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REVIEW ARTICLE

Emerging Cannabidiol Research in Neurological Disorders: Insights into Epilepsy, Multiple Sclerosis, and Depression

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ABSTRACT: The cannabis plant contains 100+ distinct cannabinoids, and the two most researched are cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC). Cannabinoids offer new treatment options for neurological disorders and their symptoms, including epilepsy, multiple sclerosis (MS), and depression. This review summarizes the recent findings in evaluating the therapeutic potential of CBD in various neurological disorders, such as epilepsy, MS, and depression, and the mechanisms behind its anticonvulsant, anti-inflammatory, and analgesic properties. CBD significantly reduces epileptic seizures in children and young adults with only mild side effects. In MS, studies on the therapeutic potential of cannabinoids have shown mixed results due to limitations in study design or other sources of variability, but they suggest that a combination of CBD and THC can reduce spasticity. In depression, higher doses of CBD appear beneficial and well tolerated, yet individual differences among patients and the limited number of clinical trials indicate that further research is needed to better understand these effects.

KEYWORDS: Biomedical and Health Sciences, Immunology, Cannabidiol, Epilepsy, Multiple Sclerosis (MS), Depression.

Introduction

Progress has been made in the exploration of the medicinal use of cannabis in humans. In particular, there has been promising evidence that cannabis could treat the symptoms of neurological disorders, including epilepsy, MS, Parkinson's Disease, Huntington's Disease, Autism Spectrum Disorder, and Complex Motor Disorders.[1] For example, a prominent single-case study of a girl named Charlotte, who was diagnosed with SCN1A-confirmed Dravet Syndrome, provided evidence that CBD administration may significantly decrease the number of epilepsy seizures. By month three of high-concentration CBD extract, Charlotte had a >90% reduction in tonic-clonic seizures. The term "Charlotte's Web" gained recognition following its use in her case, contributing to the popularization of medical marijuana for seizures.[2] The use of cannabis has doubled in the last 20 years, with medical use rising between 2013 and 2020 in the United States, where the plant is widely legalized or decriminalized, emphasizing the need to expand our research on the medicinal use of cannabis.[3] The present review aims to analyze and examine the potential of cannabinoids in treating neurological disorders, focusing on future research and therapeutic applications. As the medical use of cannabis products continues to grow in the United States, more people are becoming interested in its medicinal effects.

Cannabis, also commonly called marijuana or weed, refers to a type of plant that can produce psychoactive effects when consumed.[4] Cannabis is also a diverse plant genus known for its industrial purposes and medical compounds, with a long history of human use. This family of plants consists of three distinct species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*, all of which have psychoactive effects.[5] CBD and THC are both natural compounds synthesized in cannabis and identified as phytocannabinoids with similar chemical structures. Phytocannabinoids are mainly present in the trichomes of female cannabis plants, while male leaves produce less psychoactive substances. Both THC and CBD are biosynthesized in the plant from olivetolic acid, which is converted to cannabigerolic acid (CBGA) by the enzyme CBGA synthase using geranyl diphosphate as a substrate. CBGA is the central precursor of Δ9-THCA and CBDA. The two acids are then decarboxylated (neutralized) into their neutral forms, THC and CBD.[6] THC serves as the primary psychoactive component in cannabis, while CBD does not induce euphoria. Compared to THC, CBD's flexible structure with a free-moving hydroxyl group and open-ring conformation allows it to adopt multiple shapes and interact with many different receptors.[7] (Figure 1) Both THC and CBD have been researched as potential avenues for the treatment of anxiety, depression, sleep apnea, and neurological disorders.[8] Although both compounds have been proposed to act, at least in part, through the endocannabinoid system (ECS), they produce markedly different effects.

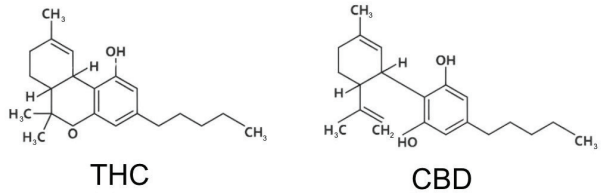

Figure 1: Molecular structures of THC and CBD.

