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Perspectives of Using Cannabidiol in Psychiatry

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ABSTRACT: In the last years there has been an international explosion of debates and studies about using cannabidiol in medicine in a diversity of diseases, from oncological pathologies, autoimmune disorders or neurology but the most promising field, from afar, is psychiatry. In 2019, Romania was one of the countries that started discussing the potential use of cannabidiol in pediatric and adult neurology and psychiatry, discussions that divided both scientific and non-scientific worlds. Regarding psychiatry, cannabidiol, as a non-psychoactive compound, could have a spectrum of usage that range from anxiety and depression, post-traumatic stress disorder and most of all, psychotic pathologies. This paper will analyze the possibilities of using this substance for psychiatric patients, both adults and children, by describing the pharmacological attributes, pathophysiological mechanism and clinical aspects, respectively, by assessing the findings and results of the latest studies.

KEYWORDS: cannabidiol, anxiety, psychosis, psychoactive, psychiatry

Introduction

Cannabidiol or CBD as it is known to the wide public, has been the subject of debates for the past few years regarding its potential multiple purposes in medicine. Cannabidiol is one of the 113 cannabinoids found in cannabis plants, substances that are known for their physical and mental effects on human body. It was first believed to be one of THC's precursors due to their similar molecular structure, until research has revealed the pharmacological differences during study on the endocannabinoid system.

Cannabis *sativa* comprises three organic groups, such as: Cannabis *sativa* australis (southern hemp), cultivated in Europe and southern Russia especially for textile fibers; *indica* variety, grown in India, Japan and China specifically for narcotics; dioecious varieties of the *Fibridia* type with male and female individuals on different plants and monoecious varieties, with male and female flowers on the same *Fibrimon* type plant (Buzatu 2015, 69).

THC versus CBD

The first aspect that differentiates the two substances is their natural provenience. There are 2 known strains of cannabis plants the *sativa* strain which has higher concentration of THC and the *indica* strain which is known for higher concentration of CBD. Cross-breeding the two strains resulted in the *hybrid* cannabis which presumably has a balanced concentration of the two substances. In fact, most of the substances that are sold nowadays come from hybrid strains.

As said before, THC and CBD have the same chemical composition, as in the same number of oxygen, hydrogen and carbon atoms. The primary difference resides in the arrangement of the atoms which will translate into discreet different effects. It has been stated that cannabidiol is a "non-psychoative" substance, unlike THC, but this statement is somehow wrong because psychoactive is a general definition for substances with direct effect on the central nervous system. CBD may not produce the same cognitive changes as THC but it crosses the blood-brain barrier and involve directly with receptors at that level. Moreover, CBD actually needs THC to bind with specific receptors as its capacity for attachment is weak and they also can work in tandem as CBD decreases some of the potential toxic effects of THC.

CBD is the first cannabinoid to be legalized in a prescription medication after passing clinical trials in the study of drug-resistant epilepsy. It's potential other effects include treatment

(or adjuvant) of different forms of pain, chronic inflammation, chemotherapy, some autoimmune diseases, and most of all, psychiatric disorders such as psychosis, depression, anxiety or post-traumatic stress disorder. Regarding psychiatry, some authors debate the uses of mainly CBD or in combination with higher doses of THC, especially in reactive depression, sleep disorders or bipolar disorder.

THC has potential uses for nausea, anorexia and cachexia, muscle spasticity, glaucoma and it may be have good results in dependencies and withdrawal syndrome.

An interesting fact comes to light when analyzing the potential side effects of these substances. It seems that some of each substance's side effects are problems that the other one could treat. Although CBD is supposed to have less negative effects, they could include nausea, fatigue, appetite changes or weight loss. On the other hand, THC could cause increased hart rate, memory loss, anxiety coordination and reactivity disruptions.

In matter of psychoactive long term use of THC is supposed to have more negative effects compared to CBD.

The endocannabinoid system. Pharmacology of CBD

The endocannabinoid system is one of the great discoveries made in the 80's, during researches on the cannabinoids on human body. Its functionality covers a large area, from cellular level up to behavioral level, covering physical and psychological grounds. Studies conducted on animal dates the phylogenetic appearance of the system back to Echinoderms (starfishes).
The system is a complex network of receptors and ligands, spread throughout the body that interact maintaining homeostasis. There are 2 types of receptors: CB1 and CB2 (De Souza Crippa and Zuardi 2004, 417-426).

CB1 receptors are localized in the central nervous system beings mostly attached to G protein of the brain. Large quantities can be found in the cerebral cortex, especially in the frontal and occipital area, thalamus, hypothalamus, substantia nigra, globus pallidus, hippocampus, cerebellum, etc. In the peripheral nervous system it can be found in the sensitive neurons of the posterior ganglionic roots. The cardiorespiratory nuclei are free of these receptors so this could be an explanation for the improbability of the lethal intoxication. The activity of CB1 receptor is normal function of neuronal circuits, cellular proliferation, they are involved in locomotion, nociception, management and balance of psycho-emotional attributes, sleep modulation, cognition, memory, temperature and sensory processing, metabolic rates, control of inflammation and ischemia (Evanson, Tasker, Hill, Hillard, and Herman 2010, 4811–4819).

