Clinical Pharmacology of Cannabinoids

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Medical marijuana use in the United States has precipitously increased over the last two decades since California first approved medical use in 1996. It is frequently self-prescribed for a variety of indications ranging from chemotherapy-induced nausea and promotion of weight gain to post-traumatic stress disorder and generalized anxiety disorder. The indications and dispensing of medical marijuana are not regulated by the traditional processes that involve rigorous clinical trials and Food and Drug Administration (FDA) approval. State health departments are often tasked with determining what indications are approved. Patients can grow their own if they so wish, buy as much as they want, and use in whatever amount they see fit for that day. Loose marijuana contains no less than 50 distinct phytocannabinoids with unique activities and kinetics in the human body, making it extremely difficult to study each compound in a scientific fashion. Compounded with the fact that marijuana plants can range in the concentration and ratio of each cannabinoid, patients can experience vastly different effects from a similar ingestion of marijuana that make it even more problematic to determine which compound in which dose has what level of effect on the human body. Drug Enforcement Agency (DEA) scheduling has also historically created barriers to research, further compounding the knowledge gap. Patients turn to medical providers for information on medical marijuana; however, the medical education system only recently began discussing marijuana as a therapeutic drug and many physicians may not feel prepared to discuss marijuana [1]. As a result, patients turn to marijuana dispensary staff (colloquially known as "budtenders") for education about the product. Some states do require dispensaries to have a pharmacist on site who may have specialized marijuana education and can provide education, screen for drug interactions, and discuss potential adverse events. As of 2020, at least 33 states approved medical marijuana in some fashion with that number likely to continue to grow as time progresses. Some states

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approved only CBD and regulate how much THC can be present in products in accordance with the 2018 Farm Bill which removed *Cannabis sativa* or "hemp" and other products with <0.3% THC content from the definition of marijuana, thus removing these products from controlled substance scheduling [2]. Unraveling the complexities of medical marijuana use and its potential benefits and risks starts with the endocannabinoid system, pharmacodynamics and pharmacokinetics of different cannabinoids, available dosage forms, adverse events, and drug interactions.

Endocannabinoid System Review [3–7]

Pharmacodynamics

The endocannabinoid (EC) system contains two main cannabinoid (CB) receptors—CB1 and CB2. In addition to these receptors, there are a number of postulated nonreceptor effects the endocannabinoid system is responsible for—ranging from immunomodulation to circulation.

CB receptors make up the majority of G-coupled protein receptors (GPCR) in the human brain. CB1 receptors are predominantly located in the central nervous system (CNS), but may also be found in peripheral organs—including the gastrointestinal tract and heart. CB2 receptors are largely located in the peripheral nervous system and immune system. CB1 receptors are thought to be the major receptor responsible for the psychoactive effects of marijuana.

CB1 receptors are highly concentrated in cognitive and emotional areas of the brain, namely the cerebral cortex and hippocampus. Activation causes downstream effects on acetylcholine, cAMP, GABA, glutamate, norepinephrine, serotonin, and dopamine, with resulting psychoactive effects. ECs also have a role in negative feedback systems. Presynaptic release of neurotransmitters triggers synthesis and release of ECs from postsynaptic cells. These ECs will bind to presynaptic CB receptors and inhibit neurotransmitter release via reduced influx of calcium, hyperpolarization, and decrease in the number of action potentials, and therefore decreasing frequency of neurotransmitter vesicle binding and release. ECs are metabolized by monoacylglycerol lipases (MAGL) and fatty acid amide hydrolase (FAAH) to inactive compounds. Development of MAGL and FAAH inhibitors (which would theoretically increase the half-life and clinical activity of ECs and reduce the production of inflammatory mediators) is ongoing (Fig. 2.1).

There are very few receptors present in the brainstem which correlates with marijuana's lack of cardiopulmonary toxicity, even at extreme doses [3]. Rat models have shown cannabinoids can inhibit the activation of serotonin subtype 3 receptors (the same receptors acted on by ondansetron), which fits with the antiemetic activity seen with cannabinoids. CB1 is activated by a number of cannabinoids, most notably delta-9-tetrahydrocannabinol (THC).