Since THC directly binds to cannabinoid receptors (CB1 and CB2) linked to the brain's reward system or dopaminergic pathway, the substance induces psychoactive effects. Thus, it can also cause adverse events such as paranoia and hallucinations if consumed in excess.[9] However, since CBD interacts with the ECS by indirectly influencing the CB1 and CB2 receptors rather than binding directly to them, it has less se-

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vere effects when consumed. CBD exhibits a low affinity for cannabinoid receptors and seems to exert its therapeutic effects in other sites. It interacts with ion channels to exert anticonvulsant effects, modulates cyclooxygenase and lipoxygenase enzymes to produce analgesic outcomes, targets the periaqueductal gray area to mediate antinociceptive responses, and engages 5-hydroxytryptamine 1A (5-HT1A) receptors to facilitate anxiolytic effects.[10] The mechanisms behind the interaction between ECS, THC, and CBD are discussed in the neurochemistry section. CBD is recognized for its antiepileptic, anti-inflammatory, antioxidant, and analgesic properties, making it a promising therapeutic agent for neurological and inflammatory conditions such as multiple sclerosis (MS), Dravet syndrome, Lennox-Gastaut syndrome, Parkinson's disease, post-traumatic stress disorder (PTSD), fibromyalgia, and other disorders associated with dysregulated immune responses. The therapeutic effects of CBD are thought to be mediated through multiple pathways that include modulation of the endocannabinoid system as well as actions at non-ECS targets such as ENT1–A2A adenosine signaling, GPR55, TRPV1, and 5-HT1A receptors.[11]

The History of Cannabis Use:

Originally from Central and Southeast Asia, the cannabis plant has been used for centuries for entheogenic and religious purposes, as well as in traditional medicine. Early historical records indicate its application in ancient China for alleviating rheumatic pain, fatigue, and inflammatory conditions, and its use in textile manufacturing.[12] In ancient Rome, the Roman historian Pliny recorded the use of *Cannabis sativa* roots for relieving pain. In India, it has been revered as a sacred plant for both medicinal and spiritual purposes since approximately 1000 BCE, subsequently disseminating through Persia, Europe, and the Americas.[13] During the 19th and early 20th centuries, cannabis began to be acknowledged in Western medicine, with notable contributions from individuals such as William B. O'Shaughnessy and Jacques-Joseph Moreau. Both experimented with their patients and demonstrated that the plant had analgesic and anticonvulsant properties. However, its popularity diminished due to ethical and economic issues, leading to the International Drug Control Treaty in 1925 followed by the Marijuana Tax Act in the U.S. in 1937.[14] Variable efficacy among patients, the emergence of alternative medications, and increasing legal restrictions—partly due to rising recreational use—contributed to its removal from the U.S. Pharmacopeia in 1941.[15] Many experimentations involving the medicinal use of the drug were terminated accordingly.

Despite the challenges, a resurgence of interest occurred in the late 20th century following the clarification of THC's chemical structure by the scientists Yehiel Gaoni and Raphael Mechoulam.[16] The finding was then followed by the discovery of cannabinoid receptors and the identification of endocannabinoids, which sparked renewed scientific exploration into their medicinal applications.

Neurochemistry and Mechanisms of Cannabis/Cannabinoids/ECS:

