Comparison of Cannabinoids: CBD vs THC

The cannabis family (e.g., hemp, marijuana) and synthetic cannabinoids have been used medicinally and recreationally for a variety of purposes for many years. There are over 100 cannabinoids in cannabis. Two of the main active components of cannabis are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). CBD and THC act differently within the body, due to differences in receptor affinities and activities. THC activates cannabinoid receptors in the brain, while CBD appears to work by other mechanisms. THC leads to a “high,” while CBD does not. The legality of CBD and THC products, both recreational and medical, varies based on where you live and which plant it is derived from (i.e., hemp-derived, marijuana-derived).

Cannabis laws can be found at https://medicalmarijuana.procon.org/view.resource.php?resourceID=006473 (U.S.) and https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/laws-regulations.html (Canada). Cannabis products come in a variety of forms including tablets, capsules, solutions, oils, edibles, topicals, inhalants, suppositories, etc. Depending on the product, it can be obtained by prescription, online, dispensaries, smoke shops, etc. It is difficult to determine the quality of unregulated products, as they may not contain claimed ingredients or may be contaminated with other ingredients or toxins. However, some sellers provide an analysis of their products and details on production methods to assist in product selection. The chart below compares the effects of CBD and THC and reviews their risk for dependence and impact on urine drug screens.

**Abbreviations:** CBD = cannabidiol; CYP = cytochrome; THC = delta-9-tetradrocannabinol.

**FDA- and Health Canada-approved cannabinoid products at time of publication include:**

- **THC-based products (synthetic):** Most often used to reduce refractory chemotherapy-induced nausea and vomiting.
  - Dronabinol (U.S. only; Marinol, generics, Syndros)
  - Nabilone (Cesamet, generics [Canada only])

- **CBD-based product:** Used to treat certain types of refractory childhood-onset seizures due to Dravet and Lennox-Gastaut syndromes.
  - Cannabidiol (Epidiolex [U.S. only])

- **Combination products:** See specific products for intended uses.
  - CBD and THC (nabiximols; Sativex [Canada only]): used for refractory pain and spasticity associated with multiple sclerosis.
  - CBD and THC (Tilray 2:100 [Canada only]): used to treat certain types of refractory childhood-onset seizures due to Dravet and Lennox-Gastaut syndromes.

*Continue to the next page for answers to your questions about CBD and THC*
### Topic/Question

<table>
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<th>Cannabidiol (CBD)</th>
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#### What are potential beneficial effects?

- Potential beneficial effects are based on a combination of data including human and animal models.22
- Effects may be different or vary in intensity based on the specific product used and the method or route of administration (e.g., inhaled, oral, topical).22

- CBD may have the following **beneficial effects**:4,8
  - Analgesia
  - Anticonvulsant
  - Anti-oxidant
  - Anxiolytic and antipsychotic effects
  - Muscle relaxant
  - Neuroprotective
  - May reduce undesirable effects of THC when used together or in a combination product (e.g., sedation, paranoia).

- THC may have the following **beneficial effects**:4
  - Analgesia
  - Antiemetic
  - Appetite stimulation
  - Muscle relaxant

#### What are potential negative effects?

- Potential negative effects are based on a combination of data including human and animal models.22
- Effects may be different or vary in intensity based on the specific product used and the method or route of administration (e.g., inhaled, oral, topical).22

- CBD may have the following **negative effects**:3
  - Decreased appetite and weight loss
  - Diarrhea
  - Dizziness, drowsiness, and fatigue
  - Liver injury (more likely with 20 mg/kg/day [17% vs 10 mg/kg/day [1%]) or when combined with clobazam or valproate).

- THC may have the following **negative effects**:4,8
  - Euphoria
  - Hyperemesis syndrome (referred to as Cannabinoid Hyperemesis Syndrome [CHS])27
  - Psychoactive effects (e.g., feeling drunk, disturbance in attention, dizziness, sedation, disorientation, dissociation, paranoia, and euphoric mood).

#### What evidence is available for specific therapeutic effects?

- Evidence supports oral use for refractory seizures in patients with Dravet and Lennox-Gastaut syndromes [Evidence Level A-1].16,19
- Limited evidence suggests that oral CBD may reduce psychotic episodes in patients with Parkinson’s disease.25
- Evidence for oral use in anxiety is conflicting, but there is limited evidence to show improvement in anxiety associated with public speaking.22

- Evidence supports use for:
  - Inhaled or oral products in refractory chronic pain, especially in patients with cancer, multiple sclerosis, rheumatoid arthritis, or neuropathic pain.21-23
  - Oral products in refractory chemotherapy-induced nausea and vomiting.21,22
  - Inhaled or oral products for appetite stimulation in patients with Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).22

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*More...*
### Therapeutic effects, continued