CB2 receptors are largely located on immune and other noncentral nervous system cells, but are also present in the central nervous system. CB2 activation does not lead to psychoactive effects, rather, it is thought that CB2 receptors are responsible

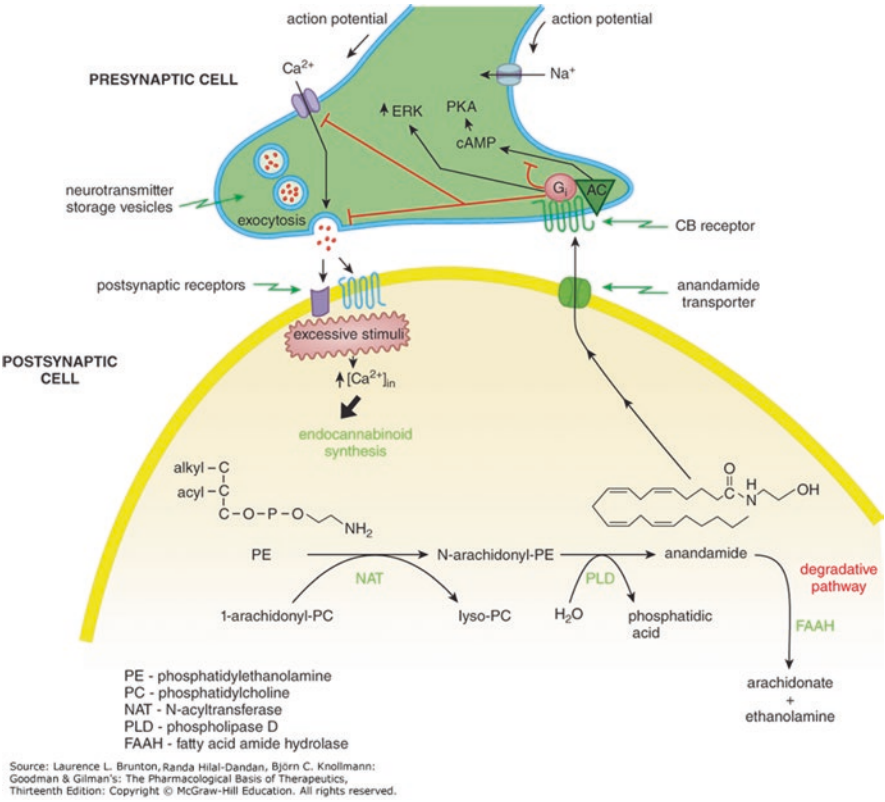


Fig. 2.1 Overview of cannabinoid neurotransmission in the central nervous system. Used with permission [8]

for immunomodulation, anti-inflammatory effects, and antineoplastic properties [5]. Development of pure CB2 modulators for immunomodulation has been attempted in the past; however, none have been successful as they have failed to eliminate CB1 activity and thus retain psychoactive properties. Cannabinoids can have various effects at CB2 receptors, including agonist and antagonist activities [3–7].

Cannabinoid Subtypes

There are three types of cannabinoids—endocannabinoids (cannabinoids our body makes), phytocannabinoids (exogenous cannabinoids found in plants), and synthetic cannabinoids (human-designed cannabinoids, generally only used recreationally).

Endocannabinoids (ECs)

Anandamide and 2-arachidonoylglycerol are the two most common ECs. Anandamide may have partial CB1 agonist activity, antagonist activity, and allosteric modulation depending on the concentration present. It has a lower affinity for the CB1 receptor than THC and 2-arachidonoylglycerol (which is a full agonist at CB

receptors) [6, 9]. In addition to postsynaptic effects which modulate a variety of neurotransmitter releases, ECs also have negative feedback activity and bind to presynaptic neurons (see above section on the EC system for more information). ECs have a wide variety of activities in the body including effects on inflammation, pain, and the immune system.

