Marijuana (Cannabis) Part 2:

Metabolic and Medical Aspects

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Part 1 presented the legal aspects of Marijuana. This Part 2 presents an overview of the metabolic and medical aspects marijuana's Tetrahydrocannabinol (THC) and Cannabidiol (CBD).

THE *CANNABIS* PLANT

Marijuana and cannabis are interchangeable terms for the whole plant and flower from which THC and CBD are derived, among many other components. Marijuana is a botanical folk medicine containing 483 known compounds. About 140 are biologically active components - called cannabinoids. THC and CBD are the two best studied active components. There are three different types of *Cannabis* plants: *Cannabis Sativa, Cannabis Indica,* and *Cannabis Ruderalis*. There are male and female *Cannabis* plants. Cannabis plants may also be hermaphroditic. Marijuana or herbal cannabis consists of the dried flowers and subtending leaves and stems of the female *Cannabis* plant. Slang names include: Weed, Pot, Grass, Herb, and Boom, among others. THC is the psychoactive compound used for medical or recreational

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purposes. Marijuana is the most commonly used illegal drug both in the United States and in the world.

TYPES OF MARIJUANA PLANTS

This segment is obtained from an Online article, and was approved for publication in the JOSMA with pictures, by Robert Bergman who for over 20 years had been growing marijuana in and around Amsterdam.[1]

Cannabis Sativa (left) is the most commonly grown of the marijuana strains, mostly in Mexico, Columbia, India, Thailand, Nigeria. It reaches a height of about 19 feet. It gets a smoker "high" and energetic feeling instead of "stoned"; it has more THC than CBD.

Cannabis Indica (right) can reach a height of about 10 feet. It flowers rather quickly. It grows well in countries like Lebanon, Morocco, Nepal, and Afghanistan. Indica buds contain a high quantity of resin sometimes with more CBD than THC. It is often used to make hashish, and gets a more relaxed "stoned" sensation than with sativa.

Cannabis Ruderalis (left) plants reach a maximum height of about two feet with dense branches and leaves; it is a bushy plant. It is not as psychoactive as the indica or sativa strains and is less often smoked. It is generally grown up north since its flowering cycle begins quite early.

Nowadays, most marijuana strains on the market are *hybrids*, falling into one of the above categories and are aimed at cultivating all the positive qualities of multiple strains to materialize into one useful plant.

Male marijuana plant have small flower stalks, called "racemes", at the base of its flowers. When the flowers open, pollen is released to stick to the female plant pistils in order to carry out the fertilization process.

Females marijuana plants have pistils and calices. Each calyx has an ovule on which the male pollen sticks. When pollen gets stuck to the pistil, it is pushed into the calyx and carries out the fertilization process and producing seeds with genes from the parents.

HEMP VERSUS MARIJUANA PLANTS

Both hemp and marijuana plants are part of the Cannabis family, but they serve different purposes.[2] Hemp plants contain most often <0.3% THC. They are used in a variety of applications, including automobiles, body care, skin products, clothing, construction, food, plastic, and accessories. Hemp plants requires minimal care and are adaptable to grow in most climates.

Marijuana plants contain from 5% to 35% THC. They are widely known and used for medicinal or recreational purposes. They are grown in carefully controlled atmospheric conditions.

MEDICAL MARIJUANA

Medical marijuana refers to treating symptoms of illness and other conditions with the whole, unprocessed marijuana plant or its basic extracts. Marijuana is available as:

- Herbal cannabis products, called *phytocannabinoids*, such as "weed", oils, and edibles. Herbal cannabis is a green, brown, or gray mix of dried, crumbled parts from the *Cannabis* plant. It can be rolled up and smoked like a cigarette or cigar or smoked in a pipe.
- *Synthetic cannabinoids*, for example dronabinol (*synthetic delta-9 THC*), include sublingual sprays, tinctures, topical salves, suppositories, and snacks, such as cookies, wafers and potato chips.