- Evidence for use may be slightly stronger for nabiximols (combination of CBD and THC) than nabilone (synthetic THC) in patients with refractory pain or spasticity due to multiple sclerosis.\(^2\)\(^1\),\(^2\)\(^4\)
- Limited evidence supports use to reduce the number of voids per day in patients with urinary frequency (evidence is primarily with nabiximols).\(^2\)\(^4\)
- There is limited evidence to support improving short-term sleep in patients suffering from obstructive sleep apnea, fibromyalgia, chronic pain, and multiple sclerosis (evidence is primarily with nabiximols).\(^2\)\(^2\)
- Limited evidence for use in improving symptoms of:
  - Tourette syndrome
  - Dementia
  - Post-traumatic stress disorder (PTSD)

### What are potential drug-drug and drug-food interactions?

- THC and CBD are both primarily metabolized by CYP P450 enzymes 1A2, 2C9, 2D6, 2C19, and 3A4.\(^7\)
  - Medications that inhibit these enzymes could possibly increase CBD and THC levels.\(^7\)
  - Medications that induce these enzymes could possibly lower CBD and THC levels.\(^7\)
- See our chart, *Cytochrome P450 Drug Interactions*, to identify medications that inhibit or induce, or are substrates for particular enzymes.
- Consider reducing CBD doses when used with moderate to strong inhibitors of:\(^3\)
  - CYP3A4 (e.g., ritonavir, verapamil, voriconazole)
  - CYP2C19 (e.g., fluconazole, omeprazole)
- Monitor for a need to increase CBD doses when used with inducers of:\(^3\)
  - CYP3A4 (e.g., carbamazepine, St. John’s wort)
  - CYP2C19 (e.g., primidone, rifampin)
- CBD inhibits CYP enzymes 2C8, 2C9, and 2C19 and uridine 5’-diphospho-glucuronosyltransferase (UGT) enzymes 1A9 and 2B7. CBD use could increase drug levels of substrates of:\(^3\)
  - CYP2C8 (e.g., amiodarone, carbamazepine, warfarin)
  - CYP2C9 (e.g., amitriptyline, phenytoin)
  - CYP2C19 (e.g., active metabolite of clobazam, citalopram, clonidogrel, phenytoin, valproic acid)
- THC may displace highly protein bound drugs, leading to higher drug levels and possible adverse effects or toxicity.\(^4\),\(^9\)
  - For example, monitor and adjust cyclosporine or warfarin doses as necessary when starting or changing THC doses.\(^9\)
- THC may have additive effects with hypnotics, sedatives, psychotropics, and alcohol.\(^4\),\(^15\)
- Consider reducing THC doses when used with inhibitors of:\(^1\),\(^2\)
  - CYP2C9 (e.g., ginkgo, sulfamethoxazole)
  - CYP3A4 (e.g., ritonavir, verapamil, voriconazole)
- Monitor for a need to increase THC doses when used with inducers of:\(^1\),\(^2\)
  - CYP2C9 (e.g., carbamazepine, phenytoin)
  - CYP3A4 (e.g., carbamazepine, St. John’s wort)

