Cannabinoids and Mental Health, Part 2

The Search for Clinical Applications

ABSTRACT

Patients with psychiatric conditions are increasingly using cannabinoids, particularly cannabidiol (CBD), to treat their own symptoms. After reviewing the mechanism of action of CBD, the current article examines the existing evidence for CBD in the treatment of schizophrenia, anxiety, autism, posttraumatic stress disorder, and insomnia, and discusses the challenges in translating these studies, often using very high doses of CBD, into clinical practice. Until additional, well-designed studies that examine the more common practice of lower doses of CBD are performed, a harm-reduction, patient-centered, empiric approach is encouraged to optimize symptom reduction while at the same time avoiding the known risks of cannabis. [*Journal of Psychosocial Nursing and Mental Health Services, 57*(10), 7-11.]

Psychiatric clinicians are often asked to treat patients with evidence-based methods, but the evidence to guide practice does not always reflect the reality that they confront every day. As such, providers are often forced to make clinical decisions based on a minimum amount of evidence. The role, if any, for cannabis and cannabinoids in psychiatric practice highlights this tension between evidence and clinical practice.

Currently, many patients are using cannabinoids, particularly cannabidiol (CBD), to treat their own symptoms, ranging from insomnia to anxiety to depression. What evidence is there that this will help? What are the risks? What doses of CBD should they be using? What route? How will CBD interact with other medications?

In the first part of this article series (Penn, 2019), the mammalian endocannabinoid system was explained, including the neurotransmitters anandamide (AEA) and 2-Arachidonoylglycerol (2-AG), their synthesizing and degrading enzymes, and their activity as partial and full agonists, respectively, at the Cannabinoid 1 and 2 (CB1, CB2) receptors. How this neurotransmitter system works as a retrograde signaling mechanism to fine tune other neurotransmitters, such as serotonin, norepinephrine, dopamine, and GABA, was explored. In this second part, the action of CBD on the endocannabinoid system will be further explored, and this laboratory science will be taken into practice in an attempt to make rational choices about the role of exogenous cannabinoids in psychiatric practice.

If providers choose not to recommend cannabinoids to patients, it is still important to understand that many patients have already begun to treat themselves with various preparations of these substances. The existing

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empirical evidence, thin as it is, will be explored to help inform the robust amounts of anecdotal evidence coming from patients, the internet, and the cannabis industry. A measured, harm reduction–informed framework is proposed for partnering with patients to create a way of practicing that acknowledges patients' mounting lived experiences with cannabinoids and attempts to temper them with caution where it is warranted and curiosity whenever possible.

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CANNABIS BOTANY

The cannabis plant (cannabis being the botanical genus) exists as three typically hybridized cultivars: the species *sativa*, *indica*, and *ruderallis*. Cannabis is a complex manufacturer of more than 500 different chemicals (Aizpurua-Olaizola et al., 2016; Andre, Hausman, & Guerriero, 2016). Approximately 100 chemicals are cannabinoids, such as CBD and 9Δ-Tetrahydrocannabinol (THC). The remainder are terpenes, phenolic compounds, steroids, and enzymes. Although the tradition of reductionism is interested in isolating and testing a single compound from a complex botanical composition, the cannabis plant presents a particular challenge, as different chemicals within the plant often work in concert with one another, a synthesis known as the "entourage effect" (Ben-Shabat et al., 1998, p. 23). CBD limits the intoxicating effects of THC. THC may need to be present in small amounts to optimize the effects of CBD. Terpenes, such as myrcene, which are best known for giving cannabis its characteristic odor, may also serve to change the permeability of the blood/brain barrier, thus changing the psychoactivity of that cannabinoid; however, additional study of this phenomenon is needed (Hartsel, Eades, Hickory, & Makriyannis, 2016).

One cannabinoid receiving the greatest attention in the lay and professional press is CBD. CBD is often described as the "non-psychoactive" cannabinoid (to distinguish it from the decidedly active THC) but a more accurate description would be "non-intoxicating." Although it is clear that CBD may not have the euphoriant or stimulus-distorting qualities of THC, it appears to have potential psychoactive benefits in the treatment of anxiety, depression, and psychosis, if early studies prove to be replicable (Leweke et al., 2012; McGuire et al., 2018; Russo, Burnett, Hall, & Parker, 2005).

