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Cannabidiol in Drug-Resistant Epilepsy and Beyond

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Since ancient times, products derived from the *Cannabis* plant have been used for medicinal purposes, mainly in Asia.[1] In India, they were traditionally employed to treat conditions such as pain, insomnia, epilepsy, inflammation, fever, skin diseases, and gastrointestinal disorders. Similarly, in China, cannabis was used for ailments like arthritis, gout, and malaria. Through cultural exchanges, trade, and warfare, these medicinal practices spread to other parts of the ancient world. Recently, there has been a reemerging interest in the medical applications of cannabis, fueled by advancements in research and a growing understanding of its potential therapeutic benefits.

The *Cannabis sativa* plant produces more than 100 cannabinoids, with cannabidiol (CBD) and delta-9 tetrahydrocannabinol (THC) being the two major ones. THC is a psychoactive compound that directly interacts with CB1 cannabinoid receptors in the brain, producing effects such as euphoria and hallucinations, which contribute to its high addictive potential. In contrast, CBD is nonpsychoactive and does not induce euphoria, making it a safer option for medical use. While the precise mechanism of action of CBD in epilepsy is not fully understood, it is believed to work by modulating intracellular calcium (Ca^{2+}) mobilization and influencing adenosine-mediated signaling pathways.

Different variants of the *C. sativa* plant produce varying concentrations of CBD and THC during extraction. For medicinal purposes, CBD products should ideally contain less than 0.3% THC. Variants of the *Cannabis* plant with such low THC levels are classified as hemp. The production of pharmaceutical-grade CBD involves a rigorous manufacturing process, including extraction from hemp, multi-step purification, and precise measurement of CBD and THC concentrations. These steps ensure batch-to-batch consistency, purity, and safety. While much attention is given to THC levels in CBD formulations, the potential health effects of other cannabinoids present in these products are often overlooked. Further research is needed to understand the broader implications of these additional cannabinoids on patient outcomes.

Due to the high cost of pharmaceutical-grade CBD, cheaper alternatives are available in the market as over-the-counter (OTC) CBD products. However, these OTC products often lack standardized manufacturing practices, leading to inaccurate labelling of CBD and THC concentrations. Significant batch-to-batch variations in CBD and THC content pose challenges to consistent efficacy and may increase the risk of adverse effects. Additionally, these OTC products may contain harmful contaminants, such as pesticides and heavy metals, further compromising their safety and reliability. These issues underscore the importance of using rigorously tested and regulated CBD formulations to ensure both efficacy and patient safety.

In 2018, the U.S. Food and Drug Administration (FDA) approved Epidiolex, a CBD product manufactured by GW Pharmaceuticals, for the treatment of specific drug-resistant epilepsy syndromes in patients aged 1 year and older. Epidiolex is exclusively available as an oral liquid formulation in sesame seed oil, with a concentration of 100 mg/mL. The recommended starting dose of Epidiolex is 2.5 mg/kg twice daily (5 mg/kg/day), which can be gradually titrated to 5 mg/kg twice daily (10 mg/kg/day). The maximum dose is 20 mg/kg/day, depending on patient response and tolerability.

Current evidence suggests that CBD may be effective in treating specific drug-resistant childhood epilepsy syndromes, such as Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex, which often respond poorly to traditional antiseizure medications. Randomized controlled trials have demonstrated a 40 to 50% median reduction in seizure frequency among Epidiolex-treated patients, surpassing the placebo efficacy by at least

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twofold or more.[2–6] However, the majority of patients continue to use CBD as an adjunctive therapy alongside ongoing antiseizure medications, as complete seizure freedom is achieved in only a small subset of patients.[7,8]

A recent randomized clinical trial investigating transdermal CBD gel application in adults with focal epilepsy did not show significant efficacy compared to placebo but confirmed the treatment's safety and tolerability.[9] These findings underline the need for further research to explore the potential of CBD across different formulations, populations, and epilepsy subtypes.

Drowsiness, lethargy, diarrhea, loss of appetite, and weight loss are among the common adverse effects observed with CBD use.[10,11] Drug interactions with CBD can be a significant concern, particularly for patients on polytherapy. CBD has been shown to increase plasma levels of medications such as clobazam, brivaracetam (but not levetiracetam), topiramate, zonisamide, and certain antidepressants, which may exacerbate drowsiness and other adverse effects when used concomitantly.

A synergistic interaction between CBD and clobazam has been suggested, with some attributing CBD's efficacy in part to the increased plasma levels of N-methylclobazam. However, the potential for adverse effects remains a concern. There is also a risk of liver toxicity associated with CBD, particularly when combined with sodium valproate or other hepatotoxic drugs. Some patients may develop asymptomatic transaminitis, which is usually reversible upon drug withdrawal. Therefore, periodic monitoring of liver function tests is strongly recommended, and dosage adjustments are necessary for patients with impaired liver function.[10,11]

While CBD has been shown to be generally safe for short- and medium-term use, the long-term effects on children's brain development and mental health remain unclear. There are ongoing concerns that cannabinoids, including CBD, may contribute to mental health issues such as schizophrenia, although further research is needed to establish causality.

More recently, pharmaceutical-grade CBD in oral liquid formulation has been approved in India for the same indications as the U.S. FDA. Until more data, evidence, and clinical experience become available, CBD should be prescribed judiciously and strictly for approved indications. The use of CBD in an open-label manner for other drug-resistant epilepsy cases beyond the currently approved indications is not supported by evidence at this time. In India, while the cost of locally available CBD is significantly lower than international prices, it remains substantial, particularly when combined with the expense of other ongoing antiseizure medications. This economic burden further underscores the need for careful consideration before prescribing CBD.

In addition to epilepsy, CBD is being explored for its potential role in managing conditions such as chronic pain, spasticity, anxiety, depression, cancer palliative therapy, and dementia. While preliminary findings are promising, more rigorous, high-quality research is necessary to establish its efficacy and safety in these areas. A significant concern with the widespread availability of CBD in the market is its open-label use, often lacking adequate regulation and oversight. Until robust scientific evidence supports its use, prescribing CBD for nonapproved indications should be approached with caution.

To conclude, CBD has demonstrated proven efficacy and an acceptable safety profile in selective patients with drug-resistant epilepsy caused by Dravet syndrome, Lennox–Gastaut syndrome, and tuberous sclerosis complex. Ongoing research aims to extend this evidence to other etiologies of drug-resistant epilepsy and explore its potential in expanded neurological and nonneurological indications. However, despite the enthusiasm surrounding CBD as a potential "magic bullet" for epilepsy, it should be regarded like any other antiseizure medication—evaluated critically for its efficacy and safety. A nuanced and balanced approach is essential, carefully weighing its benefits against potential long-term risks before considering its use in patients.

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Conflict of Interest
None declared.

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