VIEWPOINT

Leading the Next CBD Wave—Safety and Efficacy

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Cannabidiol (CBD), a phytocannabinoid with potential medicinal properties, has recently hit all levels of society with tidal wave force that very few saw coming. After being virtually unknown by most people not even a decade ago, CBD is now in the general lexicon with numerous companies riding the CBD wave: more than 1000 products are being sold through the internet, dispensaries, pharmacies, large national retail stores, boutique shops, and local bodegas. This, along with extensive media coverage, has made CBD a household name and spawned an international business with an estimated market value of more than $60 billion within the next few years.

Despite the growing CBD wave in society, it is clear that scientists, physicians, and the government were not prepared for the huge explosion of CBD use. The initial few scientists and clinicians interested in studying CBD faced regulatory roadblocks owing to its status as a schedule 1 drug. As such, there are today only approximately 21 published clinical studies investigating CBD alone (not in combination with Δ^9-tetrahydrocannabinol [THC], such as Savitex). The disorders span anxiety, cannabis use disorder, Crohn disease, diabetes, epilepsy, graft vs host disease, Huntington disease, opioid use disorder, Parkinson disease, and schizophrenia/psychosis. Several open-label studies have also been conducted in relation to autism, cancer, pain, and sleep. Of these, CBD has received US Food and Drug Administration approval only for treating 2 rare and severe forms of childhood epilepsy (Dravet syndrome and Lennox-Gastaut syndrome).[1] Despite such limited clinical studies, CBD has been widely touted as a wonder drug to treat a multitude of disorders and symptoms. Yet, governmental regulations have been slow to respond to the marked increase of CBD use. This continues to play out in conflicting governmental polices enacted federally (where CBD extracted from cannabis is illegal) and in many states (where CBD is legal for medicinal and/or recreational use). So, the major question finally now being asked is whether CBD is hype or if there is true medicinal potential.

CBD, a Nonintoxicating Cannabinoid

CBD is 1 of approximately 140 cannabinoids identified in the cannabis plant. The highest CBD/THC ratio is found in hemp strains, which are defined as containing less than 0.3% THC. The full mechanism of CBD's pharmacologic actions is still being investigated. What is clear is that CBD does not bind strongly to the endogenous cannabinoid type 1 and type 2 receptors. This is in contrast to THC, the main psychoactive component of cannabis. Instead, CBD might function as a negative allosteric modulator at the cannabinoid receptor, thus having inhibitory effects. CBD also appears to be a competitive antagonist at the G protein–coupled receptor 55 highly expressed in the brain and periphery. Moreover, it has broad actions on multiple systems, such as modulating opioid, serotonin, and adenosine transmission.[2] CBD's modulatory actions on these diverse biological systems would be expected to affect multiple functions including anxiety, cognition, inflammation, mood, and nociception.

Interestingly, the CBD explosion has revolved heavily around mental health issues. The general claims of CBD leading to homeostatic well-being stems in part from initial studies indicating that CBD could have anxiolytic properties.[2] Anxiety is a core component of many psychiatric disorders and a common reaction to the high-stress conditions in society today. This has also recently spawned new marketing of CBD with low THC levels as light cannabis in attempts to promote a so-called healthier version of the normal high-THC cannabis. CBD is not the generic cannabis, and a clear distinction must be made between the two. In contrast to THC, CBD is nonpsychomimetic and has been demonstrated to reduce psychosis.[3] Moreover, compared with THC, CBD is nonaddictive. Indeed, CBD has been shown to have beneficial properties that could help to alleviate addiction, such as reducing craving in individuals with opioid use disorders.[4]

CBD Safety

Although CBD has been implicated in a large spectrum of biological effects, a consistent finding in clinical studies is that it is safe, generally well tolerated, lacks toxicity, and is nonintoxicating with no reinforcing properties. The daily dose range mainly studied is approximately 100 to 600 mg (normally taken orally), but doses even up to 6000 mg investigated in healthy individuals resulted in no severe effects.[5] The most notably adverse events are gastrointestinal including diarrhea with none being severe. However, increased liver enzymes have been reported in combination with antiepileptic medication in children.[1] Still lacking are systematic studies to determine whether, for example, general safety extends beyond oral routes of administration or how CBD may interact with medications that are metabolized by the same cytochrome P450 enzymes as CBD, which could affect the therapeutic levels of each drug.

While CBD used for research has been shown to have a safe profile, CBD sold in various commercial products is not always safe. Pesticide, mold, lead, and other adulterants including even synthetic cannabinoids, which induces marked psychosis, have been detected in products.[6] An unregulated CBD market poses a significant threat to public health. At a minimum, products should have proper manufacturing control, standardized testing, and accurate labeling of the contents supported by clear evidence of such quality controls. Wherever CBD is presented as a health benefit, we must ensure that existing rules and regulations are followed.

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Large-Scale Efficacy Clinical Trials

The development of CBD as medicine requires that it follows the established pipeline by which medications are normally developed with placebo-controlled double-blinded clinical trials. Should it take 20 years within such a pipeline before CBD medications are approved? No. New fast-track Food and Drug Administration models that in part mirror those currently in place for rare disorders provides a pathway. This will urgently give patients and physicians the critical information needed to guide treatment and safety concerns essential for addressing the already widespread use of CBD. The fact that the US Drug Enforcement Administration has moved CBD in the form of Epidiolex to a schedule V drug is an important step. So too is the Farm Act of 2018 that changed the status of CBD derived from hemp from schedule I to a regular agricultural commodity that is unscheduled.[7] However, chemically, CBD is CBD, and clinical trials with pure CBD extracted from cannabis are still handcuffed, limiting the potential to better inform health risk/benefits.

Another critical path toward greater evidenced-based research is the collaboration between legitimate companies and researchers that is important for developing appropriate medicinal formulations and routes of administration best suited for targeted medical indications. Such collaborations can help address challenges such as the fact that CBD, like most cannabinoids, has a low bioavailability when taken orally owing to extensive first-pass metabolism. Novel delivery and formulation strategies often require partnerships with industry.

The Next Wave

This next wave of large-scale clinical trials is essential for patients and families who are desperate for new treatments and thus are now part of the CBD frenzy. This is particularly critical for individuals with psychiatric disorders for which there has been a virtual drought for decades of new medicines that has contributed to the CBD self-medication without waiting for sound clinical guidance and Food and Drug Administration approval.

Success in the next wave requires a true sense of urgency in forming partnerships between scientists, clinicians, government, industry, and patients. Together, they will develop the strategic roadmap required for the success of large-scale evidence-based clinical trials. This will lead to critical policy changes and improved health outcome.

ARTICLE INFORMATION

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