CBD can be ingested through multiple routes. Historically, CBD was a component of whole-plant cannabis, along with other cannabinoids, such as THC. When cannabis is inhaled, CBD is approximately 31% bioavailable. Increasingly, CBD isolates, or in an admixture with THC, are ingested orally as tinctures or oils or in food products. Oral bioavailability ranges from 13% to 19%. CBD is metabolized through multiple CPY450 isoenzymes, most notably 3A4 and 2D6, and glucuronyl transferases 1A9, 2B7, and 2B17 (Stout & Cimino, 2014; Zendulka et al., 2016). Clobazam levels have been found to be elevated in the presence of CBD, and the 3A4 inhibitor ketoconazole has been speculated to inhibit metabolism of CBD and THC (Geffrey, Pollack, Bruno, & Thiele, 2015). However, there are few in vivo studies on drug–drug interactions with CBD

CBD MECHANISM OF ACTION

CBD has a complex mechanism of action, with activity across different components of the endocannabinoid system. At the receptor, it is a partial agonist, specifically at the allosteric site of the CB1 receptor where it functions as a negative allosteric modulator. This is in contrast to THC, which binds at the orthosteric site of the CB1 receptor. When CBD binds at the allosteric site, it changes the configuration of the orthosteric site, making THC less able to activate the CB1 receptor (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015). Subjectively, this complex interaction results in decreased intoxication and reduction in paranoia occasioned by THC (Englund et al., 2013). The limitation of THC's intoxication is advantageous to patients who might want the benefits of CBD without the negative side effects of THC. These patients should be advised to use a low-THC, high-CBD cannabis preparation.

CBD also acts as an inhibitor of the degrading enzymes diacylglycerol (DAG) and N-arachidonoylphosphatidylethanolamine (NAPE), thus indirectly increasing the activity of endocannabinoid or exogenous cannabinoids at the synapse in much the same way that older monoamine oxidase inhibitor antidepressant agents allowed for increased serotonin signaling by inhibiting the breakdown of the neurotransmitter. In addition, CBD inhibits the reuptake of AEA and 2-AG by inhibiting the endocannabinoid reuptake pump (similar to how a selective serotonin reuptake inhibitor inhibits the reuptake of serotonin) (Ohno-Shosaku, Tanimura, Hashimotodani, & Kano, 2012; Zhornitsky & Potvin, 2012).

CBD also acts as a monoamine reuptake inhibitor, slowing the presynaptic reuptake of serotonin, norepinephrine, and dopamine. There is evidence that CBD is also a partial agonist at the 5HT1A receptor, which may account for its purported antidepressant qualities. Finally, CBD is also a transient receptor potential vanilloid type 1 receptor agonist. This is the same receptor activated by capsaicin and may help explain some of the antinociceptive qualities of CBD (Costa, Giagnoni, Franke, Trovato, & Colleoni, 2004).

This complex and nonspecific activity of CBD, while at the same time avoiding common receptor "collateral damage" (e.g., blocking acetylcholine or histamine receptors), may account for some of the wide-reaching utility of the drug with a fairly tolerable side effect profile. Liver function test elevation, gastrointestinal distress, and fatigue were the most commonly reported adverse effects of high doses of CBD approved by the U.S. Food and Drug Administration (FDA) in the prescription drug Epidiolex® (GW Pharmaceuticals, 2018), a schedule V product indicated for pediatric seizure disorders. Early findings that CBD was effective against certain pediatric seizure disorders (made most famous by the development of a high CBD strain known as "Charlotte's Web" in honor of Charlotte Figi, a young girl in Colorado with Dravet's syndrome [Velasquez-Manoff, 2019]) helped create the perception that CBD was a more acceptable cannabinoid than THC.

In states where cannabis is available (either medically or recreationally), the demand for CBD-rich cannabis products increased as anecdotal evidence spread in the media and on the internet about the use of this cannabinoid for the treatment of anxiety, insomnia, and pain. Interest in the antiproliferative, anti-inflammatory, anti-spasmodic, and vasorelaxation qualities of CBD led to interest across a wide degree of disease states, but is beyond the scope of this article.

CBD PATIENT EDUCATION

Increasingly, patients are asking about or have already begun to add CBD to their psychopharmacological regimens. What evidence is there for the efficacy of CBD in clinical psychiatry? Small trials in humans have examined the use of high-dose CBD (typically 300 to 1,000 mg per day, taken orally) in the adjunctive treatment of schizophrenia (Boggs et al., 2018; Leweke et al., 2012; McGuire et al., 2018), social anxiety in a simulated public speaking model (Bergamaschi et al., 2011; Zuardi et al., 2017), and behavioral issues in children with autism (Aran, Cassuto, Lubotzky, Wattad, & Hazan, 2019). Eating disorders are another area of interest, as the endocannabinoid system is a key regulator of appetite, but have not been examined in clinical trials. Finally, the antidepressant potential of CBD (possibly due to 5HT1A agonism, similar to some antidepressant medications) has been explored in animal studies, but not human studies (Sales, Crestani, Guimarães, & Joca, 2019).

