

Delta-What? Deciphering the World of Cannabinoids

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ABSTRACT

Delta-9-tetrahydrocannabinol (D9-THC) is the driving cannabinoid within cannabis that produces its psychoactive effects. However, the plant itself contains over 400 individual chemicals, many with unique pharmacological properties. Further complicating the cannabis market, chemical modifications have been identified to convert naturally derived cannabinoids to alternative cannabinoids and the collection of synthetic cannabinoids, manmade chemicals designed to act at cannabinoid receptors, continues to grow. Recent years have seen a rise in popularity of these alternative cannabinoids, and this trend is likely to continue with the continuing legalization of recreational cannabis throughout the United States. It is vital for medical providers to not only be aware of the wide range of available cannabinoid products, but to be conscious of their differing properties. The current work aims to identify commonly used alternative cannabinoids, examine their complicated legality, and summarize the available literature regarding their clinical effects.

KEYWORDS: cannabis, alternative cannabinoids, cannabis regulation

INTRODUCTION

With the passing of the Rhode Island Cannabis Act, the state became the 19th across the country to legalize recreational cannabis. The plant has been cultivated for millennia for materials and oil but has been restricted over the past century due to its psychoactive effects.¹ Its prohibition unfortunately hindered clinical research regarding its properties, including medical benefits and safety effects.

To most, cannabis is synonymous with delta-9-tetrahydrocannabinol (Δ 9-THC). Δ 9-THC is the driving cannabinoid which gives users its psychoactive effects. More recently, cannabidiol (CBD) has received media attention for potential anti-inflammatory, immune-boosting, anxiolytic, and antiepileptic health effects, with a lack of subsequent intoxication. Most cannabis-related medical literature to date has been focused on these two cannabinoids, but the

cannabis plant itself contains over 400 different chemicals, with 18 of these shown to have pharmacological and toxicological properties.² The effect of differing cannabinoid combinations, ratios, and how isolating specific cannabinoids compared to whole plant use impacts clinical effects is understudied. Some studies suggest that differing concentrations and ratios of THC:CBD result in divergent subjective effects.³ For example, at some concentrations, CBD has been reported to dampen psychoactive effects of THC, but at other ratios paradoxically amplify THC effects. These limited studies reveal we have only started to uncover the complexity of cannabinoid effects and interactions.

The discovery of the endogenous cannabinoid system shifted pharmacologic focus in an attempt to separate the psychoactive effects from certain medical benefits. Limited research led to the discovery of the endogenous cannabinoid system, where endocannabinoid ligands (e.g., 2-arachidonoyl glycerol and anandamide) act on both CB₁ and CB₂ receptors throughout the body.⁴ CB₁ receptors are present primarily in presynaptic neurons and help dictate neurotransmitter release while CB₂ receptors are typically found outside the CNS and are primarily expressed on immune cells. The discovery of these receptors and their effects has played a role in the rise of synthetic cannabinoids, manmade chemicals designed to act at the cannabinoid receptors. This led to the development of Marinol, a synthetic THC derivative, FDA-approved as an antiemetic agent for chemotherapy patients.² Additionally, Rimonabant, a CB₁ antagonist to combat obesity, was briefly approved in Europe, but the drug was eventually discontinued due to psychiatric side effects. Many of these new synthetic cannabinoids are structurally similar to Δ 9-THC with only slight variations in chemical structure. This allows them to bind the same receptors, without being their own defined illicit substance, enabling people who use them to circumvent federal laws.

Each cannabinoid's differing psychoactive profile is dictated by its specific chemical structure. Chemical modifications have been identified to convert naturally derived cannabinoids to alternative cannabinoids. As an example, THC-O, a potent alternative cannabinoid, can be synthesized from Δ 9-THC with a similar laboratory technique that forms aspirin (acetylsalicylic acid) from willow bark (salicylic acid).⁵ Aging of cannabinoids may also naturally

lead to decarboxylation of these compounds. Even the heat from smoking itself has been shown to alter chemical bonds,⁶ studies assessing the volatilization of cannabinoids have shown that CBD is partially converted to THC during smoking.

Additional confusion stems from the colloquial distinction between two available cannabis products: *Cannabis sativa* and *Cannabis indica*. It is typical for cannabis dispensaries to recommend the latter for anxiety as there is a preconceived notion that *Cannabis indica* is more relaxing than the uplifting *sativa* species.⁷ However, research has yet to validate this distinction, and it is important for providers to be aware that both can contain drastic ranges of THC and CBD. The degree of interbreeding and hybridization in recent decades has also made it difficult to adequately identify a cannabis plant's species and subsequent proposed psychoactive properties based solely off its physical structures such as leaf morphology or branching.