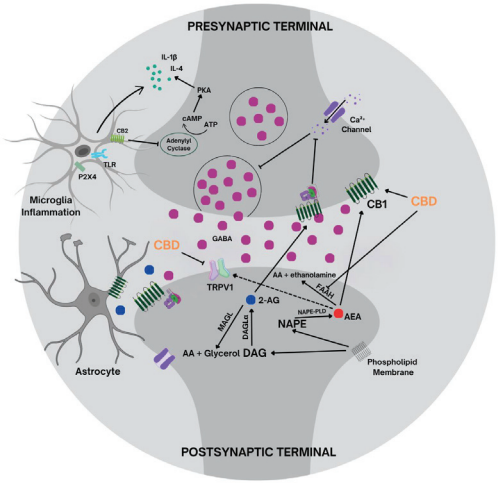

Figure 2: Molecular mechanisms of CBD on cannabinoid signaling pathways in the ECS. These interactions could take place not only at GABAergic synapses but also at other neurotransmitter synapses, such as those involving glutamate. Cannabinoids act on CB1 and CB2 (GPCRs) as well as other non-cannabinoid signaling pathways that are involved in neuroinflammation. CBD promotes the desensitization of TRPV1 channels and the modulation of neurotransmission. Through these interactions, CBD affects neuroinflammatory and excitatory processes associated with epilepsy and MS.

ECS serves as a regulatory system that maintains homeostasis within the body by activating various physiological processes, including pain perception, emotional regulation, appetite control, and memory function.[17] This system operates through endogenous cannabinoids, N-arachidonoylethanolamine (AEA), and 2-arachidonoylglycerol (2-AG), which act as ligands on CB1 and CB2 cannabinoid receptors. CB1 receptors are G protein-coupled receptors (GPCRs) that, for the most part, are located on neuronal terminals of the brain cells, whereas CB2 receptors are primarily associated with the immune system.[18] 2-AG is synthesized from diacylglycerol (DAG) by diacylglycerol lipase-α (DAGLα), and AEA is formed from N-acyl-phosphatidylethanolamine (NAPE) by NAPE-specific phospholipase D (NAPE-PLD). AEA and 2-AG are synthesized depending on membrane phospholipid precursors through activity-dependent activation of specific phospholipase enzymes. 2-AG crosses the postsynaptic membrane and binds to the CB1 receptors located in the presynaptic membrane. Activated CB1 receptors are responsible for the suppression of neurotransmitter release by inhibiting voltage-gated Ca2+ channels, which reduce presynaptic Ca2+ influx, and by coupling to Gi/o proteins.[19] The coupling inhibits adenylyl cyclase, which reduces the production of cyclic adenosine monophosphate (cAMP) and activation of protein kinase A (PKA) subsequently. Reduced PKA activity decreases the phosphorylation of proteins involved in neurotransmitter release. 2-AG is degraded by the monoacylglycerol lipase (MAGL) and, to a lesser extent, by alpha/beta domain-containing hydrolase 6 and 12 (ABHD6,12). On the other hand, AEA mainly activates membrane-bound receptors, including CB1 and transient receptor potential vanilloid 1 (TRPV1).[20]

TRPV1 increases its sensitivity during neuroinflammatory conditions, and CBD acts as a full agonist for TRPV1, desensitizing the channel and reducing neuronal hyperexcitability.[21] The system also involves astrocytes, which are specialized glial cells, as they produce 2-AG when CB1 receptors are activated[22] (Figure 2).

CBD and THC can both alleviate pain, but they do so through distinct mechanisms involving different cannabinoid receptors. THC acts as a partial agonist of CB1 receptors, which inhibits the release of neurotransmitters including glutamate, GABA, acetylcholine, and serotonin (5-HT) when activated. The inhibition causes excessive dopamine release due to a reduction in the release of inhibitory neurotransmitters like GABA in areas such as the ventral tegmental area. This leads to increased dopamine release in the nucleus accumbens, a key reward center in the brain, and induces a high.[23] Likewise, the inhibition of excitatory neurotransmitters like glutamate reduces the transmission of pain signals, indirectly reducing pain. On the contrary, CBD works as a negative allosteric modulator on the CB1 receptor, reducing the euphoric effects of THC.[24] (Figure 2) CBD can alleviate neuropathic pain by indirectly activating CB2 receptors through the elevation of endocannabinoid levels. CB2 receptors are mainly located in immune cells and the spleen. Their expression is limited under normal physiological conditions but increases in response to reactive (proinflammatory) microglia after inflammation or injury. Reactive microglia induce the expression of Toll-like receptors and purinergic P2X4 receptors, subsequently leading to the production of inflammatory cytokines and chemokines that may contribute to neurodegenerative diseases. The stimulation of the CB2 receptors inhibits the neuroinflammatory signaling pathways by a negative feedback mechanism and promotes the return of microglia to a homeostatic, anti-inflammatory state.[25] CB2 receptors can improve inflammation by modulating various immune cells, such as eosinophils, macrophages, neutrophils, and lymphocytes.[26]

