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Cannabidiol (CBD)

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Continuing Education Activity

CBD is a medication used to manage and treat the seizure disorders Lennox-Gastaut syndrome and Dravet syndrome. This activity describes the indications, action, and contraindications for CBD as a valuable agent in the treatment and management of Lennox-Gastaut syndrome and Dravet syndrome, and also highlights the mechanism of action, adverse event profile, and other key factors such as current research trials ongoing for CBD use.

Objectives:

- Review the current and future indications for CBD.
- Explain the importance of monitoring patients on CBD.
- Summarize the contraindications and factors to consider when prescribing CBD.
- Describe the importance of collaboration and communication amongst the interprofessional team to improve outcomes for patients receiving CBD.

Access free multiple choice questions on this topic.

Indications

Cannabis sativa or Indian hemp (subfamily *Cannaboideae* of family *Moraceae*) is an annual herbaceous plant native to central and western Asia. The plant is cultivated for medicinal properties and hemp, a natural textile fiber. The plant contains over 400 chemical compounds, of which approximately 80 biologically active chemical molecules. The most important cannabis compounds are cannabinoids formed by a terpene combined with resorcinol or, according to a different nomenclature, by a benzopyranic ring system. There are about sixty cannabinoids, of which the most important psychoactive compound is tetrahydrocannabinol (TCH), particularly the isomer delta (Δ9-THC). Other identified compounds are cannabidiol (CBD), cannabigerol (CBG), cannabinol (CBN), cannabichromene (CBC), and olivetol. In addition to cannabinoids, the plant contains terpenoids such as beta-myrcene, beta-caryophyllene, d-limonene, linalool, piperidine, and p-cymene as well as flavonoids such as quercetin.

Of note, in contrast with Δ9-THC, CBD is nonintoxicating as it does not present psychoactive activity. Again, it exerts several beneficial pharmacological effects. The compound, in fact, has analgesic and anti-inflammatory activities mediated by the inhibition of cyclooxygenase and lipoxygenase. The anti-inflammatory action is several hundred times higher than that of acetylsalicylic acid. Furthermore, cannabidiol inhibits the synthesis of leukotriene TXB4 in polymorphonuclear cells.[1] Moreover, several investigations proved its anxiolytic, antiemetic, antipsychotic, and

neuroprotective antioxidant properties.[2][3]

To date, although in a recent document the FDA highlights the potential beneficial effects of cannabis derivatives, the agency has not approved a marketing application for cannabis, whereas it approved three synthetic cannabis-related drug products: a product containing dronabinol, dronabinol, or nabilone) and the cannabis-derived compound CBD. A licensed healthcare provider must prescribe these approved drugs per an FDA report.

In brief, the FDA approved products are:

- Synthetic cannabis-related drug products
    - Two products containing the active ingredient dronabinol (a synthetic Δ9-THC) for the treatment of anorexia associated with weight loss in AIDS patients.
    - Another product that contains nabilone and prescribed for the treatment of nausea and vomiting associated with anticancer chemotherapy
- The cannabis-derived compound CBD

Currently, CBD has only been approved for children ages two and older who suffer from the seizure disorders Lennox-Gastaut syndrome and Dravet syndrome.[4] The FDA approved CBD in 2018, and it is the only FDA-approved treatment for patients with Dravet syndrome.[5] Further, it is the first and only FDA-approved use of CBD, although the product is currently under investigation for potential use in various psychiatric, neurodegenerative, inflammatory, and cancerous diseases.[6][7]

Lennox-Gastaut syndrome is first diagnosed between the ages of 3 and 5 and persists into adulthood. It is characterized by multiple types of seizures, with the most common being tonic seizures. On EEG, it has a characteristic slow spike-wave (<3 hertz) with a spike or sharp wave. The exact pathophysiology is unknown. First-line treatment consists of various anti-epileptic drugs, with CBD being adjuvant therapy. Children with Lennox-Gastaut syndrome usually have learning and intellectual disabilities.[8]