As more is learned regarding each cannabinoid's specific properties, there is inevitably going to be a proliferation of products utilizing alternative cannabinoids. CBD has been the face of the alternative cannabinoid world due to its availability, but specialized breeding is currently increasing the concentrations of other minor cannabinoids. Their popularity has drawn attention in the media and there has already been a shift toward commercial use, particularly within the

beauty and wellness sectors. Because of this, it is important for physicians and other healthcare providers to be conscious of the differing products available and their wide range of cannabinoid profiles. The present work aims to provide a review on existing literature regarding common cannabinoids, their legality, and the clinical response to their use. (See **Figure 1**.)

DELTA-9 (Δ 9-THC)

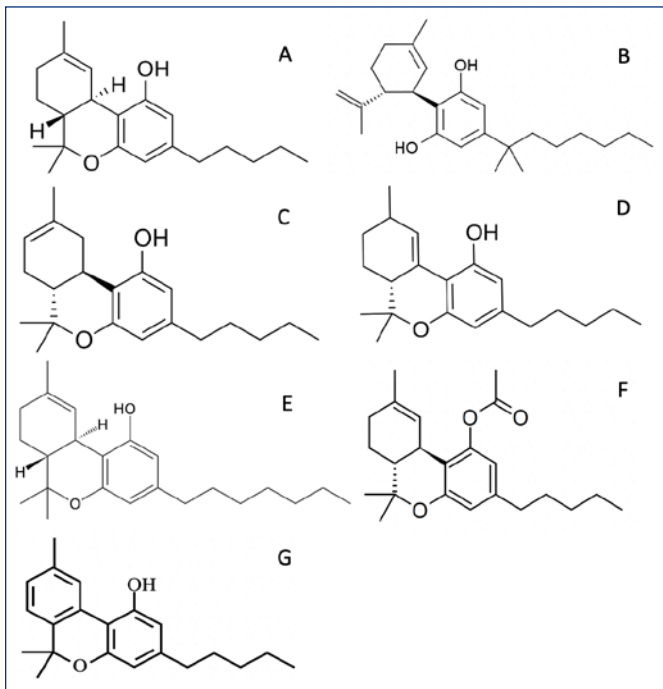
The everchanging recreational and medical legality of cannabis within the United States typically refers to Δ 9-THC. The compound itself is directly extracted from the cannabis plant, in contrast to most alternative cannabinoids which are chemically modified. As it is the most abundant psychoactive cannabinoid, most research regarding cannabis directly investigates its properties. Both the nausea suppression in patients receiving chemotherapy and the pain-reducing benefits in those with multiple sclerosis have been shown to be driven by this specific isomer.⁸

Like most psychoactive drugs, the effects of Δ 9-THC are dose dependent. The concentrations of cannabis products are typically described by the amount of Δ 9-THC per dry weight. The average cannabis potency today is estimated to be ~20%, meaning that a gram of cannabis is 200mg of Δ 9-THC. Breeding and specialized genetics have led to drastic increases in percent THC within lines of the cannabis plant. Since 1970, these concentrations have increased an average of 0.29% per year.⁹ In nearly all previous cannabis studies looking at analgesia, Δ 9-THC concentrations were lower than 10%, which will need to be accounted for as medicinal research moves forward and potencies continue to increase.

Δ 9-THC is primarily hepatically metabolized through the cytochrome P450 system, but alternative extrahepatic metabolism has been shown in other organs through hydroxylation pathways.² Based off previous clinical studies which utilized receptor antagonists,¹⁰ it has been shown that the psychoactive effects of Δ 9-THC are largely driven through the forementioned CB₁ receptor, leading to adenylyl cyclase inhibition. The cannabinoid has been shown to have a wide range of bioavailability depending on the route of administration, typically inhalation of cannabis smoke or in an edible form. In addition to these routes, there has been an increase in popularity over recent years of vaporizing high potency Δ 9-THC oil. This form gained notoriety in 2019 due to EVALI (E-cigarette or Vaping Use-Associated Lung Disease). It has been hypothesized that unregulated oil compounds contained Vitamin E at this time, leading to an aggressive inflammatory response within the lungs.¹¹ Similar to tobacco products, the long-term effects of vaping are yet to be identified.

The majority of drug tests in the United States assess for

Figure 1. A: Delta-9-tetrahydrocannabinol (Δ 9-THC), **B:** Cannabidiol (CBD), **C:** Delta-8-tetrahydrocannabinol (Δ 8-THC), **D:** Delta-10-tetrahydrocannabinol (Δ 10-THC), **E:** Tetrahydrocannabiphorol (THC-P), **F:** O-acetyl- Δ 9-THC (THC-O), **G:** Cannabinol (CBN)



cannabis by testing for Δ^9 -THC metabolites, but there is overlap with other cannabinoids. Δ^9 -THC, along with all other reported cannabinoids, is highly lipophilic, leading to its storage within adipose tissue in the body. This leads to delayed excretion, particularly when compared to other commonly used drugs, as heavy users can test positive in urine testing up to 30 days from last use.

