepam, trimethadione and ethosuximide.

Health Risks Associated With Medical Cannabis

A concern about the health risk associated with medical cannabis is the fact that individuals using it are fully or partially self-medicating. Growers have been breeding cannabis to increase either the THC or the CBD content, and some strains approach 33% THC; while in nature the percentage of THC rarely exceeds 15%. There are risks associated with most pharmacological substances. The medical use of cannabis is no different, and clinicians referring patients to a consulting prescriber of cannabis or those prescribing will need to show evidence of educating patients on the benefits and risks of medical cannbis.[17,57-64]

Physical Risks

Cardiovascular effects, as mentioned, must be considered because THC can induce tachycardia. Higher rates of myocardial infarctions have been associated with cannabis use.

Decreased volumes of regions of the hippocampus, amygdala, and cerebellum in adolescent heavy users has been noted.

Use of cannabis during pregnancy is not recommended as fetal exposure can result in impaired fetal growth, and impaired development and behavior disorders have been seen. Cannabis use may significantly affect reproductive health. It can disrupt the menstrual cycle, disrupt sperm motility and viability.

In addition, driving while impaired is a significant issue. In the state of Washington, the pre-legalization rates of detection of THC and metabolites in those arrested while driving impaired was 19.1%. The post-legalization rate was 24.9%. The rates of alcohol and other drug-detection remained stable during the same period.

Mental Health Risks

A number of mental health risks have been associated with cannabis use. Cannabis Use Disorder (CUD) is listed in the DSM-5, noting that CUD may be exacerbated by THC and mitigated by CBD. The DSM-5 working group recommended that revisions combined the prior 'abuse and dependence' criteria into a single substance use disorder, and added cannabis withdrawal symptoms.

Diagnosis of CUD requires the presence of two or more of the following criteria during a 12-month period. *Hazardous use* involves a failure to stop an activity despite clear potential for harm, *i.e.*, driving while under the

influence. Social or interpersonal problems related to use involves continuing to use cannabis in the face of work, personal, family issues related to cannabis use, and avoiding social, family or community activities and contact.

Neglecting major roles to use refers to either work, school, family or social obligations. There may be legal problems as a result of cannabis use. There may also be withdrawal symptoms when cannabis use is stopped for any reason. Symptoms of withdrawal include:

- Insomnia
- Headaches
- Night sweats and sweaty hands
- Anxiety
- Depression
- Mood changes
- Irritability
- Stomach and abdominal pain
- Loss of appetite
- Nausea

Tolerance may develop and involves using larger amounts of cannabis to obtain the same effect. This may be pain reduction, reducing symptoms of depression or anxiety, reduction of muscle spasms or simply escaping and getting high. It could involve using larger amounts or using for a longer period of time. Generally, there are repeated attempts to control or quit use, large amounts of time spent using, physical and/or psychological problems related to use, and activities given up to use cannabis.

Depersonalization-Derealization Disorder

Depersonalization-derealization disorder can be defined as a feeling of being outside the body or a sense that things around an individual are not real (derealization), or both depersonalization/derealization. Symptoms can include a sense or feeling that the individual is an outside observer of personal thoughts, feelings, body or parts of the body. It can be described as *floating in air above oneself*, a robotic feeling or a feeling that control has been lost, particularly control of speech or movements, and a sense of distortion surrounding the body, and legs or arms appear enlarged or shrunken. The head may feel as if it is wrapped in cotton or other materials. There is a sense of emotional or physical numbness, and that memories lack emotion and a lack of belief in memories, as if they belonged to another person.

Derealization involves a sense of being alienated from or unfamiliar with surroundings. This can be described as if the individual was living in a movie. The person has a sense of emotional disconnection from people in his/her family or community. Individuals report feeling as if they were separated by a wall they can see through, but not get through. The environment surrounding affected individuals appear distorted, flat, false, blurry, or colorless. Alternatively, there may be a heightened awareness of surroundings or hypervigilance. There is a sense of distorted time, distance, shapes of objects, or textures of objects.

The causes and risk factors for depersonalization-derealization disorder can involve drug use, including cannabis, trauma, stress, other mental disorders, seizure disorders, and depression and anxiety. Long-term use of cannabis

may increase the risk of depression, anxiety, increased suicidal ideation and risk of suicide attempts. This association appears to be particularly related to development. Young adults and adolescents appear to be at highest risk. In this population, according to a recent prospective cohort study, frequent or heavy cannabis use was predictive of later depression and anxiety.