Phytocannabinoids [10, 11]

THC is one of the most predominant phytocannabinoids present in marijuana. It has balanced CB1 and CB2 activity; however, it is responsible for most of the psychoactive effects that occur after consumption. It is available in two FDA-approved products, both of which are synthetic and do not rely on growing cannabis. Dronabinol (Marinol®) contains the active enantiomer of THC, whereas nabilone (Cesamet®) mimics the actions of THC in the body, but is structurally different.

Cannabidiol (CBD) is a phytocannabinoid with unique pharmacodynamics, as it shows little to no affinity to the CB1 or CB2 receptors. It displays antiemetic, antiepileptic, and anti-inflammatory effects through other mechanisms which are not fully known. It is available in an FDA-approved formulation (brand name Epidiolex®) for Lennox-Gastaut syndrome and Dravet syndrome [12]. It is commonly used for sleep and pain when purchased from medical dispensaries. CBD will be discussed in more detail in Chap. 3.

While not available in the United States, nabiximols (Sativex®) is an oromucosal spray made up of cannabis extracts. The primary components are equal ratios of THC and CBD; other cannabinoids are present in minor concentrations. It is approved for muscle spasticity related to multiple sclerosis in several countries in Europe and Asia. At the time of writing, clinical trials for United States approval are ongoing, and it is not FDA approved for use [13].

Patients may use the term "medical marijuana" to refer to high CBD content products with low THC or think that "medical marijuana" has little to no psychoactive properties. Some states, such as Indiana, have only approved CBD products and require that THC concentrations are below a certain threshold (0.3%) in accordance with the 2018 Farm Bill [2]; however, many states do not regulate cannabinoid content. It is important to clarify with patients if they are using predominantly CBD or THC products, what their usual product ratio is, what preparation is being used (concentrates, loose flower, dabs, etc.), and how they are administering (i.e., vaping, dabbing, smoking, oral, topical, etc.). It can be helpful to talk through information they receive from "budtenders" (people working at the dispensary who commonly make recommendations on which specific product/strain to use for specific indications—a largely unproven and unvalidated recommendation) to address potentially incorrect information provided.

Synthetic Cannabinoids [14]

Synthetic cannabinoids are generally used only recreationally. They are designed to have very high CB1 affinity [5]. After being synthesized in laboratories, they are usually sprayed onto plants and smoked. Consumer packaging often will state "not for human consumption" and will sometimes be marketed as potpourri to avoid

legal consequences. There are many different molecules in this class and many different slang names, including "K2," "Spice," and "Black Mamba." [14] Just like other designer drugs, when a certain chemical compound in these products becomes illegal, manufacturers will alert the molecule very slightly to continue to sell legally. Patients using these drugs should be advised that they are even less regulated than medical marijuana, can have a variety of effects on users, and may have many negative medical and psychiatric effects. They should not be used for any medical purpose. Patients presenting with acute intoxication of these substances may present as agitated and delirious or obtunded and comatose. Reports of seizures, cerebral ischemia, myocardial infarction, acute kidney injury, and psychosis have all been reported in the literature. Mental status can vary widely during the course of their intoxication—some patients going from comatose to severely agitated within minutes.

Tolerance to Exogenous Cannabinoids [9, 15–18]

Tolerance to phytocannabinoids develops via downregulation of cannabinoid receptors over weeks to months of persistent use. Animal studies have showed that exposure to THC for 21 days leads to reduced CB receptor binding (i.e., desensitization) [9]. Reduction in CB receptor density and downstream coupling of GPCRs has also been observed in rodents with frequent exposure [15, 16]. Depending on the patient's desired effects, tolerance may lead to increased use as well as other adverse events, such as cannabinoid hyperemesis syndrome (discussed in Chap. 5.2). More potent CB agonists, including synthetic cannabinoids, have been shown to cause greater desensitization and receptor downregulation. Reversing tolerance to cannabinoids is variable but is generally on the order of weeks. A human study comparing chronic users (at least 2 years of regular use) with nonusers using radioactively labeled CB ligands showed 15% less binding of CB receptors in chronic users (due to receptor downregulation). Within chronic users, those with less binding reported more withdrawal symptoms. At both two and 28 days of observed abstinence, no difference in CB binding was detectable between chronic users and nonusers [17]. An earlier study by Ceccarini et al. showed 10–15% reduction in CB1 receptor binding after 4 days of abstinence in chronic users (using for an average of 10 years) when compared to nonusers. Together, these studies show CB receptor downregulation begins to reverse quickly, within days of cessation, and at 4 weeks, differences should be minimal, if present at all [18].