CBD (CANNABIDIOL)

Cannabidiol has become popular in recent years as a cannabinoid with minimal to no psychoactive effects. There has been a large uptick in CBD-labeled health products in recent years due to its proposed benefits and the global market of CBD is estimated to reach US \$47 billion by 2028.¹² While it is widely available, it is not federally legalized and is instead dictated by individual states. That said, even the strictest states have avenues to obtain it legally.

Commonly taken orally or as a topical cream, CBD has been shown to have both analgesic and anti-inflammatory effects by acting as a cyclooxygenase and lipoxygenase inhibitor.¹³ It has low affinity for the forementioned CB_1 and CB_2 receptors, but rather has been shown to work primarily through GPR55, a receptor expressed primarily in the caudate nucleus and putamen.¹⁴ Like other cannabinoids, CBD is primarily hepatically metabolized. It has been recommended that patients receiving CBD have their bilirubin and transaminase levels monitored before and during treatment to assess for hepatotoxicity.

While CBD can be found in many stores, the FDA has only approved its use through Epidolex. The drug is a purified form of CBD for the treatment of seizures in patients with Lennox-Gastaut or Dravet syndrome.¹⁵ Studies regarding this medication have shown side effects including diarrhea, decreased appetite, and poor sleep quality. Currently, clinical trials are investigating the use of CBD in other disorders, such as anxiety, chronic pain, and neurodegenerative diseases.

A CBD specific drug test exists, but it is not typically performed due to the cannabinoid's lack of psychoactive properties. The compound itself should not lead to a positive THC drug screen, but many products have been shown to contain small amounts of THC, even if not labeled this way.

DELTA-8 (Δ^8 -THC)

Delta-8 is a natural yet historically ignored derivative of cannabis. While it has seen an increase in use in recent years, the ability to synthesize the isomer from CBD has been known for over 80 years.⁵ It is nearly identical to Δ^9 -THC, only differing in the location of a single carbon double bond, which is enough to drive its divergent psychoactive properties. The alternative cannabinoid has been shown in studies

to have a stronger affinity for CB_1 receptors than Δ^9 -THC.¹⁶ However, Δ^8 -THC is roughly half as potent as Δ^9 -THC and some sources state that the cannabinoid has greater appetite stimulating effects and less anxiety.¹⁷ Based on limited data, the reported side effect profile of Δ^8 -THC is similar to Δ^9 -THC. It can be taken orally but is typically smoked like common strains of cannabis.

The slight alteration in its structure has led to a federal debate and laxity in its regulations, leading to its rise in popularity in recent years. In September of 2021, the DEA deemed that cannabinoids extracted from the cannabis plant with Δ^9 -THC concentrations under 0.3% by dry weight meet the definition of hemp and thus are not controlled substances. Many have argued that this statement protects Δ^8 -THC as it is a cannabinoid which doesn't contain Δ^9 -THC. Even more confusion stems from the fact that the majority of available Δ^8 -THC in the country should be deemed synthetic, which would seemingly exclude it from the DEA's stance. While Δ^8 -THC can naturally be extracted from the cannabis plant, it is found in such small quantities that the process isn't economical. Because of this, the most available product is formed through a conversion process from CBD with the use of acids, typically hydrochloric or sulfuric acid.⁶ This process can lead to impurities and small amounts of other cannabinoids, such as Δ^{10} -THC.¹⁷ Because of this, it is important for clinicians to recognize that available products are often not pure Δ^8 -THC, even if advertised this way. Recent years have seen more states become stringent against this cannabinoid. Prior to the Rhode Island Cannabis Act, the state had made note that it deems Δ^8 and any other isomer to be treated the same as a Schedule 1 Controlled Substance. Alternative cannabinoids were not specifically addressed in this recent passed law. As of now, the cannabinoid is regulated to at least some degree in 19 other states.¹⁸

From a clinical standpoint, common immunoassays cannot note the difference between Δ^8 -THC and Δ^9 -THC so patients will test positive for THC after using either isomer. If there is any necessity to delineate, chromatographic methods can be used.¹⁹ There has been little research looking into the pharmacokinetic profile of Δ^8 -THC, particularly from an oral route. However, based on limited data, its distribution around the body unsurprisingly appears to be like that of Δ^9 -THC.

DELTA-10 (Δ^{10} -THC)

Like Δ^8 -THC, Δ^{10} -THC is also an isomer solely differing in the location of its double carbon bond. The cannabinoid isn't typically found as a natural component of cannabis but has been known since the 1980s when it was first synthesized. While it can be synthesized directly from Δ^9 -THC, it is typically formed as an impurity when Δ^8 -THC is synthesized from CBD.

