Is CBD effective as medicine and when can it be helpful?

Botanical (herbal) medicine is the practice of using medicinal plants and extracts to improve overall health, support wellness, and treat disease. Plants have been used as medicine throughout history and to this day natural plant extracts, natural product-inspired pharmacophores and natural product analogies remain an important source of new pharmaceuticals. Modern researchers generally consider purified chemicals from plants that are promising therapeutically or their synthetic equivalents for natural-product based drug discovery. CBD (cannabidiol) is one such purified chemical that has risen significantly in profile in recent years. Its growing popularity among researchers, patients and casual users alike merits a discussion of its therapeutic promise.

While CBD is becoming increasingly accepted as potentially effective as medicine and the pharmaceutical companies are starting to mount clinical trials to prove the health benefits, people are turning to CBD for improving their health and well-being without waiting for industry approvals. In particular, the interest among older generations is rising. A survey carried out in May 2020 shows that 51% of seniors have seen improvement in their quality of life after using CBD and 89% of them would recommend it for recurring health problems. Are there health benefits or is it merely a hyped miracle cure-all with no real clinical evidence? This paper provides an overview of clinical applications of CBD that are currently under investigation by the pharmaceutical industry and offers some remarks on the future prospects of CBD-based products.

CBD market overview

CBD is used either as a synthetic small molecule (cannabidiol) or high purity natural extracts (e.g. CBD oils). The natural CBD as a low tetrahydrocannabinol (THC) product derived from *Cannabis sativa* plant has been widely acknowledged to be a potentially fruitful area of clinical research for various indications including pain management, inflammatory conditions and rare diseases. Despite many market barriers—from the sparse clinical evidence to the recent regulatory crackdown—CBD products market has become a rapidly growing sector with a remarkably broad consumer offering from clinical use in humans to wellness to veterinary applications. According to Global Market Insights, global CBD market exceeded $2.8b in 2019 and is set to grow at 53% CAGR between 2020 and 2026.

The impressive market size and growth rate propagated a recent explosion in clinical work on CBD as a drug candidate. A recent review **[1]** suggests a favourable safety profile of CBD. However, some areas of CBD safety research—especially on vulnerable population groups—still need to be extended. In particular, longer-term safety data are needed to fully ascertain CBD's benefit-to-harm balance though in some indications the clinical work is well underway.

Pain Management

CBD is a non-euphoriant, anti-inflammatory analgesic with CB_1 receptor antagonist and endocannabinoid modulating effects. As such, it has been approved for medical use as a component of various pain-management drugs (in some of them in combination with THC) in many jurisdictions including USA and Canada since mid-2000s. For example, many multiple sclerosis patients often experience combinations of dysaesthesia, headaches and/or back or muscle and joint pain and anecdotal reports suggest that major cannabinoid components have beneficial effects on pain, particularly neuropathic pain.

More recently, many reviews **[2-5]** agree that cannabis might have a positive effect on pain in MS. In 2010, a CBD:THC oral spray for alleviating neuropathic pain (neuralgia) has gained market approval in the EU (Nabiximols, sold as Sativex® in the UK; GW Pharmaceutical, Cambridge, UK). There is a concern that MS patients, who are more likely to experience impaired cognition and executive dysfunction, may gain further negative effect from chronic use of cannabinoid products, especially those with high THC content. Currently, it is still unconfirmed whether pure CBD will have a significant beneficial effect on neuropathic pain and it is unknown whether its chronic use might impact cognition and executive function in MS patients. It could be that the benefit of pure CBD-based drug might result in better patient outcomes long term but this claim remains to be substantiated by dedicated randomised double blind clinical trials in humans.

Epilepsy

Epilepsy is a chronic neurological disorder. About 30% of epilepsy patients are affected by Treatment-Resistant Epilepsy (TRE) due to the failure of common anti-epileptic therapies. CBD has known anticonvulsant effects **[6]**. Several studies confirmed its efficacy in the treatment of epileptic seizures, especially in pediatric age **[7]**. In 2016, the first results of phase 3 clinical trials showed beneficial effects of CBD-based drug (Epidiolex®; GW Pharmaceutical, Cambridge, UK) in treatment-resistant seizure disorders. In 2018, The US Food and Drug Administration (FDA) approved Epidiolex® as an oral solution for the treatment of seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients two years of age and older. Epidiolex® is the first FDA-approved drug that contains a purified drug substance derived from the cannabis plant. The European Medicine Agency (EMA) approved the drug in 2019 under the brand name Epidyolex®.