Since 2-AG also serves as a major source of arachidonic acid, its breakdown by MAGL links the endocannabinoid system to pro-inflammatory eicosanoid production. Thus, inhibition of MAGL by JZL184 reduces arachidonic acid availability and consequently decreases the synthesis of pro-inflammatory mediators.[27] CBD also competes with AEA to indirectly reduce neuropathic and inflammatory pain by binding to fatty acid amide hydrolase (FAAH), as shown in Figure 2. FAAH is an enzyme responsible for AEA degradation. This results in elevated levels of AEA that could interact with CB2 receptors and enhance the modulation of pain perception and neuroinflammation. Additionally, CBD shows strong anti-inflammatory effects by increasing adenosine signaling responses. This is induced because CBD blocks the equilibrative nucleoside transporter 1, which usually removes adenosine from the extracellular space. By preventing this uptake, CBD increases extracellular adenosine levels, leading to greater activation of A2A adenosine receptors on immune cells and a subsequent reduction in pro-inflammatory mediators such as TNFα.[28] Also, CBD acts as an antagonist of the lipid-activated receptors, GPR55s, which are in both inhibitory and excitatory neurons of the hippocampus. By blocking GPR55, CBD restores the balance between excitation and inhibition by increasing the excitability of inhibitory interneurons and reducing excitatory.[29] The mechanism is especially important in seizure conditions such as Dravet syndrome.

Methods

This review aims to analyze recent clinical trials to assess CBD's potential in treating symptoms of epilepsy, MS, and depression. A literature search was conducted to compile a list of clinical trials where researchers evaluated the efficacy of CBD in these various neurological disorders. A search for relevant literature was conducted in PubMed with a focus on papers published in the last 15 years, by searching the keywords cannabinoids, epilepsy, multiple sclerosis, depression, entourage effect, and clinical. This method yielded 9 relevant papers, and the papers were categorized together based on their relation to similar cases. There are three groups for analysis: multiple sclerosis, epilepsy, and depression. They were research publications freely accessible to the public. Diagrams (Figure 1 and Figure 2) showing the molecular structure of CBD and its mechanisms within the endocannabinoid system were created by the author using Canva to visually provide key signaling pathways. Furthermore, a comparative analysis of similar articles was performed, identifying both consistencies and inconsistencies between the data to examine potential differences in interpretations or methodological limitations. CBD appears to be a promising treatment for epileptic seizures and MS spasticity, as different trials demonstrate its effectiveness in reducing neuroinflammation and activities of pro-inflammatory cytokines such as interleukins (IL-4, IL-5, IL-13, and IL-1β). Although clinical trials are limited, CBD additionally exhibits antidepressant-like effects. Furthermore, this paper explores the boundaries of contemporary research and speculates on the methodological improvements for future studies on CBD.

Results and Discussion

1. CBD and Epilepsy:

Many existing studies have successfully proven the efficacy of CBD in reducing epileptic seizures.[30] Epilepsy is a chronic neurological disorder accompanied by severe seizures. There are different types of seizures, such as tonic (sudden muscle stiffness or tension) and tonic-clonic seizures (a loss of consciousness and muscle contractions). Due to ethical reasons, CBD experiments are typically conducted with subjects with Drug-resistant epilepsies such as Lennox-Gastaut Syndrome, Dravet Syndrome, and Tuberous Sclerosis Complex, who are mostly already treated with a variety of antiepileptic medications. The optimal dosage of CBD varies, considering CBD's interaction with other drugs. Data generated from 39 randomized clinical trials and 13 meta-analyses suggest the optimal dose of purified CBD oral solution to be 20 mg/kg/day in children and adolescents with Drug-resistant epilepsies.[31] A pharmacokinetic study concluded that CBD was shown to reduce seizure frequency in both children and young adults with epilepsy. Key findings included higher doses of CBD resulting in greater seizure reduction, and CBD reached its steady state