Dosage Forms

FDA-Approved Cannabinoids [10–12]

Dronabinol, nabilone, and cannabidiol are the three FDA-approved cannabinoid products currently available. Dronabinol and nabilone are controlled substances (schedule three and two, respectively). Cannabidiol was originally a schedule five controlled substance; however, in 2020, the DEA removed pharmaceutical

cannabidiol from the list of controlled substances in response to data from animal and human studies that compared the abuse potential of cannabidiol, dronabinol, alprazolam, and placebo. Some states or institutions may still treat it as a controlled substance. All three of these products have quality and safety standards that are identical to other prescription drugs. While labeling of marijuana with cannabinoid concentrations and the dose present (especially in edibles) is becoming more widespread, the production of these products is less regulated than traditional prescription products. They may have other ingredients the patient (and dispensary) is not aware of. Cleanliness of these products is not guaranteed either. Reports of aspergillosis (a type of fungal pneumonia) after inhalation of contaminated marijuana have been published. Certain states, including Colorado, mandate either testing marijuana products for contaminants such as bacteria and mold, or labeling that it has not been tested for contaminants.

Dronabinol (Marinol®) [10] is indicated for anorexia associated with weight loss in adult patients with acquired immunodeficiency syndrome (AIDS) and for nausea and vomiting associated with chemotherapy in adult patients who failed conventional antiemetics. It is synthetic THC with similar pharmacologic activity.

Nabilone (Cesamet®) [11] is another THC analog with FDA indications for the treatment of nausea and vomiting associated with chemotherapy in patients who have failed to adequately respond to conventional antiemetics. It is not indicated for AIDS-related anorexia and weight loss. Like dronabinol, it has similar pharmacologic activity to THC and carries the same psychoactive properties.

Cannabinol (Epidiolex®) [12] is made by purifying cannabinoid extracts from cannabis grown in the United Kingdom. It is indicated for seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients one year of age or older. Clinical trials, as expected, showed very little clinical psychoactive properties outside of somnolence.

In addition to the three FDA-approved formulations, marijuana is available in a wide variety of dosage forms, including loose plant (mainly used for smoking), concentrated oils used for vaping or "dabbing," oral and sublingual products, topical creams, and even suppositories for menstrual cramping. Use of noninhalation dosage forms has risen significantly with legalization of medical and recreational marijuana. While some states have only legalized medical marijuana and some states do regulate THC and CBD ratios in products, for the most part, the products themselves can be dispensed as either recreational or medical. That is, there is nothing special about the medical marijuana product itself, outside of the fact that a prescription or physician order is required, different age limits may exist, and the tax structures are different.

Patients should be advised that smoking marijuana (i.e., burning of loose plant/flower) can still produce hydrocarbons that can be carcinogenic. For this reason, I generally recommend that patients using marijuana for medical reasons use edible or topical products.

Concentrations of THC present in marijuana have continually increased over the past 3 decades. In 2014, a study by the DEA showed that THC concentrations had almost tripled since 1995, largely attributed to the ability of growers to crossbreed

hybrids of different strains of the *Cannabis* plant itself to increase THC and CBD concentrations and alter ratios of which phytocannabinoids are present [19]. Concentrates (i.e., butane hash oil, hash oil, dabs) are also increasing in popularity and have significant health implications. These products are highly concentrated THC products, with upwards of 80–90% THC content versus 15–30% seen in flower form. Patients can become extremely intoxicated very quickly and usually only need one or two inhalations. These products, because of their high concentration and fast onset, cause intense nervous system effects immediately, rather than a slower progression seen with smoking flower or using edibles. Patients who use concentrates may experience psychosis, hallucinations, agitation, paranoia, and cardiac adverse effects including palpitations. They may also become tolerant more quickly and experience more severe withdrawal effects. There are risks with certain dabbing devices, including burns. Production of concentrates can also be risky since a large amount of heat and combustible chemicals are needed. Like smoking, inhaled concentrates should not be recommended for medical use.