As noted in Part 1 of this article, the FDA has *not* recognized or approved the marijuana plant as medicine, but it has approved the following marijuana drugs:

1. **Epidiolex®**, a cannabidiol (CBD) product for controlling seizures in people with difficult-to-treat childhood-onset epilepsy. The U.S. Drug Enforcement Administration (DEA) has assigned Epidiolex a Schedule V classification.
2. **Cesamet** (nabilone), **Marinol** (dronabinol capsules) and **Syndros** (dronabinol oral solution) are orally active synthetic cannabinoids containing THC, to treat nausea and boost appetite caused by chemotherapy and increase appetite in patients with extreme weight loss caused by AIDS.

PRECURSORS OF CBD AND THC

Cannabigerolic acid is the natural compound in cannabis plants. It is transformed by the enzyme cannabidiolic acid synthase to cannabidiolic acid. The latter is then converted into cannabidiol (CBD) through the process of decarboxylation. This process is accomplished usually through heat application, either with cooking or smoking the plant. Long exposure to sunlight and a warm environment can also decarboxylate the acid precursor in the form of water vapor and carbon dioxide to form CBD. Of the 483 cannabinoid compounds unique to cannabis, the most abundant cannabinoids found in industrial hemp are the precursor cannabidiolic acid and its byproduct CBD.

The tetrahydrocannabinol acid is the precursor of active THC. Some cannabis plants may have little or no active THC, until they are heated. Smoking cannabis yields approximately 30% conversion of THC acid precursor to active THC. Other methods such as cooking or heated solvent extractions will yield 70-90% conversion to THC.

HUMAN ENDOCANNABINOID SYSTEM

The human body has its own endocannabinoid system with many of the effects from THC and CBD occurring via agonism or antagonism at two primary receptors, CB1 (Cannabinoid receptor type 1) and CB2 (Cannabinoid receptor type 2). CB1 is the most densely populated receptor in the brain and responsible for many of the mood, motor, and cognitive effects of cannabis. CB2 receptors are mostly expressed on T cells of the immune system, on macrophages and B cells, and in hematopoietic cells.

CBD binds to CB2. It does not bind to cannabinoid receptors in the brain and hence is less psychoactive than THC.

CBD PHARMACODYNAMICS AND PHARMACOKINETICS[3]

The route of administration affects the pharmacokinetics of CBD and high intra- and inter-subject variability is common in humans.

CBD can be ingested by mouth, inhaled as smoke or vapor, or applied as an aerosol spray into the cheek. It is available as an oil containing only CBD as the active ingredient, a full-plant CBD-dominant hemp extract oil, capsules, dried cannabis, or as a prescription liquid solution. A large portion of the administered CBD is excreted in stools and urine. The most abundant metabolites are hydroxylated 7-COOH derivatives of CBD that are excreted either intact or as glucuronide conjugates.

CBD interacts with the endocannabinoid system in a way that produces very few unintended side-effects. While CBD is safe for use and consumption, it does pose a few dangerous risks, e.g. inhibition of the cytochrome P450 enzyme system, which contains more than 50 enzymes that process and eliminate toxins.

CBD can inhibit the cytochrome P450 system's ability to metabolize certain drugs, leading to an overall increase in processing times, similar to grapefruit, watercress, St. John's Wort, and goldenseal. This leads to higher levels of certain drugs causing unwanted side effects, and possibly an overdose.

Any drug metabolized by CYP450 enzymes could potentially interact with CBD including: Steroids; HMG CoA reductase inhibitors, Calcium channel blockers, Antihistamines, Prokinetics, HIV antivirals, Immune modulators, Benzodiazepines, Antiarrythmics, Antibiotics, Anesthetics, Antipsychotics, Antidepressants, Anti-epileptics, Beta blockers, PPIs, NSAIDs, Angiotension II blockers, Oral hypoglycemic agents, and Sulfonylureas. Additionally, CBD may affect "prodrugs" that need to be metabolized via the CYP450 system to produce the therapeutic compound. For example, codeine is a prodrug that is metabolized into morphine which provides the effect.