In schizophrenia, interest was sparked by an early study (Leweke et al., 2012) showing that 800 mg per day of CBD was as effective as amisulpride (an antipsychotic medication that is not FDA approved for use in United States). A study by McGuire et al. (2018) found 1,000 mg per day of CBD added to existing antipsychotic medications was well-tolerated and decreased positive symptoms in schizophrenia. CBD did not improve negative symptoms or cognition, a finding that was replicated by Boggs et al. (2018). However, Boggs et al. (2018) did not find a reduction in psychotic symptoms, unlike the earlier study.

In studies of anxiety, CBD was found to have a bimodal distribution of efficacy, with a modest dose (300 mg by mouth) of CBD as effective as 1 mg of clonazepam in a simulated public speaking test of social anxiety, whereas lower (100 mg) and higher (900 mg) doses did not demonstrate this same effect (Zuardi et al., 2017). An earlier study (Bergamaschi et al., 2011) demonstrated 600 mg of CBD orally outperformed placebo in a similar public speaking task.

It is important to note that the doses used in these studies were in the range of 300 to 1,000 mg per day of CBD, which is impractical for most patients who would be buying CBD over the counter from their local dispensary. For example, products containing 250 mg of CBD cost approximately $50 to $75 at dispensaries in California (Harborside Dispensary, n.d.).

There have been several small, open-label studies adding smaller doses of CBD (between 2 and 100 mg per day) to ongoing medication treatments, finding the drug well-tolerated and showing modest improvement in measures of posttraumatic stress disorder and insomnia (Elms, Shannon, Hughes, & Lewis, 2019; Shannon, Lewis, Lee, & Hughes, 2019). However, more well-controlled research is needed before it can be said, from the standpoint of evidence-based medicine, that low-dose CBD is an effective treatment for psychiatric ailments. In addition, the FDA has not yet approved any CBD products for a psychiatric condition.

HARM REDUCTION AND CBD

If a patient is interested in using cannabinoids, a decision should be made if a single cannabinoid will be used in isolation (e.g., CBD alone) or in combination (e.g., THC with CBD). The risk of using THC in conjunction with CBD is an increase in intoxication side effects. However, the entourage effect of CBD with THC may enhance therapeutic outcomes, particularly if a very low dose of THC is used. The patient must first determine the threshold at which he/she experiences effects from THC. MacCallum and Russo (2018) suggest an oral dose of 2.5 mg as threshold for many but suggest using ≤1.25 mg for those sensitive to the effects of THC. This dose should be given 2 to 3 hours before bed. Hence, if it is too sedating

or intoxicating, the patient can metabolize the THC as he/she sleeps. It is important to remember that because orally ingested 9Δ-THC is converted in the liver to 11-hydroxy-THC (a more potent compound than the parent drug), doses for oral THC are often lower than when it is used in an inhaled form. By establishing the dose that begins to result in intoxication, patients can avoid crossing this threshold as they begin to add CBD. CBD can then be started at 0.5 mg per pound of body weight and titrated up to targeted effect, bearing in mind that higher doses are more likely to cause CYP450 modulated drug interactions (M. Mangini, PhD, FNP, personal communication, July 23, 2019).

MOVING FORWARD WITH CBD

Ideally, more double-blind, placebo-controlled trials of cannabinoids will be performed in psychiatric practice. However, patients are not waiting for the empirical research to be completed. They have begun using CBD, either alongside conventional psychiatric medications or as a substitute. This use is in part a result of a growing cannabis industry that makes health claims that are not subject to FDA scrutiny. However, the dearth of evidence is largely because the Controlled Substance Act, in conjunction with prohibitionist drug policy, did not permit research into the claims that cannabinoids could be effective treatments for psychiatric illnesses. As such, we are at least 20 years behind where we need to be with regard to evidence. So, how can we best advise our patients about cannabinoids?