Oral dosage forms are commonly used in both medical and recreational settings. They lack the quick onset seen with inhalation and may result in fewer adverse psychiatric events. One of the largest risks associated with oral dosage forms is delayed onset. With inhalation, the effect is seen within minutes and the user can titrate their own dose as they see fit. With oral ingestion, patients may not see the effects for up to 3–4 h [20], so they might consume more before the first product has fully absorbed and consequently, find themselves more intoxicated and for a longer time than they hoped. This has become a public health issue as it relates to driving as a patient may consume an edible product, feel fine 1–2 h later, drive, and then become more and more intoxicated and sedated while driving.

Topical products, such as oils and lotions, are becoming more and more common. These products usually contain CBD only; however, THC products are also available. National brands such as Burt's Bees have started producing CBD-infused lotions marketed to improve skin hydration and moisturization. Most dispensaries market these products for pain, inflammation, and even psoriasis and eczema. Systemic absorption of these products is minimal and few people will report clinically relevant psychoactive effects, especially compared to inhalation. Transdermal THC patches are also available, and these products generally have higher systemic absorption and psychoactive properties.

Pharmacokinetics [3, 5–7, 9, 20]

Absorption

Absorption is route dependent. Patients should be advised that smoking marijuana products leads to rapid absorption and clinical effects within minutes, while edible products can take up to 3–4 h to have their peak effect [20]. Oral ingestion is subject to first pass metabolism in the liver which reduces the effective dose compared to inhalation. For example, dronabinol only has 10% bioavailability. This is in line

with data on other oral cannabinoids of approximately 10–30% bioavailability. The figure below shows this difference in peak concentration and total absorption of oral vs. inhaled. Ingestion of oral cannabinoids with other food may increase the maximum concentration [11]. Topical products have very low bioavailability and generally do not reach the bloodstream in clinically significant amounts.

Distribution

The majority of cannabinoids, including THC and the metabolites 11-hydroxy THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH), are very lipophilic compounds and readily distribute into the brain and adipose tissue. THC has an initial volume of distribution of 2.5–3.5 L/kg (i.e., around 210 L for a 70 kg patient), with chronic users displaying higher volumes of distribution of up to 100 times this [5], or about 21,000 L for a 70 kg patient—an incredibly high value which suggests extensive adipose tissue deposits. Some data suggests that CBD has a volume of distribution of 30 L/kg, or ten times that of THC. The clinical trials for cannabidiol (Epidiolex®) showed volumes of up to 42,000 L after only 7 days of use [12]. Distribution models with up to 6 compartments have been suggested, but most literature agrees that at least 2 phases exist [5]. Phase 1 involves distribution mainly with the plasma volume and is highly protein bound. This phase also distributes THC to highly vascularized tissues, such as the heart, lungs, and brain. Phase 2 involves distribution of THC and metabolites (inactive and active) to adipose tissue and less vascularized tissues. Chronic users redistribute inactive metabolites from adipose into blood and urine which is the underlying reason for positive urine drug screens weeks after last use and prolonged half-lives of different compounds. Cannabinoids cross the placenta easily and are also found in breastmilk. The relative infant dose possible during breastfeeding can be variable dependent on the mother's use patterns. Epidiolex® trials in animals showed increased risk of developmental toxicity. Cannabinoid use during pregnancy or breastfeeding is not recommended.