The therapeutic potential of CBD, beside epilepsy, is being investigated for a number of indications including anxiety disorders, substance use disorders, schizophrenia, cancer, pain, inflammatory diseases and others.[4]

The side effects of CBD include somnolence, decreased appetite, diarrhea, fatigue, malaise, weakness, sleeping problems, and others. It does not have intoxicating effects like those caused by THC. It may have an opposing effect on disordered thinking and anxiety produced by THC. CBD has been found to interact with a variety of different biological targets, including cannabinoid receptors and other neurotransmitter receptors.

THC PHARMACODYNAMICS AND PHARMACOKINETICS

Orally ingested THC reaches a peak plasma concentration in approximately 2.5 hours. Its half-life is 20-30 hours. Ingestion of THC undergoes 1st pass metabolism through the liver and is converted to an even more psychoactive 11-hydroxy-THC metabolite. The slow onset of oral cannabis may prompt a patient to ingest more THC, and then 1st pass metabolism in liver

boosts its psychoactive action, producing undesirable side effects. THC undergoes oxidation to the psychoactive metabolite 11-OH-THC by the polymorphic CYP2C9 enzyme.[5] The 11-OH-THC is then oxidized to the inactive, 11-nor–9-carboxy-THC (THC-COOH) acid which appears in the blood, and is excreted in the urine and feces.

Inhaled THC achieves peak plasma concentration within 2 1/2 (two and a half) minutes. It dissipates rapidly over 30 minutes. It has less psychoactive effects than oral ingestion because it largely avoids 1st pass metabolism by the liver. Using inhaled cannabis allows more flexibility and control over the administered dosage. When THC is smoked, far less 11-OH-THC psychoactive metabolite is formed and the magnitude of the effect is less than with 11-OH-THC and THC together.

When THC is injected intravenously, it gradually disappears from the plasma with a half-life of 28 hours in chronic marihuana smokers as compared to 57 hours for nonusers of marihuana.[6] Within 10 minutes after i.v. administration of THC, its psychogenic metabolite, 11-hydroxy-delta(9)THC is present in the plasma of both nonusers and chronic marijuana users. The final inactive THC metabolites are present for more than one week in the urine and feces of nonusers and long-term marihuana smokers.

The cannabinoid receptors, CB1 and CB2, are both coupled to G-proteins. THC and its psychogenic metabolite, 11-hydroxy-delta(9)THC, bind to CB1 receptors which are present in the central nervous system thus affecting the psyche.

The cytochrome P450 enzymes are also involved in the metabolism of THC, as with CBD, by human hepatic microsomes. CYP2C9 and CYP3A4 are the major enzymes involved in the 11-hydroxylation and the 8-(or the 7-) hydroxylation, respectively, of the cannabinoids.[7]

In 1973, Lemberger and co-workers[8] compared the physiologic and psychologic effects of intravenously administered THC and its active metabolite, 11-hydroxy-THC in nine casual marihuana smokers. The peak psychologic “high” was delayed 10-20 min after the i.v. administration of THC (1 mg). In contrast, a marked tachycardia and psychologic “high” occurred within 3-5 min after the i.v. administration of the metabolite, 11-OH-THC (1 mg) to all subjects. The psychologic effects correlated well with plasma levels of unchanged 11-OH-THC.

About 75% of the administered 11-OH-THC dose was excreted, 25% in the urine and 50% in the feces. The researchers suggested that THC is converted to its psychogenic metabolite, 11-OH-THC, which is mostly responsible for the psychologic effects in humans.

THC administration appears to be better for **chronic pain** than acute pain. It does not affect the pharmacokinetics of **opiates**, but seems to be **synergistic** for pain relief.