One blanket approach is to categorically advise patients not to use cannabinoids. Historically, this has been the general approach of psychiatry, and in the current climate, with the cannabis industry and anecdotal evidence purporting benefit, it is unlikely to result in anything other than patients using cannabis surreptitiously. The antipodal position is to join the panacea chorus that cannabis is useful for all manner of ailments and, because of its natural status, is inherently safe. The evidence showing risk of earlier development of psychosis and cognitive impairment in young people who use high THC cannabis would indicate that cannabis is certainly not without risk (Helle et al., 2016; Meier et al., 2012).

With my own patients, I use a "pre/post marketing" approach. *Post-marketing surveillance*, sometimes referred to as Phase 4 of the FDA approval process, is the practice of gathering observations about the effect of an approved drug once it is in widespread use. Although cannabis may not be FDA approved, it has already erupted in the marketplace and attempts to prevent patients from using it will likely be met with failure. I advocate an educational harm-reduction approach in which I work with patients to learn from them about how they are already using cannabinoids; offer evidence about known risks and the potential benefits; and then use a slow, cautious, transparent approach where I partner with patients to find the most optimum combination of medications, which may or may not include cannabinoids, to best treat their conditions. Harm reduction also involves using safer routes, so when possible, smoking cannabis is discouraged in favor of oral or vaporized routes (Fischer et al., 2017). Patient anecdotes should be aggregated and published in case reports and case series so that researchers can test these hypotheses in better controlled trials.

But we cannot wait for the evidence to emerge first, as patients have already begun to use cannabinoids. The question is will we walk with them or watch them walk away?

REFERENCES

Aizpurua-Olaizola, O., Soydaner, U., Öztürk, E., Schibano, D., Simsir, Y., Navarro, P.,... Usobiaga, A. (2016). Evolution of the cannabinoid and terpene content during the growth of cannabis sativa plants from different chemotypes. *Journal of Natural Products, 79,* 324-331. doi:10.1021/acs.jnatprod.5b00949

Andre, C.M., Hausman, J., & Guerriero, G. (2016). Cannabis sativa: The plant of the thousand and one molecules. *Frontiers in Plant Science, 7,* 19. doi:10.3389/fpls.2016.00019

Aran, A., Cassuto, H., Lubotzky, A., Wattad, N., & Hazan, E. (2019). Brief report: Cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems: A retrospective feasibility study. *Journal of Autism and Developmental Disorders, 49,* 1284-1288. doi:10.1007/s10803-018-3808-2

Ben-Shabat, S., Fride, E., Sheskin, T., Tamiri, T., Rhee, M.H., Vogel, Z.,…Mechoulam, R. (1998). An entourage effect: Inactive endogenous fatty acid glycerolesters enhance 2-arachidonoyl-glycerol cannabinoid activity. *European Journal of Pharmacology, 353,* 23-31.

Bergamaschi, M.M., Queiroz, R.H.C., Chagas, M.H., de Oliveira, D.C., De Martinis, B.S., Kapczinski, F.,...Crippa, J.A. (2011). Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients. *Neuropsychopharmacology, 36,* 1219-1226. doi:10.1038/npp.2011.6

Boggs, D.L., Surti, T., Gupta, A., Gupta, S., Niciu, M., Pittman, B.,…Ranganathan, M. (2018). The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia: A randomized placebo controlled trial. *Psychopharmacology, 235,* 1923-1932. doi:10.1007/s00213-018-4885-9

Costa, B., Giagnoni, G., Franke, C., Trovato, A.E., & Colleoni, M. (2004). Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. *British Journal of Pharmacology, 143,* 247-250. doi:10.1038/sj.bjp.0705920

Elms, L., Shannon, S., Hughes, S., & Lewis, N. (2019). Cannabidiol in the treatment of post-traumatic stress disorder: A case series. *Journal of Alternative and Complementary Medicine, 25,* 392-397. doi:10.1089/acm.2018.0437

Englund, A., Morrison, P.D., Nottage, J., Hague, D., Kane, F., Bonaccorso, S.,...Kapur, S. (2013). Cannabidiol inhibits THC-elicited paranoid symptoms and hippocampal-dependent memory impairment. *Journal of Psychopharmacology, 27,* 19-27. doi:10.1177/0269881112460109

Fischer, B., Russell, C., Sabioni, P., van den Brink, W., Le Foll, B., Hall, W.,...Room, R. (2017). Lower-risk cannabis use guidelines: A comprehensive update of evidence and recommendations. *American Journal of Public Health, 107,* e1-e12. doi:10.2105/AJPH.2017.303818

Geffrey, A.L., Pollack, S.F., Bruno, P.L., & Thiele, E.A. (2015). Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia, 56,* 1246-1251. doi:10.1111/epi.13060

GW Pharmaceuticals. (2018). *Epidiolex prescribing information*. Retrieved from https://

www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

Harborside Dispensary. (n.d.). *Extract*. Retrieved from https://harborsideoakland.treez.io/onlinemenu/category/extract

Hartsel, J.A., Eades, J., Hickory, B., & Makriyannis, A. (2016). Cannabis sativa and hemp. In R.C. Gupta, *Nutraceuticals: Efficacy, safety, and toxicity* (pp. 735-760). Boston, MA: Academic Press.