Metabolism

In addition to first pass metabolism, THC and CBD are hepatically metabolized via cytochrome P450 enzymes, namely 2C9 and 3A4. THC has some notable metabolites, both active and inactive. THC-COOH is a nonpsychotropic metabolite of THC that has anti-inflammatory properties. It has a half-life of 5–7 days. 11-OH-THC is a psychoactive metabolite with a half-life of 12–36 h. It has a similar kinetic profile to THC.

In addition to being metabolized by the P450 enzyme system, cannabinoids can inhibit these enzymes which further complicates their clinical presentation, clearance, and interactions with medications. In addition to cannabinoid effects, hydrocarbons produced during smoking will induce CYP1A2 which is responsible for the metabolism of a number of psychiatric medications, including clozapine,

olanzapine, fluvoxamine, and duloxetine. Commonly used drug-drug interaction tools are generally not built to include interactions with marijuana; however, some drug information resources can incorporate marijuana interactions and as more research is published, these interaction tools should improve. Drug interactions will be discussed more in the next section.

Elimination

Cannabinoids and their metabolites eventually undergo glucuronidation and are eliminated in the urine and feces. As previously discussed, this process can be quite prolonged due to the highly lipophilic nature of cannabinoids that partition in adipose tissue and slowly equilibrate with the serum. Some chronic users may have detectable blood and urine concentrations up to 46 days from last use. Naïve users will have less adipose stores, shorter half-lives, and thus, will only test positive for 1–2 weeks after last use. The clinical trials for cannabidiol (Epidiolex®) showed elimination half-lives of 56–61 h after 7 days of administration in healthy volunteers. This is in line with studies evaluating THC use and a resulting half-life of up to 12 days in chronic users and as little as 2 h in naïve users, although it is difficult to compare these as serum THC half-life does not necessarily equal elimination half-life. THC-COOH is the primary urinary metabolite with a half-life of 5–7 days and causes a positive urine drug screen.

This figure below (used with permission from Goldfrank's Toxicologic Emergencies) shows the time course of THC and its metabolites. As you can see, chronic administration results in accumulation of THC-COOH (major nonpsychoactive metabolite). Oral administration results in a delayed peak of metabolites with higher concentrations versus smoking thanks to the first pass effect on THC, which shows relatively low concentrations relative to peaks seen with inhalation.

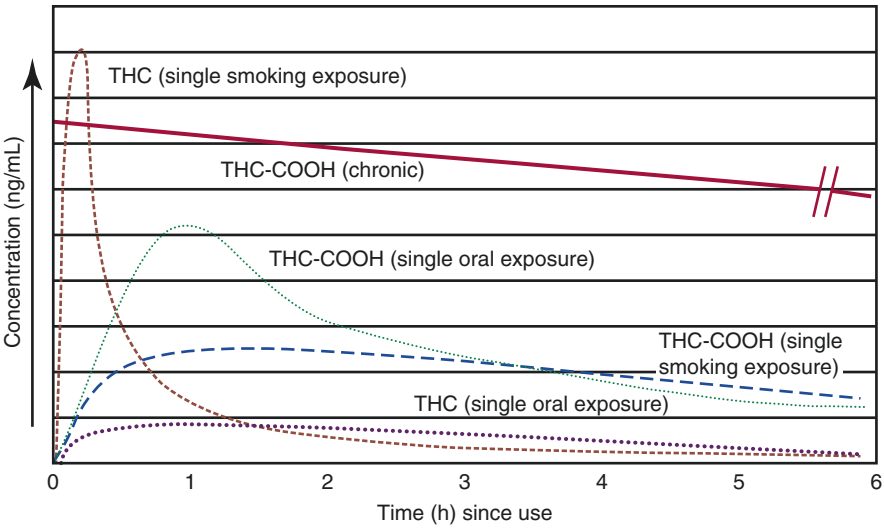
Figure 74-3, Goldfrank's Toxicologic Emergencies, 11e [21].

Estimated relative time course of delta-9-tetrahydrocannabinol (THC) and its major metabolite in the urine based on the route of exposure (Fig. 2.2).