Lower doses of THC are associated with an anxiolytic effect, but higher doses appear to produce anxiety. There is a cause-effect problem with many of the studies; individuals with anxiety and depression tend to use cannabis to self-medicate anxiety and depression, and the relationship remains obscured by multiple factors.

Cognitive Effects

Heavy and long-term use of cannabis has been shown to impair cognitive functions. These effects can be widespread and range from motor coordination to higher level executive functions. A more recent extensive review of the literature concluded that cannabis use *impairs learning, memory, attention, and working memory*. Researchers have also suggested that adolescents may be particularly vulnerable to the adverse effects of cannabis use because of critical neurodevelopment characterized by marked synaptic pruning and increased myelination found to occur in this age group. Exogenous cannabinoids during adolescence is believed to possibly disrupt normal brain development.

Researchers have also stated that there is growing preclinical and clinical evidence that cannabis can decrease individual motivation and this decreased motivation may be associated with disruptions in reward-based

learning. Evidence is also growing that heavy cannabis use can increase the risk for psychosis. Efforts to normalize cannabis use are being driven my multiple interests; however, there remains a concern about the unintended consequences of cannabis use. It is important to clarify which aspects of cannabis exposure (*i.e.*, age at initiation and the amounts and potency of cannabis used) lead to the highest risk of a cannabis use disorder as well as adverse outcomes of use, such as cognitive deficits, reduced motivation, or psychosis.

Many questions remain about the long-term benefits versus risks of cannabis use and policies surrounding its legalization. So many questions remain unanswered, and it's important for clinicians to be aware of the patterns and toxic effects of cannabis use. Of special concern, clinicians will need to be informed and educated about the expanding pool of pregnant cannabis users and the affect upon the developing fetus, as well as the growing public concern of secondhand cannabis smoke.

The Future Direction Of Medicinal Cannabis

In 2016, the cannabis industry raised over 1 billion dollars in funding from investors. It is a rapidly growing industry ranging from a 21st century "cottage industry" carried out in an unknown number of both small and larger garden plots to large, legal cannabis farms. There are various state rules and regulations that can be confusing and even intimidating. There also exists significant bias toward the use of cannabis — the 1936 movie "Reefer Madness" may seem comical to many, but the underlying bias of this entertaining film is apparent.

Every drug and herb can be misused. Many of the differences lie in the addictive potentials and the effects on behavior. In this regard, cannabis is no different. However, the increasing amounts of THC in hybrid plants is a major concern because use of these hybrid plants essentially negates millennia of understanding of the effects of the plant. While an extreme measure, the FDA report of deaths by drug classification from the time period covering 1/1/97 to 6/30/05 produced the following data:[69] deaths where the primary suspect of causing death was cannabis were zero, and then deaths where the secondary suspect of causing death (contributing to death) were 279. In the same period, the following drug classes were considered to be the primary suspect in many deaths.

- Anti-Emetics: including Compazine, reglan, marinol (a cannabinoid was linked to 5 deaths), and Zofran and others - 196
- Anti-spasmotics: including baclofen, zanaflex - 118
- Antipsychotics: including Haldol, lithium, Neurontin - 1593
- Other drugs, including Ritalin, Wellbutrin, Adderall, Viagra, Vioxx - 8101

In the same period, the following drug classes were considered to be the secondary suspect for death:

- Anti-Emetics: including Compazine, reglan, marinol (a cannabinoid was linked to 5 deaths), Zofran and others - 429
- Anti-spasmotics: including baclofen, zanaflex - 56
- Anti-psychotics: including Haldol, lithium, Neurontin - 702
- Other drugs: including Ritalin, Wellbutrin, Adderall, Viagra, Vioxx - 492

The total number of deaths from this partial list of FDA-approved drugs was 11,687. The percentage of deaths due to marijuana and cannabinoids (including marinol) was 2.43%. This is not an acceptable number by any means, but it does rather put the problem in better perspective. The fact remains that until more and better research on cannabis has been performed, what remains is questions on safety, efficacy and more practical matters of dosing.