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after approximately 2–6 days of treatment.[32] Although CBD is well tolerated overall, it has adverse events such as diarrhea, somnolence, decreased appetite, and alanine transaminase or aspartate aminotransferase elevation.[33]

Since most human clinical trials testing CBD involve participants whose symptoms are not relieved through current therapy, it is important to understand drug-drug interaction in these subjects and the use of CBD as an adjunctive treatment. Another meta-analysis demonstrated the high efficacy of CBD treatment in reducing seizures, compared with the placebo, 10, 20, and 50 mg/kg/day being the most effective doses.[34] Moreover, the study stated that CBD as adjunctive therapy in the co-administration of clobazam showed a greater reduction in seizure therapy. Clobazam is mostly used to treat LGS and DS. When administered, clobazam is biotransformed into the active metabolite N-desmethylclobazam. The cytochrome CYP2C19 plays a role in the metabolism of N-CLB, transforming it into an inactive compound. CBD inhibits the function of CYP2C19, significantly increasing the concentration of N-CLB in plasma. N-CLB can bind to GABA-A receptors, increasing GABA to reduce seizures.

There are several other conventional anti-seizure medications, including valproate, steroids, ACTH, baclofen, tizanidine, and clonazepam, that could interact with CBD. Co-administration of valproate and CBD could increase liver enzyme levels, requiring monitoring of liver function.[35] A mouse model suggested that CBD may inhibit p-glycoprotein and increase topiramate levels.[36]

Most clinical trials investigating the effects of CBD on epilepsy primarily focus on young infants, children, or young adults, leaving a gap in research on older adult populations. Age differences play a crucial role in CBD's pharmacokinetics and pharmacodynamics. Therefore, understanding how CBD interacts with anti-seizure medications in older adults with Drug-resistant epilepsies remains an important area for future research.

2. CBD and Multiple Sclerosis:

Another major neurological disorder for which CBD shows great potential in treatment is MS spasticity. MS is characterized as a neuroinflammatory disease associated with demyelination and autoimmune responses.[37] There is still a lack of clinical trials testing CBD on patients with MS, and it is crucial to investigate individual variability considering genetic and environmental factors. Nine disease-modifying therapies are available for relapsing-remitting MS, including interferons, glatiramer acetate, teriflunomide, sphingosine 1-phosphate receptor modulators, fumarates, cladribine, and 3 types of monoclonal antibodies. One additional therapy, ocrelizumab, is approved for primary progressive MS.[38] CBD does not treat the disease itself but alleviates spasticity similarly to baclofen, tizanidine, gabapentin, pregabalin, serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, dantrolene, and benzodiazepines.[39]

MS spasticity is mostly measured by the spasticity numerical rating scale (NRS), a 0-10 self-reported rating. Modified Ashworth Scale, ranging from 0-4, is also used to evaluate the spasticity of MS patients. Common adverse events of CBD usage in MS are mouth dryness, fatigue, headache, dizziness, loss of appetite, and stomachache.

The ongoing CANSEP trial is the first Canadian randomized clinical trial that investigates the safety and efficacy of CBD in adults with MS. The primary outcomes are measured using the mean Numeric Rating Scale, which scores from 1 to 10, assessing spasticity reduction. Secondary outcomes are measured through various clinical assessments such as the Mean Opinion Score Pain Effects Scale, Modified Ashworth Scale, Pittsburgh Sleep Quality Index, and Epworth Sleepiness Scale. These tests aim to document any AEs experienced by the participants. CANSEP's objective is to compare the distinct and combined effects of THC and CBD, provided in the form of softgels manufactured by PurCann Pharma, by administering varying dosages of each drug.[40]

There have been inconsistent findings of CBD use on multiple sclerosis across various studies. For example, a randomized, double-blind, placebo-controlled trial in Denmark indicated no significant difference between the placebo group and those receiving active treatment with either oral THC (max. Dose 22.5 mg/day) or CBD (max. Dose 45 mg/day) alone or in combination for treating neuropathic pain and spasticity.[41] In this study, cannabis-based medicine was an add-on to patients' ongoing treatment with analgesics and antispastic medicine. However, the study did confirm that the CBD group experienced fewer adverse events compared to the THC treatment groups, and the cannabis-based medicine had a small effect on neuropathic pain and spasticity.