Helle, S., Ringen, P.A., Melle, I., Larsen, T., Gjestad, R., Johnsen, E.,...Løberg, E. (2016). Cannabis use is associated with 3 years earlier onset of schizophrenia spectrum disorder in a naturalistic, multi-site sample (*N*=1119). *Schizophrenia Research, 170,* 217-221. doi:10.1016/j.schres.2015.11.027

Laprairie, R.B., Bagher, A.M., Kelly, M.E., & Denovan-Wright, E.M. (2015). Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. *British Journal of Pharmacology, 172,* 4790-4805. doi:10.1111/bph.13250

Leweke, F.M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C.W., Hoyer, C.,...Koethe, D. (2012). Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Translational Psychiatry, 2,* e94. doi:10.1038/tp.2012.15

MacCallum, C.A., & Russo, E.B. (2018). Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine, 49,* 12-19. doi:10.1016/j.ejim.2018.01.004

McGuire, P., Robson, P., Cubala, W.J., Vasile, D., Morrison, P.D., Barron, R.,...Wright, S. (2018). Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *American Journal of Psychiatry, 175,* 225-231. doi:10.1176/appi.ajp.2017.17030325

Meier, M.H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R.S.,...Moffitt, T.E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences, 109,* E2657-E2664. doi:10.1073/pnas.1206820109

Ohno-Shosaku, T., Tanimura, A., Hashimotodani, Y., & Kano, M. (2012). Endocannabinoids and retrograde modulation of synaptic transmission. *The Neuroscientist, 18,* 119-132. doi:10.1177/1073858410397377

Penn, A (2019). Cannabinoids and mental health, part 1: The endocannabinoid system and exogenous cannabinoids. *Journal of Psychosocial Nursing and Mental Health Services, 57*(9), 7-10. doi:10.3928/02793695-20190813-01

Russo, E.B., Burnett, A., Hall, B., & Parker, K.K. (2005). Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochemical Research, 30,* 1037-1043. doi:10.1007/s11064-005-6978-1

Sales, A.J., Crestani, C.C., Guimarães, F.S., & Joca, S.R.L. (2018). Antidepressant-like effect induced by cannabidiol is dependent on brain serotonin levels. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 86,* 255-261. doi:10.1016/j.pnpbp.2018.06.002

Shannon, S., Lewis, N., Lee, H., & Hughes, S. (2019). Cannabidiol in anxiety and sleep: A large case series. *The Permanente Journal, 23,* 18-041. doi:10.7812/TPP/18-041

Stout, S.M., & Cimino, N.M. (2014). Exogenous cannabinoids as substrates, inhibitors, and inducers of human drug metabolizing enzymes: A systematic review. *Drug Metabolism Reviews, 46,* 86-95. doi:10.3109/03602532.2013.849268

Velasquez-Manoff, M. (2019, May 14). *Can CBD really do all that?* Retrieved from https://www.nytimes.com/interactive/2019/05/14/magazine/cbd-cannabis-cure.html

Zendulka, O., Dovrtelová, G., Nosková, K., Turjap, M., Šulcová, A., Hanuš, L., & Jurica, J. (2016). Cannabinoids and cytochrome P450 interactions. *Current Drug Metabolism, 17,* 206-226.

Zhornitsky, S., & Potvin, S. (2012). Cannabidiol in humans: The quest for therapeutic targets. *Pharmaceuticals, 5,* 529-552. doi:10.3390/ph5050529

Zuardi, A.W., Rodrigues, N.P., Silva, A.L., Bernardo, S.A., Hallak, J.E.C., Guimarães, F.S., & Crippa, J.A.S. (2017). Inverted U-shaped dose-response curve of the anxiolytic effect of cannabidiol during public speaking in real life. *Frontiers in Pharmacology, 8,* 259. doi:10.3389/fphar.2017.00259

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