Dravet syndrome is a diagnosis rendered around age 1 in children with frequent febrile seizures. Throughout the course of the disease, other seizures may develop, including status epilepticus. EEG will initially be normal before progressing to slowing and severe generalized polyspikes. Dravet syndrome appears to be caused by a nonsense mutation in the SCN1A gene, though there are cases without this mutation. Treatment was purely symptomatic with benzodiazepines and anti-epileptics prescribed to prevent the development of status epilepticus. Children with Dravet syndrome often have motor, intellectual, and psychological disabilities.[9]

Current clinical studies are investigating the use of CBD in mood disorders such as anxiety, control for chronic pain, anti-inflammatory diseases, neurodegenerative diseases such as Alzheimer and Parkinson disease, and antitumorigenic properties. However, none of these trials have yet resulted in FDA approval of CBD oil to treat.[10][11]

Mechanism of Action

The mechanism of action for cannabidiol, especially its anticonvulsant effect, has not been fully elucidated. It is known to have a low affinity for cannabinoid receptors CB1 and CB2, where it can exert both antagonist and agonist effects. It is a partial agonist of serotonin 5-HT1A receptor and allosteric modulation of opioid receptors, specifically mu and delta. Researchers postulate that the pharmacological effects of CBD could involve agonizing PPARgama and affecting intracellular calcium release.[10][12]

CBD metabolism occurs in the liver and intestines. Smoking bioavailability is approximately 31%. CBD's half-life

after oromucosal spray is between 1.4 and 10.9 hours, 2 and 5 days after chronic oral consumption, and 31 hours after smoking. CBD will achieve a maximum plasma concentration between 0 and 4 hrs.[13]

Administration

Dosing with CBD should begin at lower doses and titrate up to clinical levels. CBD administration is usually via oral preparation.[14]

For patients with Lennox-Gastaut Syndrome, the maximum dose is 20 mg/kg/day. In patients ages 2 years and older, the initial dose should be 2.5 mg/kg orally twice a day. If the patient has tolerated CBD for the week, increase the dose to 5 mg/kg twice a day. Maintenance dose is 10 to 20 mg/kg/day. The dose can be increased by 2.5 mg/kg twice a day, every other day, as tolerated. For patients with Dravet syndrome, the maximum dose is 20 mg/kg/day, with a maintenance dose of 10 to 20 mg/kg/day. The dosing schedule is the same as that for patients with Lennox-Gastaut Syndrome. In patients who need a more rapid titration, they may gradually increase the dose every day.[15][16]

It is important to titrate slower in patients with hepatic impairment, as CBD can cause liver damage. In patients with mild (Child-Pugh A) hepatic impairment, the maximum dose is 20 mg/kg/day with a maintenance dose of 10 mg/kg/day. In patients with moderate (Child-Pugh B) hepatic impairment, the maximum dose is 10 mg/kg/day with a maintenance dose of 5 mg/kg/day. The starting dose for these patients should be 1.25 mg/kg twice daily. In patients with severe (Child-Pugh C) hepatic impairment, the maximum dose is 4 mg/kg/day with a maintenance dose of 2 mg/kg/day. The starting dose in these patients is 0.5 mg/kg twice daily.[15]

While better seizure control has been seen at a dose of 20 mg/kg/day, there is also an increase in an adverse reaction. It is important not suddenly to discontinue CBD use. Sudden discontinuation can cause an increase in seizure frequency and possibly status epilepticus.[15]

Adverse Effects

CBD can cause dose-related liver damage. Concomitant use of CBD and other medications such as leflunomide, lomitapide, mipomersen, pexidartinib, teriflunomide, and valproate can increase the risk of liver damage and is known to damage the liver. Clinicians should warn patients with elevated baseline transaminases about potentially worsening liver function with the administration of CBD. It is important to monitor bilirubin levels and transaminase levels before and during treatment. Discontinuation of CBD or discontinuing concomitant use has reduced elevations. In patients with moderate or severe liver damage, slow dose titration, and adjustment is the recommended approach.[17][18]

There are occasional reports of somnolence and sedation have been occasionally reported with CBD use. These side effects may diminish over time and are more likely to be reported earlier in treatment. Doctors should be wary about prescribing CBD with other sedative medications such as benzodiazepines and opioids. Concomitant use of CBD with these sedative medications can result in severe respiratory depression.[19][20]

CBD use has shown a correlation with increased suicidal thoughts and/or behavior.[21][22] When prescribing CBD, the physician should warn patients and parents/caregivers to watch for any unusual changes in mood or behaviors. Any changes in mood or behaviors require evaluation as to whether it results from other medications, CBD, or underlying illnesses.