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<td><strong>Drug and food interactions, continued</strong></td>
<td>• CBD may have mixed effects on CYP enzymes 1A2 and 2B6.³</td>
<td>• THC can produce both physical and psychological dependence.⁴</td>
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<td>• Monitor patients and adjust doses for substrates as appropriate:³</td>
<td>• Withdrawal symptoms associated with THC may include anxiety, craving, irritability, dysphoria,</td>
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<td>• UGT1A9 (e.g., fenofibrate)</td>
<td>insomnia, and nausea.¹,²,⁶</td>
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<td>• UGT2B7 (e.g., lamotrigine, morphine)</td>
<td>• Tapering by gradually reducing the amount used or taken each day or each week may lessen withdrawal</td>
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<td>• High-calorie, high-fat food may increase absorption of CBD.³</td>
<td>symptoms such as anxiety and insomnia.²,⁶</td>
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<td>• CNS depressants (e.g., alcohol, benzodiazepines, opioids) may add to side effects (e.g., dizziness, drowsiness).³</td>
<td>Simple things like limiting caffeine intake and relaxation techniques or meditation may help with withdrawal</td>
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<td><strong>What is the risk of dependence?</strong></td>
<td>• Use of pure CBD is unlikely to lead to dependence.³</td>
<td>symptoms such as anxiety and insomnia.²,⁶</td>
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<td>• Be aware that unregulated products promoted to only contain CBD may also contain some THC and therefore could lead to dependence due to THC content.⁴</td>
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<td>• Though dependence and withdrawal are not a concern, if possible, limit missed doses when used for high-risk conditions (e.g., refractory seizures).³⁷</td>
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<td><strong>What is the impact on urine drug screens?</strong></td>
<td>• Most urine drug screens test for THC or its metabolites.¹³</td>
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<td>• Most hemp oil or CBD products do not contain enough THC to lead to a positive urine drug screen.¹²</td>
<td>• Tests can come back positive for about a week to ten days after use, or up to six weeks with heavy use.¹³</td>
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<td>• However, very high doses or an impure form of CBD could lead to a positive urine drug screen.¹²</td>
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<td><strong>What are the laws and regulations surrounding CBD products?</strong></td>
<td>• In the U.S., hemp-derived products containing no more than 0.3% THC are NOT considered controlled substances and can be sold with certain restrictions, based on state laws and restrictions. Recreational cannabis is legal in Canada.⁴⁰,⁴¹&lt;br&gt;  - In the U.S., the FDA maintains the authority to regulate products containing cannabis or cannabis-derived compounds. To date, there is only one FDA-approved CBD product, <em>Epidiolex</em>.³⁰&lt;br&gt;  - According to the FDA:&lt;br&gt;    ▪ CBD-based products CANNOT be sold as dietary supplements because a CBD product was FIRST approved as a prescription (<em>Epidiolex</em>).³⁰&lt;br&gt;    ▪ Hemp-derived CBD products can be sold in cosmetics (e.g., creams, lotions, lip balms). These do not have to undergo FDA approval.³⁰&lt;br&gt;  - State laws regarding hemp-derived CBD products vary. Some states may not sell any CBD products. Some may sell hemp-derived CBD products, but only as cosmetics. Some states may sell consumable hemp-derived CBD products (e.g., capsules, tinctures) in addition to cosmetics. Travel with non-FDA approved CBD products may be tricky due to differences in state laws.</td>
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<td><strong>What to consider when selecting a hemp-derived CBD product?</strong></td>
<td>• If possible, consider buying from a medicinal dispensary, as these are regulated.³⁶ If dispensaries are not an option, things to consider when selecting a hemp-derived CBD product can include:&lt;br&gt;  - Looking for a company that:&lt;br&gt;    ▪ Lists the amount of CBD per serving or per application.³²,³⁵&lt;br&gt;    ▪ Makes testing results (e.g., <strong>certificate of analysis</strong> (COA)) from an independent lab available. Some products may have a QR code that can be scanned to download the COA.³²&lt;br&gt;    ▪ Meets “ISO 17025” standards. This means the company follows high scientific standards.³²&lt;br&gt;    ▪ Maintains the Hemp Authority Designation. This speaks to quality standards and indicates to law enforcement that products are derived from hemp and are legal.³³&lt;br&gt;  - Considering <strong>where the product is grown</strong>. States where recreational cannabis use is legal, may have more robust regulation and testing (e.g., testing THC levels and for illegal pesticides). If possible, avoid foreign sources.³²,³⁵&lt;br&gt;  - Reviewing the labeling and company website for information about <strong>contaminants</strong> (e.g., toxic chemicals, THC). Cannabis plants can easily absorb toxic chemicals (e.g., heavy metals, pesticides).³²&lt;br&gt;  - The onset of the desired effect may affect which route of administration is selected:&lt;br&gt;    ▪ <strong>Inhaling</strong> and <strong>sublingual</strong>: Seems to have the fastest onset of action.³²&lt;br&gt;      - Avoid inhalation products containing propylene glycol or ethylene glycol.³²,³⁵&lt;br&gt;    ▪ <strong>Topical</strong>: Varies from person to person. May work right away or may take several hours.³²&lt;br&gt;    ▪ <strong>Oral</strong>: may take 30 minutes or longer.³²</td>
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<td>Who should NOT use cannabinoids?</td>
<td>There are little data available to clearly define who should NOT use cannabinoids.</td>
<td>THC should be avoided in the following populations:</td>
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<td>• Women who are pregnant, planning to become pregnant, or breastfeeding.(^{28})</td>
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<td></td>
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<td>• Children and adolescents.(^{34})</td>
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<td>• Patients with:(^{29})</td>
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<td>o Mood or anxiety disorders.</td>
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<td>o Unstable cardiovascular disease.</td>
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<td>o Complex medication regimens.</td>
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CBD should be avoided in the following populations:

- Women who are pregnant, planning to become pregnant, or breastfeeding.\(^{28}\)

CBD should be avoided or only used after careful review for drug-drug interactions:

- In patients with complex medication regimens.\(^{29}\)

Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.
Levels of Evidence
In accordance with our goal of providing Evidence-Based information, we are citing the LEVEL OF EVIDENCE for the clinical recommendations we publish.

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<td>3. All-or-none study</td>
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<td>Inconsistent or limited-quality patient-oriented evidence.*</td>
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<td>4. Case control study</td>
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*Outcomes that matter to patients (e.g., morbidity, mortality, symptom improvement, quality of life).

RCT = randomized controlled trial; SR = systematic review

Project Leader in preparation of this clinical resource (340904): Beth Bryant, Pharm.D., BCPS, Assistant Editor; last modified May 2019.

References