On the contrary, a systematic review article examining the effects of add-on nabiximols, also known as Sativex, consisting of 27 mg THC and 25 mg CBD per ml, has confirmed its efficacy in alleviating spasticity. The review evaluated its efficacy across seven criteria: results from placebo-controlled trials, both short-term and long-term treatment outcomes, gait improvement, the Modified Ashworth Scale, sleep disturbance, the Barthel Activities of daily living, and the Subject Global Impression of Change. Except for the Modified Ashworth Scale and Barthel Activities of Daily Living, significant differences in the response rates were observed, underscoring the efficacy of nabiximols as an adjunctive treatment for symptomatic relief in MS spasticity and other related symptoms such as gait control, sleep disturbance, and a feeling of improvement.[42] Because the Barthel Activities of Daily Living reflects overall functional independence rather than spasticity specifically, improvements in spasticity may not correspond to significant changes in Barthel ADL scores. In patients with multiple sclerosis, motor dysfunction from the underlying disease already influences daily motor function and thereby the Barthel Index, which may explain why several trials reported no improvement or even worsening scores despite treatment.

Nonetheless, both studies have limitations for consideration. The Danish trial indicates that a higher dose of CBD, which could be well tolerated, could show potential in treating spasticity, while the oral formulation of these drugs has low bioavailability. There are several ways to improve the bioavailability of CBD: lipid-based formulations, which are consumed

with fats (sesame oil and coconut butter), polymeric encapsulation of CBD in Poly Lactic-co-Glycolic Acid (PLGA), structural modification of CBD with cyclodextrins, or modified carbohydrates.[43] Future clinical settings testing the efficacy of each method are essential in optimizing CBD formulations. Interestingly, the Danish trial suggested that, except for the THC and CBD treatment for spasticity, the maximal possible effects were clinically insignificant. This is consistent with the observations made by Kleiner *et al*. (2023) as nabiximols contain both THC and CBD. However, the presence of THC was associated with a higher frequency of adverse events among patients.

3. CBD and Depression:

A person is diagnosed with depression when they experience a persistent depressive mood and loss of interest in activities. Patients with depressive disorder take antidepressant medications such as fluoxetine (Prozac), citalopram (Celexa), and escitalopram (Lexapro). Despite the available antidepressant pharmacological options, there are limitations of existing treatments, as sometimes patients develop resistance to drugs like Selective Serotonin Reuptake Inhibitors. Therefore, it is important to explore alternative therapeutic agents that present fewer or no adverse events.

Antidepressant-like effects induced by CBD in the forced swimming test in mice substantiated its dependency on serotonin levels in the central nervous system. The forced swimming test is often used to test the efficacy of antidepressant drugs by measuring the time until the subject becomes immobile, which implies behavioral despair and helplessness. The co-administration of CBD with serotonergic (fluoxetine, FLX) (a type of Selective Serotonin Reuptake inhibitor) resulted in elevated serotonin levels, which correspondingly reduced the duration of immobility observed in the test. CBD's mechanism appears to involve enhancing serotonin neurotransmission and activating postsynaptic 5-HT1A receptors, supported by evidence that serotonin depletion (para-chlorophenylalanine treatment) prevents its antidepressant effects.[44] This data suggests that CBD may offer an alternative to classical antidepressant medication.