Opioid, Cannabis and Alcohol Dependency

In 2009, an experimental rodent model was used to examine the effects of CBD on heroin self-administration and drug-seeking behaviour **[8]**. CBD was found to specifically attenuate heroin-seeking behaviour reinstated by exposure to a conditioned stimulus cue. The behavioural effects were paralleled by neurobiological alterations in the glutamatergic and endocannabinoid systems, where discrete disturbances associated with stimulus cue-induced heroin seeking were normalised by CBD treatment. The findings highlight the unique contributions of distinct cannabis constituents to addiction vulnerability and suggest that CBD may be a potential treatment for heroin craving and relapse.

In 2019, an exploratory double-blind randomized placebo-controlled trial assessed the acute, short-term, and protracted effects of CBD administration (400 or 800 mg, once daily for 3 consecutive days) on drug cue–induced craving and anxiety in drug-abstinent individuals with heroin use disorder. The study **[9]** included 42 men and women with a history of heroin abuse who were not current users. The researchers found that CBD reduces drug cue-induced craving and anxiety in the participants.

The funding is now being sought to study the effects of CBD treatment in people with the heroin use disorder, including those being treated with the heroin substitute methadone.

In 2014, University College London has initiated clinical studies to check efficacy of CBD for the treatment of cannabis dependence. The university conducted a Phase 2a/b, randomised, double-blind, placebo-controlled, single-site, parallel group clinical trial to examine CBD as a pharmacological treatment for cannabis dependence in the young cannabis-dependent

population. The drug candidate targets CB_1 and CB_2 receptors, exhibits anti-addictive effects and acts as a behaviour modulator. The Phase 2a trial results have been published earlier this year **[10]** and indicate that CBD doses ranging from 400mg to 800mg daily have the potential to reduce cannabis use in clinical settings and does not lead to any severe adverse effects. Larger studies are needed to determine the magnitude of the benefits of daily CBD for reducing cannabis use.

There are also interesting experimental results in animal models suggesting that CBD reduces the overall level of alcohol drinking, motivation for ethanol, relapse, anxiety, and impulsivity **[11]** and improves brain and liver function **[12]**. No convincing data on humans yet exists.

Gastrointestinal Disorders

Considerable evidence demonstrates that the manipulation of the endocannabinoid system regulates nausea and vomiting in humans and other animals. The anti-emetic effect of cannabinoids has been shown across a wide variety of animals that are capable of vomiting in response to a toxic challenge. Preclinical research indicates that CBD may be effective clinically for treating both nausea and vomiting produced by chemotherapy or other therapeutic treatments **[13]**.

CBD-based drugs are also under development for ulcerative colitis indication. The most advanced is GW Pharmaceuticals' Phase 2a ulcerative colitis trial [ID NCT01562314]. The study included 60 adult patients with ulcerative colitis who had not been able to gain remission from the condition despite first line treatment with salicylates, and in some cases immunosuppressive therapy. At the end of the treatment period, 82% of the patients in the trial group showed improvement, compared with 52% in the placebo group. These results are encouraging.

Liver Disease

During the past few years, awareness of the cannabinoid system in the pathophysiology of liver disease has gained momentum. Both CB_1 and CB_2 receptors have been shown to be upregulated in the early stages of liver injury. There has been growing evidence in recent years to suggest that endocannabinoids may regulate the pathophysiology of liver diseases, including both acute forms of hepatic injury, liver fibrosis and cirrhosis **[14]**. CBD also reduces alcohol-related steatosis and fibrosis in the liver by reducing lipid accumulation, stimulating autophagy, modulating inflammation, reducing oxidative stress, and by inducing death of activated hepatic stellate cells **[11]**.

Insulin-dependent type I diabetes mellitus

Early rodent study indicated that treatment of mice, either in a latent type I diabetes stage or with initial symptoms of type I diabetes with CBD for 4 weeks, could lead to sustained inhibition of insulitis **[15]**.

In the animal models, CBD treatment inhibited specific destruction of the islets and reduced the infiltrates by mononuclear cells into the islets, thus preventing type I diabetes. Furthermore, it has been reported that rats treated with CBD for 1–4 weeks experienced significant protection from diabetic retinopathy **[16, 17]**.

Other Inflammatory Conditions

The fact that both CB_1 and CB_2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Several studies showed that cannabinoids downregulate cytokine and chemokine production and, in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses **[18, 19]**.