Very recently, the National Academies of Sciences, Engineering, and Medicine pre-released a 440-page report summarizing the implications of some 10,000 cannabis-related studies or, pending further study and funding, the lack thereof. The title of this report is: *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research.* While pending release, the text emphasizes that significant changes have taken place in the policy landscape surrounding cannabis legalization, production, and use. During the past 20 years, 25 states and the District of Columbia have legalized cannabis and/or cannabidiol (a component of cannabis) for medical conditions or retail sales at the state level and 4 states have legalized both the medical and recreational use of cannabis. These landmark changes in policy have impacted cannabis use patterns and perceived levels of risk.

However, despite this changing landscape, evidence regarding the short- and long-term health effects of cannabis use remains elusive. While a myriad of studies has examined cannabis use in all its various forms, often these research conclusions are not appropriately synthesized, translated for, or communicated to policy makers, health clinicians, state health officials, or

other stakeholders who have been charged with influencing and enacting policies, procedures, and laws related to cannabis use. Unlike other controlled substances such as alcohol or tobacco, no accepted standards for safe use or appropriate dose are available to help guide individuals as they make choices regarding the issues of it, such as when, where, and how to use cannabis safely, and (in regard to therapeutic use) effectively.

Shifting public sentiment, conflicting and impeded scientific research, and legislative battles have fueled the debate about what, if any, harms or benefits can be attributed to the use of cannabis or its derivatives, and this lack of aggregated knowledge has broad public health implications. The Health Effects of Cannabis and Cannabinoids[70] provides a comprehensive review of scientific evidence related to the health effects and potential therapeutic benefits of cannabis. This report provides a research agenda, outlining gaps in current knowledge and opportunities for providing additional insight into these issues that summarizes and prioritizes pressing research needs.

Previews of the report indicated that it was based on over 10,000 pre-clinical and clinical studies. It concluded that cannabis can provide significant therapeutic relief for chronic pain, for pain related to spasticity in multiple sclerosis and nausea related to chemotherapy. In addition, researchers found that "*The substantial layers of bureaucracy that emerge from cannabis' Schedule I categorization is reported to have discouraged a number of cannabis researchers from applying for grant funding or pursing additional research efforts ... Given the many gaps in the research of the health effects of cannabis and cannabinoids, there is need to address these*

regulatory barriers so that researchers will be better able to address key public health questions about the therapeutic and adverse effects of cannabis and cannabinoid use."[70] In addition, researchers suggested there was a pressing need for more research and recommended a number of solutions to the problem of funding and getter higher quality marijuana than the U.S. government currently provides.

While in many states researchers could, in theory, go to the local dispensary to get their samples, that hardly is an approach many researchers would support. It can also be difficult to get healthy volunteers even in those states where medical marijuana is legal due to fears of legal repercussions. Medical marijuana users, though protected to some extent by local laws, also have a number of hesitations regarding working with researchers. To a large extent, this is due to perceived bias, which may be supported by studies reflecting physician bias. Physicians and other health professionals working with medical marijuana need more data. When it appears easier to get information from popular websites titled "Green Bloom Cannabinoid Dosing Guide" or "Cure Your Own Cancer.org" or "unitedpatientsgroup.com" the current situation surrounding cannabis use does not benefit either patients or the medical community.

Summary

Since passage of The Controlled Substances Act of 1970, all forms of cannabis, including hemp, were, and today are, classified as a Schedule I drug, making it illegal to grow or use cannabis in the United States under federal law. Currently, however, the District of Columbia and 28 states have legalized medical cannabis in some form. This creates tension between

federal and state law since cannabis use that is legal under a state's law is still illegal under federal law. In the states that have legalized cannabis, the legal use is not unfettered. There are limitations for prescribing cannabis and its personal use. The limits for personal use, the responsibilities of physicians and the diseases and conditions covered by state law varies from state to state, as do the rules for positive defense if an individual is arrested under that state's laws.

There are medicinal benefits from cannabis use but there are also risks. For this reason, patients being considered for medical cannabis should have a current source of primary care, a Primary Care Provider (PCP) that they see regularly. The patient should be seen regularly for the serious illness or symptoms for which medical cannabis is used, either by the PCP or by a specialist, chiropractor, or other health clinician of the patient's choice. The fact remains that until more and better research on cannabis has been performed, what remains is questions on safety, efficacy and more practical matters of dosing.