Also, CBD is newly on the market and is usually used as an adjunct therapy; thus, further studies are necessary to better understand all potential side effects and effects on liver enzymes and drug interactions.[23][1]

Contraindications

Absolute contraindications to CBD are allergies to cannabidiol or sesame oil. At first signs of skin, cutaneous irritation, or anaphylactic reaction, the patient should stop using CBD.

There are some relative contraindications. In patients with a history of drug or alcohol addiction, caution is necessary when prescribing CBD. While CBD does not contain the part of marijuana that gives users a “high,” it may have addictive properties. Physicians should caution patients who have struggled with addiction about this and emphasize appropriate use. With these patients, clinicians should look at the risk vs. benefit.

Another relative contraindication is in patients with a history of mood disorders, depression, or suicidal thoughts; patients with such a history should be cautioned about using CBD. CBD use has correlated with increased suicidal thoughts and behavior. When prescribing these patients, physicians should weigh the risk vs. benefit and inform patients and their caregivers to watch for sudden changes in behavior.[21][22]

Monitoring

Due to the potential CBD’s negative effects on the liver, it is important to measure transaminase and bilirubin levels both before and after treatment initiation. If transaminase levels increase before treatment, this may be a sign of liver damage and change the initiation and titration dosage. By measuring transaminase levels during treatment, earlier identification of potential liver damage may be identified, and CBD may be titrated down. Levels should be obtained prior, 1 month, and 3 months after initiating treatment. After every change in dose and/or addition of a medication known to affect the liver, transaminase and bilirubin levels should be obtained every month in patients who have liver damage or take drugs known to cause liver damage valproate, clobazam, etc. At the first signs of liver dysfunction such as right upper quadrant pain, nausea, vomiting, jaundice, and/or dark urine, transaminase and total bilirubin levels should be obtained immediately. If transaminase levels are greater than five times the upper limit of normal, or greater than three times the upper limit with bilirubin levels also being greater than two times the upper limit of normal, should discontinue treatment.[24][25]

Toxicity

There have been reports of ventilation support being necessary for children and the elderly who have ingested too much cannabis containing THC and CBD.[26] CBD has been associated with worsening respiratory depression in patients taking other potential respiratory-depressing drugs such as opioids and benzodiazepines. In these scenarios, respiratory support is the mainstay of treatment; there is currently no antidote to CBD or cannabis toxicity.[4][27][24][26]

Enhancing Healthcare Team Outcomes

The approval of CBD for the treatment of Lennox-Gastaut syndrome and Dravet syndrome has revolutionized the lives of patients and their families. Managing the administration of CBD to patients requires a team. Clinicians (MDs, DOs, NPs, PAs) and nurses must first properly diagnose these patients, especially since patients are often young (less than 5). Due to CBD's side effects, particularly on the liver, laboratory technologists must help monitor liver levels. Researchers are just beginning to discover CBD's therapeutic potential. Consequently, researchers and clinicians are necessary to continue to evaluate and identify CBD's uses. Finally, due to the differing state laws on marijuana use, social workers and other relevant healthcare professionals must help parents and patients understand that 1) CBD is legal and 2) CBD is not the part of cannabis that makes its users high. Proper utilization of CBD has demonstrated a reduction in seizure frequency in these syndromes that are notorious for being difficult to treat.

CBD reduces seizures and increases seizure control. In particular,

- CBD used as an adjunct therapy in Lennox-Gastaut syndrome or Dravet syndrome patients without seizure control by anti-epileptics results in a greater reduction in seizure frequency.[5] [Level 1]
- CBD is known to affect the liver. Thus frequent liver enzyme monitoring is necessary.[24] [Level 1]

Review Questions

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