

## “Doctor, I heard CBD might help, can I start taking it?”

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Cannabidiol (CBD) has become more prominent in popular culture, and consequently physicians are increasingly asked by patients about the risks and benefits of CBD use. Gallup polls in August of 2019 showed that 14% of the U.S. population states they are using CBD.<sup>1</sup> However, here at Wake Forest Baptist Health, CBD is not included in the medication lists for patients, nor can it be added to the electronic medical record (EMR). Given that CBD is sold everywhere from CVS to Walmart<sup>2</sup>, it is time that we as physicians start to ask our patients about CBD use. It is also time for the medical team to arm themselves with more information about CBD. Given the evidence for increasing use among the U.S. population, this article can serve as an information tool for physicians regarding CBD products and CBD use in their patients.

### Epidiolex

The only FDA approved CBD product is Epidiolex (cannabidiol) oral solution, which obtained FDA approval in June 2018 for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients two years of age or older. It is administered only as an oral solution, and dosing is weight-based. It is recommended that prescribing physicians obtain serum transaminases (ALT and AST) in addition to total bilirubin levels prior to initiating treatment. If these lab values increase to two to three times the upper limit of normal, Epidiolex should be weaned off (to prevent seizure induction) and stopped. Epidiolex can cause some side effects including dry mouth, diarrhea, reduced appetite, drowsiness, anemia, fatigue, hepatocellular injury, suicidal ideation, hypersensitivity reactions, and withdrawal reactions. Epidiolex is a moderate to strong inhibitor and strong inducer of CYP3A4 and CYP2C19. Thus, any drug that potentiates this system will have interactions, especially ones like warfarin and other anti-epileptic drugs.<sup>3</sup>

### FDA Consumer Update

In November 2019, the FDA released a consumer update about CBD. The update noted that it is currently illegal to market CBD as a dietary supplement or to add CBD to food. Additionally, the FDA has received only limited data about CBD safety, which includes safety risks that need to be considered prior to starting CBD. The FDA also points out that CBD products are marketed with unproven claims, and that CBD products are of an unknown quality. The update highlights some of the questions that need to be answered to deem CBD safe, including: What happens with prolonged CBD use? What effect does CBD have on a developing brain? How does CBD interact with other herbs and botanicals? Does CBD cause male reproductive toxicity, as has been reported in animal studies?<sup>4</sup>

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### What Does CBD Oil Claim to Treat?

Discussion of medicinal supplements among patients is a regular occurrence, and many are using CBD for various conditions. During clinical rotations, one of the authors (AD) noted patients were using it for cancer related anorexia, nausea, pain, anxiety, arthritis, and tremor related to Parkinson and Huntington Disease. One distributor of a CBD product claims that CBD has analgesic, anti-inflammatory, antioxidant, anti-emetic, anxiolytic, anti-neoplastic, antipsychotic, anti-spasmodic, neuroprotective, anti-ischemic, and anti-epileptic properties. Additional claims include reduction of tetrahydrocannabinol (THC) psychoactivity, sleep promotion, and appetite reduction.<sup>5</sup> The August 2019 Gallup poll stated the top three reasons people use CBD are: pain (40%), anxiety (20%), and sleep/insomnia (11%).<sup>1</sup>

### What Does CBD Treat According to the Evidence?

In regards to chronic pain, an overwhelming body of convincing preclinical evidence indicates that cannabinoids produce antinociceptive effects in inflammatory and neuropathic rodent pain models; however, significant human studies are lacking.<sup>6,7</sup> CBD represents an attractive option in chronic pain treatment, particularly in the context of opioid abuse, not only because of its potential efficacy, but also because of its limited misuse and diversion potential as well as safety profile.<sup>8</sup>

In regards to anxiety, studies have very small sample sizes. This means exaggerated responses or lack of significant effects could be due to a lack of statistical power. In addition, most of the studies used normal human volunteers.<sup>9</sup>

There are three randomized trials assessing the impact of moderate-length CBD therapy on patients with schizophrenia. They all demonstrate a reduction of schizophrenia symptomatology over time for at least some measures but differ as to the impact of CBD therapy on the disease.<sup>9</sup>

The only available trial of CBD in Parkinson disease did not find benefits in the movement aspect of the disorder but may impact sleep.<sup>10</sup> However, in an outpatient psychiatric population with insomnia without Parkinson disease, sleep scores displayed no sustained improvements during a three-month study.<sup>11</sup>

There are no human studies that investigated the effects of CBD in either Alzheimer disease or unipolar depression. Treatment with CBD alone was insufficient at managing choreic movements in patients with Huntington disease.<sup>12</sup>

### Drug Interactions

CBD exhibits both pharmacodynamic and pharmacokinetic properties that could lead to adverse drug interactions and drug-drug interactions.<sup>13</sup> CBD has been seen in concentrations ranging from very low to potentially supratherapeutic doses that exceed FDA-approved dosing for seizure disorders.

CBD has activity at CYP450 isoforms including 3A4, 2C9, 2C19, 1A2, 2C8, 2B6, and 2E1.<sup>13,14</sup> However, CYP450 isoforms 3A4 and 2C19 are the most important to CBD metabolism and as such, other drugs that are either substrates, inducers, or inhibitors of 3A4 or 2C19 need to be used cautiously with CBD oil; some examples of which are: immunosuppressants, chemotherapeutics, antidepressants, antipsychotics, opioids, benzodiazepines, z-hypnotics, statins, calcium channel blockers, carbamazepine, topiramate, phenobarbital, efavirenz, pioglitazone, proton pump inhibitors, cimetidine, ketoconazole, clopidogrel, fluconazole, rifampin, phenytoin, and St. John's Wort. In addition, CBD has inhibitory effects at clinically relevant dosing on UGT1A9 and UGT2B7 medicines such as acetaminophen, canagliflozin, sorafenib, irinotecan, propofol, mycophenolate, valproic acid, dabigatran, dapagliflozin, hydromorphone, losartan, ibuprofen, naproxen, and ezetimibe.<sup>14</sup> These medications need to be adjusted.

### Conclusion

The only certainties about CBD are that patients are using it, and more studies are needed to prove claims of efficacy as well as drug interactions. Patients using CBD should get baseline liver tests including AST, ALT, and total bilirubin. If these serum blood counts elevate to within two to three times the upper limit of normal while using CBD, CBD should be stopped. It is recommended that CBD be weaned down, versus being stopped abruptly due to the anti-epileptic properties of CBD. Care must be taken when directing patients toward CBD products because there is little regulation, and studies have found inaccurate labeling of CBD and THC quantities, even among the same manufacturers.<sup>15</sup> Knowing that CBD can have drug-drug interactions, it is important for prescribers to ask patients about CBD use. At Wake

Forest Baptist Health, the EMR system has been updated to include electronic cigarettes in the patient history section of their chart, but not CBD. To provide our patients with the best quality health care, it is time that CBD is added as well. Until then, prescribers need to start asking their patients about CBD use and ensure that liver function, adverse drug reactions, as well as drug-drug interactions are monitored in patients using CBD.

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