Another study showed, using an animal model, CBD applied on the skin could help lower inflammation due to arthritis. Another study demonstrated the mechanism by which CBD (in a form of Sativex®) inhibits inflammatory pain, one of the most difficult types of chronic pain to treat **[20]**.

Mental health

Exploratory Phase 2 placebo-controlled clinical trial [NCT02006628] of CBD in patients with schizophrenia (GW Pharmaceuticals, Cambridge, UK) who had previously failed to respond adequately to first line anti-psychotic medications showed that CBD was consistently superior to placebo when taken together with one of the leading first line anti-psychotic medications. The majority of endpoints in the study was in favour of CBD. The safety profile of CBD was particularly reassuring in this clinical study, with no serious adverse events and an overall frequency of adverse events very similar to placebo.

Another exploratory trial **[21]** suggests that CBD in addition to routine psychiatric care can promote PTSD symptom reduction in adults suffering from PTSD. CBD also appeared to offer relief in a subset of patients who reported frequent nightmares as a symptom of PTSD. These preliminary results are very encouraging. Though the findings do not support the claims often

found in online CBD-promoting sites that CBD provides relief from stress related sleep disorders, anxiety, depression and other mental health concerns, comprehensive, large clinical studies (such as double-blind placebo-controlled trials) are necessary to support any such claims.

Palliative Care

A comprehensive review has been carried out on efficacy, tolerability, and safety of cannabinoids including CBD in palliative medicine **[22]** showed that there were no significant differences between cannabinoids and placebo for improving caloric intake, appetite, nausea, or sleep problems in cancer patients. In human immunodeficiency virus (HIV) patients, cannabinoids were found superior to placebo for weight gain and appetite but not for nausea. No convincing evidence suggesting that cannabinoids are of value for anorexia or cachexia in cancer or HIV patients was found using meta-data analysis of 9 studies with a total of 1561participants selected from The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO, PubMed, Scopus, and clinicaltrials.gov.

Conclusions

CBD may offer therapeutic benefits for a large variety of disorders. The effects of CBD confirmed in clinical studies to date suggest that this compound might become a candidate pharmacological adjunct to any disorder presenting with high levels of inflammation. In most cases, studies show an action profile with fewer side effects than the pharmacological therapy currently used to treat the disorders investigated. Even in high doses, CBD is well tolerated with acceptable adverse event profiles when administered short term and has confirmed antioxidant and immunomodulatory properties.

This has raised increasing interest in CBD for various inflammatory or immunological diseases, including important investigations into major disorders such as cancer, neurodegenerative diseases and cardiovascular diseases **[23-26]**, which all can be classified as diseases of ageing and are the focus area of public health interventions. However, only early experimental data is available on these important indications today.

However, even in the face of evidence pointing to the good safety profile of CBD, more studies are needed to develop a better understanding of the biological mechanisms involved in CBD responses. Additional controlled studies showing the efficacy of CBD in humans at scale are also needed. We hope that the current surge of interest in CBD as a drug candidate will not dissipate and both the safety and potential efficacy of naturally derived and synthetic CBD will continue to be investigated with both clinical curiosity and healthy scepticism.

References

[1] Iffland K, Grotenhermen F. An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies. Cannabis Cannabinoid Res. 2017; 2 (1): 139-154. doi:10.1089/can.2016.0034

[2] Zhornitsky S, Potvin S. Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). 2012; 5 (5): 529-552. doi:10.3390/ph5050529

[3] Jawahar R, Oh U, Yang S, et al. A systematic review of pharmacological pain management in multiple sclerosis. 2013. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews [Internet]. York (UK): Centre for Reviews and Dissemination

[4] Koppel BS, Brust JC, Fife T, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014; 82 (17): 1556-1563. doi:10.1212/WNL.0000000000000363

[5] Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis [published correction appears in JAMA. 2015 Aug 4; 314 (5): 520] [published correction appears in JAMA. 2015 Aug 25; 314(8): 837] [published correction appears in JAMA. 2015 Dec 1; 314 (21): 2308] [published correction appears in JAMA. 2016 Apr 12; 315 (14): 1522]. JAMA. 2015; 313 (24): 2456-2473. doi:10.1001/jama.2015.6358

[6] Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, Stephens GJ. Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo. J. Pharmacol. Exp. Ther. 2010; 332: 569–577. doi: 10.1124/jpet.109.159145

[7] Mudigoudar B, Weatherspoon S, Wheless JW. Seminars in pediatric neurology. Elsevier; Amsterdam, The Netherlands: 2016. Emerging antiepileptic drugs for severe pediatric epilepsies; pp. 167–179. doi: 10.1016/j.spen.2016.06.003