Future drug tests may be able to incorporate ratio of metabolites to CBD and THC to determine when a patient last used. This is notably an issue in law enforcement where driving under the influence of marijuana is very subjective compared to alcohol use where clinical effects correlate well with blood alcohol levels.

Drug-Drug Interactions [5, 10–12, 22–25]

As previously discussed, CBD and THC have a variety of effects on CYP450 metabolism and effect a number of common enzymes responsible for drug metabolism. The purpose of this section will not be to detail every possible drug interaction. For patient-specific drug interactions, consultation with a pharmacist is recommended. Several drug databases, including Lexi-Comp®, have the ability to enter "marijuana" as a drug to screen for pharmaceutical drug interactions. This will



Source: L.S. Nelson, M.A. Howland, N.A. Lewin, S.W. Smith, L.R. Goldfrank R.S. Hoffman: Goldfrank's Tosicologic Emergencies, Eleventh Edition

Fig. 2.2 Estimated relative time course of delta-9-tetrahydrocannabinol (THC) and its major metabolite in the urine based on the route of exposure. Used with permission

often group all cannabinoid containing products into one syntax, but one should evaluate this closely, especially if a patient is on high-risk medications or using pure CBD products (in which case "cannabidiol" should be entered as well). Some of this information relies on the FDA-approved package insert for pharmaceutical cannabinoids. Because of this grouping, it is possible for an interaction to alert when it actually does not exist based on the specific product being used. Route of administration also may further compound this issue. For this reason, consultation with a pharmacist is recommended, especially with high-risk interactions such as immunosuppressants, anticoagulants, antiepileptic drugs, cardiac medications, antiretrovirals, and many others.

Antidepressants go through a variety of CYP enzymes. For example, citalopram is metabolized by 2C19 and 2D6 to a certain extent. CBD's inhibition of both of these enzymes may increase the patient's concentrations of citalopram and cause adverse events (including serotonin syndrome) with a possible need for dose decreases. Venlafaxine has minor metabolism to active metabolites through 2C19, 2C9, 2D6, and 3A4. Use of CBD in a patient on venlafaxine may cause a reduction in active metabolites (desvenlafaxine) and high venlafaxine concentrations. Since venlafaxine and desvenlafaxine have different serotonin and norepinephrine activities at different doses, this change in activity at different receptors could cause decreased efficacy or increased side effects, and the patient should be counseled on this potential interaction.

If a patient is electing to begin using medical marijuana, it is important to screen their current medication list for possible new interactions and discuss these with the patient. This is yet another reason that providers should ask patients about the cannabinoid content and makeup of the products they are using.

CYP450 Properties of THC and CBD [5, 9, 25]

Enzyme	THC	CBD
3A4	Substrate	Substrate, inhibitor
2C9	Major substrate, weak inhibitor	Substrate, inhibitor
2C19	Substrate	Substrate, inhibitor
2D6	n/a	Substrate, inhibitor
1A2	Induced by smoking	Induced by smoking

Pharmacodynamic interactions exist as well and should be considered, especially in elderly patients or those using other psychoactive prescription or recreational drugs. Marijuana can cause additive sedation with other CNS depressants such as alcohol or benzodiazepines. Anticholinergic medications may cause even more profound dry mouth, red eyes, and other effects.

Drug interactions can differ based on the route of administration as well. Inhaled marijuana will be more susceptible to drug interactions due to CYP1A2 induction (responsible for clozapine and olanzapine metabolism) caused by the burning of hydrocarbons. Topical preparations may have few drug interactions due to low systemic absorption.

Adverse Events

Adverse events from marijuana use are common and quite variable. Psychiatric adverse events will largely be discussed later in this book, but acute psychiatric events including psychosis, paranoia, and anxiety are all possible, especially with synthetic cannabinoids and high potency marijuana concentrates. Medical adverse events can range from tachycardia, hypertension, and dry mouth to stupor, coma, ataxia, bradycardia, and hypotension. Medical adverse events are becoming more common with increased ED visits reported in Colorado by Monte et al. since legalization [26]. Toxic ingestions of edible marijuana products by children have increased numerically every year since legalization [27]. Some states now have more restrictions on edible products. Colorado, for example, now requires a large symbol on all edible products, requires each serving (10 mg of THC) of product to be individually packaged and labeled, and no longer allows the use of words such as “candy” or “gummy” on the packaging to help deter children from thinking it is only candy. Additionally, products must now have a potency statement [28].