References

1. Booth, M. (2015). Cannabis: a history. Macmillan.
2. Fonseca, B. M., et al. (2013). Endogenous cannabinoids revisited: a biochemistry perspective. Prostaglandins & other lipid mediators;13-30.
3. Wiley JL, Marusich JA, Huffman JW. (2014). Moving around the molecule: relationship between chemical structure and in vivo activity of synthetic cannabinoids. *Life Sci.*97(1):55-63

4. Skaper SD, Facci L, Giusti P. (2013). Glia and mast cells as targets for palmitoylethanolamide, an anti-inflammatory and neuroprotective lipid mediator. *Mol Neurobiol*. 48(2):340-52.
5. Pertwee RG. (2015). Endocannabinoids and Their Pharmacological Actions. *Handbook of Exp Pharmacol*;231:1-37.
6. Grabner GF, Zimmermann R, Schicho R, Taschler U. (2017). Monoglyceride lipase as a drug target: At the crossroads of arachidonic acid metabolism and endocannabinoid signaling. *Pharmacol Ther*.
7. Maccarrone M, et al (2015). Endocannabinoid signaling at the periphery: 50 years after THC. *Trends Pharmacol Sci;*36(5):277-96.
8. Rohleder C, Müller JK, Lange B, Leweke FM. (2016). Cannabidiol as a Potential New Type of an Antipsychotic. A Critical Review of the Evidence. *Front Pharmacol*;7:422.
9. Volkow, N., et al. (2017). Don't Worry, Be Happy: Endocannabinoids and Cannabis at the Intersection of Stress and Reward. *Annual Review of Pharmacology and Toxicology*;285-308.
10. Lutz, Beat, et al. (2015). The endocannabinoid system in guarding against fear, anxiety and stress. Nature Reviews Neuroscience;705-718.
11. Cheang, W.S., et al. (2016). PPARδ Is Required for Exercise to Attenuate Endoplasmic Reticulum Stress and Endothelial Dysfunction in Diabetic Mice. *Diabetes.*
12. Cristino, Luigia, Thorsten Becker, and Vincenzo Marzo. (2014). Endocannabinoids and energy homeostasis: an update. *Biofactors*;389-397.
13. Prospéro-García, Oscar, et al. "Endocannabinoids and sleep." Neuroscience & Biobehavioral Reviews 71 (2016): 671-679.
14. Whiting PF, et al. (2015). Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015;313(24):2456-2473.
15. Bloomfield MA, Ashok AH, Volkow ND, Howes OD., The effects of Δ9tetrahydrocannabinol on the dopamine system. Nature. 2016 Nov 17;539(7629):369-377.
16. Englund A, Freeman TP, Murray RM, McGuire P., Can we make cannabis safer? Lancet Psychiatry. 2017 Mar 1. pii: S2215-0366(17)30075-5.
17. World Health Organization (2016). The Health and Social Effects of Nonmedical Cannabis Use. Retrieved online at http://www.who.int/substance_abuse/publications/msbcannabis.pdf.
18. McPartland JM, Duncan M, Di Marzo V, Pertwee RG. (2015). Are cannabidiol and Δ(9) -tetrahydrocannabivarin negative modulators of the endocannabinoid system? A systematic review. Br J Pharmacol;172(3):737-53.