[8] Ren Y, Whittard J, Higuera-Matas A, Morris CV, Hurd YL. Cannabidiol, a Nonpsychotropic Component of Cannabis, Inhibits Cue-Induced Heroin Seeking and Normalizes Discrete Mesolimbic Neuronal Disturbances. Journal of Neuroscience 2009, 29 (47) 14764-14769; doi: 10.1523/JNEUROSCI.4291-09.2009

[9] Hurd YL, Spriggs S, Alishayev J, et al. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals With Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. Am J Psychiatry. Published Online: 21 May 2019 https://doi.org/10.1176/appi.ajp.2019.18101191

[10] Freeman TP, et al. Cannabidiol for the treatment of cannabis use disorder: a phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. Lancet Psychiatry Published online: July 28, 2020 doi:https://doi.org/10.1016/S2215-0366(20)30290-X

[11] De Ternay J, Naassila M, Nourredine M, et al. Therapeutic Prospects of Cannabidiol for Alcohol Use Disorder and Alcohol-Related Damages on the Liver and the Brain. Front Pharmacol. 2019; 10:627. doi:10.3389/fphar.2019.00627

[12] Avraham Y, Grigoriadis N, Poutahidis T, et al. Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice. Br J Pharmacol. 2011;162(7):1650-1658. doi:10.1111/j.1476-5381.2010.01179.x

[13] Parker LA, Rock EM, Limebeer CL. Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol. 2011;163(7):1411-1422. doi:10.1111/j.1476-5381.2010.01176.x

[14] Bazwinsky-Wutschke I, Zipprich A, Dehghani F. Endocannabinoid System in Hepatic Glucose Metabolism, Fatty Liver Disease, and Cirrhosis. Int J Mol Sci. 2019;20(10):2516. Published 2019 May 22
doi:10.3390/ijms20102516

[15] Weiss L, Zeira M, Reich S, et al. Cannabidiol arrests onset of autoimmune diabetes in NOD mice. Neuropharmacology. 2008;54(1):244-249. doi:10.1016/j.neuropharm.2007.06.029

[16] El-Remessy AB, Al-Shabrawey M, Khalifa Y, et al. Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes. Am J Pathol. 2006;168(1):235-244. doi:10.2353/ajpath.2006.050500

[17] Gruden G, Barutta F, Kunos G, Pacher P. Role of the endocannabinoid system in diabetes and diabetic complications. Br J Pharmacol. 2016; 173 (7): 1116-1127. doi:10.1111/bph.13226

[18] Eisenstein TK, Meissler JJ. Effects of Cannabinoids on T-cell Function and Resistance to Infection. J Neuroimmune Pharmacol. 2015; 10 (2): 204-216. doi:10.1007/s11481-015-9603-3

[19] Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. Future Med Chem. 2009;1(7):1333-1349. doi:10.4155/fmc.09.93

[20] Russo EB. Cannabinoids in the management of difficult to treat pain. Ther Clin Risk Manag. 2008;4(1):245-259. doi:10.2147/tcrm.s1928

[21] Elms L, Shannon S, Hughes S, Lewis N. Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series. J Altern Complement Med. 2019; 25(4): 392-397. doi:10.1089/acm.2018.0437

[22] Mucke M, Weier M, Carter C, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. J Cachexis, Sarcopenia and Muscle. 2018; 9(2): 220-234. https://doi.org/10.1002/jcsm.12273

[23] Massi P, Solinas M, Cinquina V, Parolaro D. Cannabidiol as potential anticancer drug. Br J Clin Pharmacol. 2013;75(2):303-312. doi:10.1111/j.1365-2125.2012.04298.x

[24] Fernández-Ruiz J, Moro MA, Martínez-Orgado J. Cannabinoids in Neurodegenerative Disorders and Stroke/Brain Trauma: From Preclinical Models to Clinical Applications. Neurotherapeutics. 2015;12(4):793-806. doi:10.1007/s13311-015-0381-7

[25] Watt G, Karl T. In vivo Evidence for Therapeutic Properties of Cannabidiol (CBD) for Alzheimer's Disease. Front Pharmacol. 2017;8:20. Published 2017 Feb 3. doi:10.3389/fphar.2017.00020

[26] Sultan SR, Millar SA, England TJ, O'Sullivan SE. A Systematic Review and Meta-Analysis of the Haemodynamic Effects of Cannabidiol. Front Pharmacol. 2017;8:81. Published 2017 Feb 24. doi:10.3389/fphar.2017.00081