One common symptom of depression is anhedonia, or a lack of interest or pleasure in activities that were enjoyed.[45] To evaluate the effects of CBD on depressive-like Wistar-Kyoto (WKY) rats, 30 mg/kg of oral CBD was administered to these animals and they were assessed using Saccharin Preference Test, which measures the animal's preference for saccharin and ability to experience pleasure, and the Novel Object Exploration test which demonstrated increased exploration of the novel object and locomotion at a dosage of 45 mg/kg and increased locomotion at 15 mg/kg. Prohedonic effects were observed in both tests, further suggesting that CBD provides antidepressant-like effects. However, effective doses of CBD in WKY rats varied, reflecting underlying individual variability in the optimal dose required for specific treatment.[46]

One potential explanation of the antidepressant effects of CBD is that CBD interacts with serotonin (5-HT1A) receptors, CB1, G-protein coupled receptor 55 (GPR55), and PPAR-γ. It is essential to recognize the mechanisms behind the antidepressant effects of CBD, as there are few available human clinical trials, and depression is largely dependent on individual differences. A randomized, double-blind, placebo-controlled trial substantiated CBD's antidepressant effects in 31 treatment-resistant young individuals (12-25 years) and found a reduction in mean scores using the Overall Anxiety Severity and Impairment Scale (OASIS).[47] However, contradictory results were seen in bipolar depression by a randomized, double-blind, placebo-controlled pilot study, as there was no significant difference in Montgomery-Asberg Depression Rating Scale (MADRS) scores between the placebo and CBD groups.[48] The inconsistent reports may be partly explained by the different scalings and subtypes of depression implemented by each study. Even though many preclinical studies provided strong evidence for the antidepressant properties of CBD, there are only a handful of clinical studies that explore the primary outcomes of CBD on depression in limited age groups. This points to an urgent need for more studies, especially longitudinal, to allow the development of better treatment strategies for subjects with depression. Additionally, clinical studies on depression advocate higher CBD doses (usually 600 mg/day) as they come with fewer side effects and are well-tolerated.

Another emerging cannabinoid-related therapeutic effect in conditions like depression and anxiety is the "entourage effect." It suggests that the combined presence of terpenes and cannabinoids enhances the overall therapeutic effects beyond what each component could achieve separately. This concept was first proposed by Mechoulam and Ben-Shabat, and this introduced the synergy between cannabinoids and terpenes to maximize pharmacological benefits.[49] Several reviews confirmed this cannabis synergy and supported botanical drug development.[50,51] A study explored the entourage effect by showing that acute *Cannabis sativa* L. leaf extract (THCA, CBCA, β-caryophyllene, α-humulene, limonene, etc.) induced an antidepressant-like effect in depressive rodent models. Furthermore, *Cannabis sativa* L. leaf extract and inflorescence extracts (THCA, CBCA, CBGA, myrcene, limonene, β-caryophyllene, etc.) demonstrated anti-inflammatory effects by decreasing the expression of inflammatory mediators and pro-inflammatory cytokines.[52] Thus, further future clinical studies of the entourage effect are necessary to optimize cannabis appliances containing mixtures of terpenes.

4. Future Directions:

CBD is shown to significantly reduce epileptic seizures in children and young adults and is well-tolerated with mild adverse events such as diarrhea, decreased appetite, and somnolence. Drug-drug interactions are also important in their effectiveness, and seizure frequency seems to decrease even more when CBD is used in combination with clobazam. Thus, it is necessary to explore the positive or negative impact of CBD in combination with other first-line epilepsy medications. Clinical trials examining the use of CBD in elderly populations with epilepsy are still limited and require further attention. Studies investigating the use of cannabinoids in MS

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have shown inconsistent results: one clinical trial reported a reduction in spasticity frequency in MS, whereas the other found no significant differences between placebo and treatment in either spasticity frequency or overall quality of life. Research design limitations may be responsible for such differences, including the use of inappropriate spasticity scaling methods, ineffective administration methods, or different drug formulations. Despite these inconsistencies, both studies suggested that a combination of CBD and THC is effective in reducing spasticity. However, it is important to note that THC-containing formulations are associated with a greater risk of adverse events. Future research should focus on developing testing methods with higher bioavailability to obtain more accurate results. Clinically defining depression is challenging, and severity depends on individuals; therefore, conducting case studies is important to develop personalized treatments for individual patients. Many trials have recommended higher doses of CBD since CBD is well-tolerated, and these higher doses are considered acceptable in clinical use. However, there is still a limited number of trials in testing CBD in depression, highlighting the need for further clinical research.