MARIJUANA TREARTS

Marijuana THC treats pose hidden dangers, as noted in the following cases.[9] Use of high oral dose of marijuana can produce anxiety and panic attacks. Psychotic breaks may also occur mostly after oral ingestion. Blood levels of the psychopharmacologically active 11-OH-THC metabolite can combine its psychotropic effects with those of THC to produce a more robust psychotropic effect in the CNS. Here are some examples:

1. In 2014, a 19-year-old student ate a marijuana-laced cookie and shortly thereafter began rambling incoherently and subsequently jumped to his death from the balcony of a Denver hotel. The Denver coroner listed marijuana intoxication as a significant factor in his death, and reported that he had a blood level of 7.2 ng/ml, (equivalent to 14 ng/ml plasma concentration), a concentration that would be found approximately 2 hours after smoking a 3.55% THC marijuana cigarette.
2. Another case involved a man who developed hallucinations and rambling speech after eating marijuana candy with concomitant ingestion of an unidentified prescription medication. In the midst of an apparent psychotic break, he fatally shot his wife while she was calling 911 for help.
3. In early September, five high school students in the San Francisco area, ages 14-16, became ill after eating brownies that had been laced with marijuana. Three developed nausea and vomiting and two became unconscious and were hospitalized. The brownies were sold to the students by a classmate.

The magnitude of the effect of the combined 11-OH-THC and THC was most likely the cause of the psychotic reactions and loss of consciousness described in the cases reported above.

The package insert for the FDA-approved *synthetic* Δ^9- tetrahydrocannabinol, dronabinol, indicates that during clinical trials, adverse psychotropic effects similar to those reported above, occurred in 3-10% of patients and that the dronabinol is the most probable cause of the dizziness, euphoria, paranoid reaction, somnolence and abnormal thinking reported in the manufacturer's labeling. After marketing, severe overdoses of dronabinol reportedly caused panic reactions in apprehensive patients and other significant CNS symptoms which were not specifically defined.

Dronabinol (synthetic delta-9 THC) is approved for chemotherapy-induced nausea, vomiting and anorexia associated with AIDS wasting. Marijuana is also recommended for weight loss, pain, sleep, depression, and anxiety in cancer patients. It is better for chronic pain than acute pain.

Marijuana has mental and physical effects, such as creating a "high" or "stoned" feeling, a general change in perception, heightened mood, and an increase in appetite. Short-term side effects may include a decrease in short-term memory, dry mouth, impaired motor skills, red eyes, and feelings of paranoia or anxiety. Long-term side effects may include addiction, decreased mental ability in those who started as teenagers, and behavioral problems in children whose mothers used cannabis during pregnancy. Studies have found a strong relation between cannabis use and the risk of psychosis, though the cause-and-effect relationship is debated.

THC overdose deaths are *not* seen because CB-1 receptors are nearly absent in the brainstem. It does not seem to potentiate opioid overdose. Cannabis is probably safer than tobacco, alcohol, and perhaps sugar. Its side effects include diminished cognitive functions, increased heart rate, and variations in blood pressure. Postural hypotension may increase the risk of falls in the elderly. The risk of motor vehicular accidents is doubled under the influence of cannabis. Cannabis may increase risk for chronic bronchitis, and may rarely induce a hyperemesis syndrome.

CANNABINOID HYPEREMESIS SYNDROME[10]

Cannabinoid hyperemesis syndrome (CHS) is a very rare syndrome. It occurs in long-term heavy users of THC-rich cannabis. Symptoms include nausea, vomiting and abdominal

pain. It was first reported in the medical literature by Allen *et al*[11] in 2004. But in 1968, Hill[12] described "psychogenic vomiting" which is often a cannabis related illness, similar to CHS.

CHS is characterized by chronic cannabis abuse that predates the onset of hyperemesis. It exhibits a cyclical pattern occurring every few weeks or months, often for many years. More than 90% of the patient will also have a compulsion to bathe in hot water during the episode, reporting that it alleviates the discomfort. This compulsion to bathe differentiates CHS from other abdominal diagnoses such as stomach flu, gastritis, cholecystitis, and appendicitis where there is no compulsion to bathe in hot water. Patients who present at Emergency Rooms with cyclical hyperemesis should be asked about chronic cannabis use and compulsive bathing in hot water. Medical cannabis patients usually figure out that overuse of THC-rich cannabis is not effective in treating their medical conditions, as tolerance develops if too much THC is used. Tolerance can lead to loss of therapeutic effects.