Drug and Genetic Testing

Drug Testing

THC is one of the "federal five" drugs that is on routine employment drug screens (the other four being amphetamines, opiates, phencyclidine, and cocaine). Even as more states adopt medical and recreational marijuana, individual organizations can still elect to terminate employment based on failing this drug screen.

Urine drug screens (UDS) utilize enzyme-linked immunosorbent assays (ELISA) to detect drug in the urine. Antibodies in the test bind antigens (drugs and metabolites) in the urine. Different tests have different cutoffs for resulting as positive, but most facilities use the federal workplace cutoffs (50 mcg/mL). These screening tests are prone to false positives and false negatives, but they are relatively fast and inexpensive compared to gas chromatography and mass spectrometry (GC/MS) tests which isolate and identify specific molecules in the urine. GC/MS tests are used for confirmation testing and in detailed drug testing since many opioids and benzodiazepines have different structures, making it difficult to develop a single antibody that would bind all drugs in that class. Lastly, most cannabinoid UDSs do not report urine concentrations. Because of the wide variability in urine dilution, specific gravity, metabolism, and timing of last dose, any UDS that provides urinary concentrations does not necessarily mean the patient is clinically intoxicated.

Cannabinoid ELISA UDSs generally use a THC antibody to detect THC and the major metabolites (11-OH-THC and THC-COOH). THC-COOH's long half-life of 5–7 days and lack of psychoactive properties are the reason chronic marijuana users can have a positive UDS up to 30 days from their last use and display no clinical signs of intoxication.

Secondhand smoke should not trigger a positive UDS [29–32]. A recent study in 2015 by Cone et al. exposed patients to secondhand marijuana smoke in small rooms without ventilation for prolonged periods of 60 min each. They found only one subject tested positive at the federal cutoff (50 mcg/mL) 6 h after session 2 (total time of 2 h of exposure to secondhand smoke in a sealed room). At the 8-h mark, the subject fell below the federal cutoff. They concluded that positive UDS results from secondhand smoke were possible, but only under extreme conditions of a sealed room without ventilation and prolonged duration of exposure with obvious knowledge by the subjects that others in the room were consuming marijuana, and only if the patient was tested in the 6–8 h after exposure [29].

Summary

- THC and CBD are the two main phytocannabinoids present in marijuana. THC acts primarily as a CB1/2 receptor agonist. THC is responsible for psychoactive properties of marijuana.
- Medical marijuana comes in a variety of unregulated forms with variable contents and cannabinoids ratios. Providers should discuss which formulation a

patient is using, the route of administration, what the usual THC:CBD ratio is, how frequently they use, why they use, and what adverse effects they notice from use. Providers should educate patients about the potential adverse effects of marijuana if a patient is considering using medical marijuana for a specific condition.
- Providers should not hesitate to discuss and educate patients on marijuana use, as patients receive information from many sources of varying credibility.
- Recently, especially among recreational marijuana, THC content of loose marijuana has been increasing.
- When using marijuana medically, oral or topical use is preferred due to the known carcinogenic risk associated with hydrocarbons produced during smoking or burning marijuana and a lower risk of adverse psychiatric effects, including acute psychosis.
- Both pharmacokinetic and pharmacodynamic drug interactions can be an issue with marijuana use, and THC and CBD can have different effects on metabolism of other drugs. For patients on high-risk medications (including but not limited to immunosuppressants, anticoagulants, and antiepileptic drugs), consultation with a pharmacist is recommended.
- Chronic use can result in urine drug tests being positive for up to 30 days after cessation. Secondhand smoke will not cause a positive urine drug test.

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