It has been shown to bind and utilize the same CB₁ and CB₂ cannabinoid receptors throughout the body. There is little data regarding this alternative cannabinoid, but most reports deem it to be less potent than Δ⁹-THC. While there have been no clinical trials directly comparing the two,²⁰ users typically report more stimulating properties than the mellowness associated with Δ⁸-THC. Because of this, there are many products that contain a mix of both Δ⁸-THC and Δ¹⁰-THC. Like other alternative cannabinoids, Δ¹⁰-THC will lead to a positive THC immunoassay drug test in patients.

THC-P (Tetrahydrocannabiphorol)

The highest potency cannabinoid naturally found in both hemp and cannabis, albeit in small concentrations, is THC-P. It has been reported to have potencies up to 33 times that of Δ⁹-THC. Its differences are hypothesized to be secondary to additional carbon atoms within its alkyl side chain.²¹ While most cannabinoids have a pentyl side chain, THC-P has two additional carbon atoms. It has the highest binding affinity to CB₁ receptors of any naturally occurring cannabinoid, but newer synthetic cannabinoids are actively being created with reported higher potencies.

Minimal research performed in mice has indicated similar cannabimimetic activity to Δ⁹-THC, inducing analgesia, hypomobility and decreased temperature.²¹ THCP breakdown within the body leads to THC-COOH, the same metabolite formed by Δ⁹-THC. Because of this, users of THC-P would have a positive immunoassay standard THC drug screen.

The heptyl homologue of CBD, Cannabidiphorol, was identified in the same Italian study performed in 2019.²² Little is known regarding its clinical properties or pharmacokinetics. Future research is necessary to examine possible increased anti-inflammatory properties secondary to its presumed higher binding affinity.

THC-O (O-Acetyl-Δ⁹-THC)

THC-O, also referred to as THC-O-acetate, is an alternative cannabinoid that is not naturally found within the cannabis plant but has been gaining popularity over recent years. It is available in vape cartridges, edibles, and tinctures. Reports have noted a potency up to three times that of Δ⁹-THC.²³ In contrast to THC-P, its potency doesn't stem from extra carbon atoms in its alkyl chain. Rather, an acetate group within the molecule significantly increases its bioavailability, furthering its psychoactive effects.

Clinically, it is the only cannabinoid to have reported pseudo-dissociative effects and in high doses patients may present like they consumed hallucinogenic drugs.²³ THC-O typically refers to the acetate ester of Δ⁹-THC, but those of

Δ⁸-THC and Δ¹⁰-THC have also been synthesized. It is not specifically scheduled at the federal level within the United States but falls in the same gray area of other alternative cannabinoids. There are reports of THC-O being studied as far back as 1948 during the infamous Edgewood Arsenal Experiments, where the US government was studying incapacitating agents.²⁴

As most of the information regarding THC-O stems from anecdotal reports, further scientific research needs to be performed to fully elucidate its effects and pharmacokinetics. It is not currently scheduled at the federal level within the United States.

Cannabinol (CBN)

Cannabinol, the first compound to be isolated from cannabis extract, is naturally found as a degradation product from Δ⁹-THC as it oxidizes. The average cannabis plant ranges between 0.1-1.6% CBN.²⁵ Opposed to many other cannabinoids,²⁶ CBN has a higher affinity to CB₂ receptors than CB₁. Unlike the forementioned THC alternative cannabinoids, CBN does not have any double bond isomers or stereoisomers. It is not specifically scheduled in the United States, but its legality is similarly in question as it could be deemed a THC derivative.

CBN has shown initial promise as a sleep aid in patients. However, the studies performed so far have not utilized polysomnography or validated sleep questionnaires.²⁷ Concerningly, studies in zebrafish have shown teratogenic effects of CBN, leading to yolk sac anomalies, tail bending and pericardial edema.²⁵

Future Alternative Cannabinoids

The forementioned cannabinoids do not encompass all known cannabinoids throughout the world, but rather are a sample of the most studied and frequently used by the general population. Additional cannabinoids that may increase in popularity include cannabigerol and cannabichromene. Cannabigerol (CBG), found in small quantities in cannabis,²⁸ is sold as a dietary supplement. Cannabichromene (CBC), also naturally occurring, has begun to show promising results regarding anti-inflammatory properties.²⁹ Epidemiological data shows that alternative cannabinoids are typically used by young adults and have been drastically increasing in frequency in recent years. As the number of discovered and synthesized alternative cannabinoids grows and the array of cannabis products and preparations expand and become easily accessible, further research will be required to assess the effects of these new cannabinoids, including long-term and in-utero effects. It is vital for medical providers to stay up to date regarding these differing cannabinoid products in order to best evaluate, treat, and counsel patients.

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