19. National Institute of Drug Abuse (2017). Is marijuana addictive. *NIH*. Retrieved online at https://www.drugabuse.gov/publications/research-reports/marijuana/marijuana-addictive.
20. Johnson L, et al (2014). Monitoring the future national survey results on drug use: 1975– 2013: overview. Key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan; 2014.
21. Porter BE, Jacobson C. (2013). Report of a parent survey of cannabidiol enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy Behav;29(3):574–7.
22. Gedde M, Maa E. (2013). Whole cannabis extract of high concentration cannabidiol may calm seizures in highly refractory pediatric epilepsies. American Epilepsy Society, 67th annual meeting.
23. Cilio, Maria Roberta, Elizabeth A. Thiele, and Orrin Devinsky. (2014). The case for assessing cannabidiol in epilepsy. *Epilepsia* 55.6: 787-790.
24. Porter BE, Jacobson C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav*;29:574–577.
25. Hussain, Shaun A., et al. (2015). Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: a potential role for infantile spasms and Lennox–Gastaut syndrome. *Epilepsy & Behavior* 47: 138-141.
26. Devinsky, Orrin, et al. (2016). Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. *The Lancet Neurology* 15.3: 270-278. https://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm
27. Devinsky, O. et al (2014). Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*; 55(6):791-802.
28. Jensen, Bjorn, et al. Medical marijuana and chronic pain: a review of basic science and clinical evidence. *Current pain and headache reports*.
29. Moffitt TE, Meier MH, Caspi A, Poulton R. (2013). Reply to Rogeberg and Daly: no evidence that socioeconomic status or personality differences confound the association between cannabis use and IQ decline. *Proc Nat Acad Sci USA*;110.11:E980-982.
30. Rogeberg O. Reply to Moffitt et al. (2013). Causal inference from observational data remains difficult. *Proc Nat Acad Sci USA*;110.11:E983.
31. Lynch, M. E., and Mark A. Ware. (2015). Cannabinoids for the treatment of chronic non-cancer pain: an updated systematic review of randomized controlled trials. *Journal of neuroimmune pharmacology*; 293-301.

32. Kluger, Benzi, et al. (2015). The therapeutic potential of cannabinoids for movement disorders. *Movement Disorders*; 313-327.
33. Cilio, Maria Roberta, Elizabeth A. Thiele, and Orrin Devinsky (2014). The case for assessing cannabidiol in epilepsy. *Epilepsia;*787-790.
34. Wright, Stephen, et al. (2014). Summary of evidence-based guideline: complementary and alternative medicine in multiple sclerosis: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*;1484-1486.
35. Cao, Chuanhai, et al. (2014). The potential therapeutic effects of THC on Alzheimer's disease. *Journal of Alzheimer's Disease*;973-984.
36. Shelef, Assaf, et al. (2016). Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: an-open label, add-on, pilot study. Journal of Alzheimer's;15-19.
37. Giacoppo, S and Mazzon, E (2016). Can cannabinoids be a potential therapeutic tool in amyotrophic lateral sclerosis. *Neural Regen Res*. 2016 Dec;11(12):1896-1899.
38. Koppel, B. et al. (2014). Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*; vol. 82 no. 17, 1556-1563.
39. Lutge EE, Gray A, Siegfried N. (2013). The medical use of cannabis for reducing morbidity and mortality in patients with HIV/AIDS. *Cochrane Database Syst Rev*; 4:CD005175.
40. Waissengrin, Barliz, et al. (2015). Patterns of use of medical cannabis among Israeli cancer patients: a single institution experience. *Journal of pain and symptom management*;223-230.
41. Bachhuber, Marcus A., et al. (2014). Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA internal medicine*;1668-1673.
42. Naftali T., et al. (2013). Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol*;1276–80.
43. Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. (2014). Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. *Inflamm Bowel Dis*;472–80.
44. Sun, Xiaoshen, et al. (2015). Focus: Addiction: Marijuana for Glaucoma: A Recipe for Disaster or Treatment?. *The Yale journal of biology and medicine*;265.
45. Bossong, M.G., Jansma, J.M., Bhattacharyya, S., Ramsey, N.F. (2014). Role of the endocannabinoid system in brain functions relevant for schizophrenia: an overview of human challenge studies with cannabis