Abstinence from THC-rich cannabis resolves the cyclical vomiting illness, as confirmed by a negative urine drug screen for cannabinoids. Some CHS sufferers are able to re-introduce THC in very low doses without a return of symptoms, but others find that they can no longer tolerate THC. A return to cannabis abuse heralds a return of the hyperemesis syndrome many weeks or months later.

Cannabis abuse with other cannabis-induced disorder is billable using **F12.188,** a specific ICD-10-CM code, that can be used to indicate a diagnosis for reimbursement purposes.

SUMMARY: BENFICIAL AND ADVERSE EFFECTS OF MARIJUANA

1. Cannabis may help prevent severe forms of epilepsy and may ease nausea caused by chemotherapy.
2. It may help treat chronic pain in some adults, and may improve muscle spasms in adults with multiple sclerosis.
3. Using cannabis as a whole plant, which contains other terpenoids, flavonoids, and cannabinoids, may support the beneficial aspects of THC and may downplay some of the adverse effects.

4. Cannabis impair driving and negatively affects skills needed for safe driving. Driving under the influence of any substance, including cannabis, is dangerous. The risk of MVA is doubled under the influence of cannabis.
5. When smoked, it has many of the same cancer-causing substances as tobacco.
6. If smoked or ingested during pregnancy, it may be linked to lower birth weight in babies. Additionally, chemicals from cannabis, especially THC, can be passed to a baby through a mother's breast milk.
7. Postural hypotension with increased falls risk is a concern in the elderly.
8. Cannabis may significant increase in the risk of heart attack in the hours after cannabis use. It may also lead to greater risk of bronchitis, cough, and phlegm production; symptoms generally improve when cannabis smokers quit.
9. Cannabis may impair learning, memory, attention, decision-making, coordination, emotions, and reaction time. The damage may last even after discontinuing cannabis. It may permanently affect the developing brains of adolescents and young adults. If an adolescent uses cannabis before the age of 16 and for a prolonged period, it can lead to a number of significant health problems. And teen cannabis users are more likely to become addicted to cannabis than people who start using the drug when they are older. Furthermore, it may negatively affect adolescents' and young adults' health and well-being, including their school performance, education level, social lives, and future employment and income.
10. It may be associated with the development of schizophrenia and other psychoses, thoughts of suicide, social anxiety disorder, and worsened symptoms in individuals with bipolar disorder. The risk is highest for the most frequent users.
11. It may lead to cannabis use disorder, dependence, abuse, or other varying levels of hazardous or potentially harmful behavior. Starting cannabis use at a younger age increases the likelihood of developing problem cannabis use.
12. It may lead to becoming dependent on and/or abusing other substances, including alcohol, tobacco, and other illicit drugs.

CONCLUSION

The concluding remarks were obtained from the two articles cited. The positive aspects[13] of legalized medical marijuana include: (1) Wider access for medicinal use; (2) Medical benefits

for patients with cancer, multiple sclerosis, severe epilepsy; (3) Improving quality and safety control system to minimize the risk coming from smoking marijuana, for example, to avoid problems like fentanyl-laced-heroin which translates into less of a burden on the medical system; (4) Dismantling of the black market and loss of business for drug dealers and less money to support organized crime; (5) More effective criminal justice and law enforcement and allowing the police and courts to focus on more violent crimes; (6) Decreasing in gang-related drug violence; and (7) Boosting tax revenue to state and federal government.

The negative aspect[14] of legalized medical marijuana include: (1) As many as a tenth of marijuana users may develop dependence over time; (2) Low to moderate doses of marijuana may distort perception and cause traffic accidents resulting in fatal injuries by impaired drivers; other crimes, such as robbery and rape, can also be caused by the lapse in judgment due to smoking marijuana; (3) Marijuana may potentially introduce users to more serious illegal substances of abuse and possibly a higher risk of prescription drug use; (4) Increase chances of the drug falling into the hands of children; (5) Possible damage to the brain, mental health, lungs and heart; and (6) Possible danger of second-hand smoke.

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