The integration of CBD into existing neurological treatment options faces challenges, ranging from legal restrictions to research biases and patient-specific responses. Global cannabis regulations create significant barriers, especially in the United States, where CBD's legality varies between federal and state laws. The 2018 Farm Bill legalized CBD with less than 0.3% THC at the federal level, and the Food and Drug Administration (FDA) has approved only one CBD-based medication, Epidiolex, for epilepsy. State-by-state variations in medicinal cannabis policies further complicate clinical access, restricting patient inclusiveness and physician prescriptions. Internationally, there are still countries permitting medical cannabis under strict guidelines or even completely banning cannabis-derived products.

Furthermore, industry-sponsored studies often structure their design, sample selection, and statistical reporting in ways that favor positive outcomes, raising concerns about bias in clinical findings. Additional confounds can arise from individual variability, including differences between cannabis users and non-users, first-line versus adjunctive CBD therapy, duration of consumption, and age. For instance, individuals with psychiatric conditions may experience greater pre-existing symptoms that could overshadow the effects of CBD. Side effects are also more common in cannabis non-users than in cannabis user groups, as well as in older individuals.[53] Product variability also influences the therapeutic effects of CBD. It was found that about 70% of eighty-four CBD products (from 31 companies) ordered online were found to be mislabeled, reflecting discrepancies between the labeled and actual contents.[54] This can discourage them from purchasing these products freely. Lastly, CBD has a non-selective receptor binding profile, which requires further *in vivo* studies to confirm the exact mechanisms of the action of CBD.

The apprehension surrounding the administration of significant quantities of CBD, along with the possibility of severe adverse events, deters patients from engaging in such new treatment options. For example, CBD may be detrimental to the developing embryo, as demonstrated in studies using zebrafish models of early development.[55] Therefore, it is important to research and list possible adverse events under certain conditions and to develop guidelines for CBD use. In preclinical trials, researchers frequently conduct animal studies, predominantly using mice, to evaluate the effects of CBD. Nonetheless, the discrepancies between animal and human subjects, including variations in CBD dosage and neurological architecture, may influence the outcomes in human populations. Therefore, future investigations must incorporate well-designed clinical trials that assess higher doses of CBD while considering individual parameters. Moreover, further research is needed to fully understand the benefits and potential side effects of combining cannabis-based treatments with conventional pharmacological approaches.

Another emerging frontier in cannabis research is expanding knowledge on the other cannabinoids present in the cannabis plant. For example, CBN, co-produced with THC after decarboxylation of Delta 9 THCA, has been shown to serve as a sleep aid. Furthermore, studies into the interactions between the terpenes derived from cannabis leaves and the main cannabinoid components are important, as they may exhibit synergic effects at reduced dosages and associated risks. To do so, the identification of chemical structures and properties of each cannabis component is vital.

■ Conclusion

This paper presents recent clinical trials that evaluate the therapeutic potential of CBD in individuals with epilepsy, MS, and depression, and demonstrate its effects. As the field of CBD research continues to expand, the proposals presented here aim to guide future studies toward discovering broader therapeutic applications of CBD. CBD is effective in reducing epileptic seizures, and its combination with THC may further reduce MS spasticity. Further personalized research is essential to optimize CBD treatment in individuals with depression. Moreover, there are important factors to consider before conducting clinical trials, such as drug formulation, study population selection, detailed evaluation of each subject, outcome measurements, safety and adverse events monitoring, legal considerations, drug-drug interactions, and bias control. Identification of other cannabinoids and terpenes in cannabis plants is crucial for discovering new medications for neurological disorders.

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