or Δ9-tetrahydrocannabinol. *Prog. Neuropsychopharmacol. Biol. Psychiatry*;53–69.
46. Di Forti, et al (2014). Daily use, especially of high-potency cannabis, drives the earlier onset of psychosis in cannabis users. *Schizophr. Bull*;1–9.
47. Iseger, Tabitha A., and Matthijs G. Bossong. (2015). A systematic review of the antipsychotic properties of cannabidiol in humans. *Schizophrenia research*;153-161.
48. Greer, G. R., Grob, C. S., & Halberstadt, A. L. (2014). PTSD symptom reports of patients evaluated for the New Mexico Medical Cannabis Program. *Journal of Psychoactive Drugs*;73–77.
49. Roitman, P., Mechoulam, R., Cooper-Kazaz, R., & Shalev, A. (2014). Preliminary, open-label, pilot study of add-on oral Δ9-tetrahydrocannabinol in chronic posttraumatic stress disorder. *Clinical Drug Investigation*;587–591.
50. Lev-Ran, S., et al. (2014). The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychological medicine*;797-810.
51. Danielsson, Anna-Karin, et al. (2016). Cannabis use, depression and anxiety: A 3-year prospective population-based study. *Journal of affective disorders*;103-108.
52. Feingold, Daniel, et al. (2016). The association between cannabis use and anxiety disorders: Results from a population-based representative sample. *European Neuropsychopharmacology*; 493-505.
53. Kedzior, Karina Karolina, and Lisa Tabata Laeber (2014). A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population-a meta-analysis of 31 studies. *BMC psychiatry*;136.
54. Kondrad E, Reid A. (2013). Colorado family physicians' attitudes toward medical marijuana. J Am Board Fam Med;26:52-60.
55. Allsop, David J., Richard Kevin, and Jonathon Arnold (2016). Cannabis: The Pharmacokinetics and Pharmacodynamics of Recreational and Medicinal Cannabis. *The SAGE Handbook of Drug & Alcohol Studies: Biological Approaches*;194.
56. Zendulka, Ondrej, et al. (2016). Cannabinoids and cytochrome P450 Interactions. *Current drug metabolism*;206-226.
57. Volkow ND, Baler ND, Compton WM, Weiss SR. (2014). Adverse health effects of marijuana use. *N Engl J Med*;370:2219-2227.
58. Thomas G, Kloner RA, Rezkalla S. (2014). Adverse cardiovascular, cerebrovascular, and peripheral vascular effects of marijuana inhalation: what cardiologists need to know. *Am J Cardio*l;113:187-190.

59. Eisenberg, Michael L. (2015). Invited commentary: the association between marijuana use and male reproductive health. *American journal of epidemiology;*482-484.
60. Edelman, Natalie L., et al. (2015). Targeting sexual health services in primary care: A systematic review of the psychosocial correlates of adverse sexual health outcomes reported in probability surveys of women of reproductive age. *Preventive medicine*;345-356.
61. Huestis, Marilyn A. (2015). Cannabis-impaired driving: a public health and safety concern;1223-1225.
62. Couper, Fiona J., and Brianna L. Peterson. (2014). The prevalence of marijuana in suspected impaired driving cases in Washington state. *Journal of analytical toxicology*;569-574.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3767415/
63. Niesink RJ, van Laar MW. (2013). Does cannabidiol protect against adverse psychological effects of THC? *Front Psychiatry*;130.
64. Hadland SE, Harris SK. (2014). Youth marijuana use: state of the science for the practicing clinician. *Curr Opin Pediatr;*420-42
65. Beach, D.F. (2015). The Legal Implications of Medical Marijuana for Licensed Health Care Providers. Medical Liability and Health Care Law. Retrieved online at https://www.google.com/#q=Any+physician+who+%09recommends+the+use+of+marijuana+by+a+patient+should+have+arrived+at+%09that+decision+in+accordance+with+accepted+standards+of+medical+%09responsibility&*.
66. Richmond, MK, et al. (2015). Frequency and Risk of Marijuana Use among Substance-Using Health Care Patients in Colorado with and without Access to State Legalized Medical Marijuana. J Psychoactive Drugs. 2015 Jan-Mar;47(1):1-9.
67. National Conference of State Legislatures (2017). State Medical Marijuana Laws. Retrieved online at http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx#3.
68. Mead, A. (2016). The legal status of cannabis (marijuana) and cannabidiol (CBD) under U.S. law. Epilepsy Behav. Retrieved online at http://www.epilepsybehavior.com/article/S1525-5050(16)30585-6/fulltext.
69. Oregon.gov (nd). Deaths from Marijuana v. 17 FDA-Approved Drugs (Jan. 1, 1997 to June 30, 2005). Retrieved online at https://www.oregon.gov/Pharmacy/Imports/Marijuana/Public/DeathsFromMarijuanaV17FDAdrugs.pdf.
70. National Academies of Sciences, Engineering, and Medicine (2017). The Health Effects of Cannabis and Cannabinoids: The Current State of

Evidence and Recommendations for Research. The National Academy of Sciences. Washington, D.C.