CB2 receptors are widely spread throughout the immune system and hematopoietic cells but can be found also in the central nervous, being expressed by microglial cells. CB2 receptors can work by themselves or by activating CB1 receptors and they have anti-oxidant, regeneration and anti-inflammatory role, which is the reason for experimental models to conclude that these receptors could be a key in new-generation cancer therapy. Some recent studies reveal that some cannabinoid receptors could be present in neurons, and endothelium of central nervous system and they could be involved in neuro-inflammatory responses in pathologies like multiple sclerosis, encephalitis, or neurodegenerative diseases like Huntington chorea, Parkinson or Alzheimer (Piomelli, Giuffrida, Calignano and de Fonseca 2000, 218-224).

Cannabinoid receptors modulate all their processes by being activated with ligands – neurotransmitters that attach themselves to the receptors triggering signals and modulating different events throughout the body. These ligands are endocannabinoids – anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) that are secreted by human body whenever changes in body's parameters appear. CB receptors can be activated by exogenous substances that mimic the structures of endocannabinoids. These artificial ligands are phytocannabinoids – plant derived THC or CBD and synthetic cannabinoids – designed to trigger specific actions on CB receptors. Cannabinoids are lipophilic and bind CB receptors reversible being disintegrated after their usage. The interaction between receptors and ligands translates into one major task – trauma response.

Trauma can have different meaning not only direct external factors but also internal process disruptions. Presence of any imbalance will trigger the secretion of cannabinoids that activate CB receptors triggering inflammatory responses. There are also signals that monitor the pathophysiological reaction until the problem is solved and the affected area is secured, this leading to the ending of the CB receptors activity. It is believed that without this system, inflammatory responses could grow uncontrolled leading to chronic disorders or even autoimmune diseases (Leweke, Piomelli, Pahlisch, Muhl, Gerth, Hoyer and Koethe 2012, e94-e94).

Regarding phytocannabinoids, their interaction with the endocannabinoid system is different. THC is an agonist for CB1 receptors, that means that it is directly bound to them, mimicking anandamide but at at a higher level. Saturating CB1 receptors will result in the massive psychoactive effect. As said before, CBD is still a psychoactive substance because of it's effects on central nervous system. Still, the difference is in the fact that it doesn't bind directly with receptors (Henquet and Kuepper 2010, 259-260). Actually, CBD presence in the blood, triggers the production of natural endocannabinoids which will activate the specific pathways. So, CBD has an indirect effect on the endocannabinoid system, stimulating its physiological activity and inducing well-being effects with no important side effects (Hallak, Dursun, Bosi, Horta de Macedo, Machado-de-Sousa, Abrao, et al 2011).

While studying CB1 receptors, their presence in the hypothalamus raised the idea of their involvement in eating disorders. It was stated that CB1 activation is one of the reasons for hyperphagia and obesity. So, pharmaceutical studies were conducted on the inhibition of these receptors resulting in the first CB receptor antagonist – rimonabant. The results were motivating as rimonabant not only reduces the apetite and weight problems but also, it seemed to reduce the spectrum of low-density triglycerides and raise the levels of high-density triglycerides, correcting atherogenic dyslipidemia. Unfortunately, these studies revealed that inhibition of endocannabinoid system can produce important psychological side effects such as depression, anxiety, and even delirious ideation or suicidal behavior. That revealed the importance of endocannabinoid system in keeping the psychological balance and opened the road for the study of cannabinoids for psychiatric purposes (Ibarra-Lecue, Pilar-Cuéllar, Muguruza, Florensa-Zanuy, Díaz, Urigüen, ... and Callado 2018, 97-107).

CBD's antipsychotic properties

As stated above, CBD has an indirect activity over the central nervous system that stimulates the endocannabinoid network, unlike THC that is a direct stimulant for CB1 receptors with important psychoactive side effects including induced psychosis or even triggering schizophrenia in young adults through hyperactivation of endocannabinoid system during frequent use. (J.G., Hill, M.N., 2016. 80, 14–21) The indirect activity of CBD raised the hypothesis that it could not only counteract THC's psychoactive activity but also, it could have *per se, an* antipsychotic efficiency or could serve as an adjuvant for antipsychotic medication. Another explanation for its possible use in this matter could be the partial agonist activity on dopamine receptors that are similar to the mechanism of aripiprazole or the stimulating activity of releasing pre-synaptic glutamate. (McGuire, Robson, Cubala, Vasile, Morrison, Barron, ... and Wright 2018, 225-231). On the other hand, some research revealed that schizophrenic patients tend to have high levels of anandamide in the cerebrospinal fluid, similar to THC levels and activity in cannabis users (Favrat, Ménétrey, Augsburger, Rothuizen, Appenzeller, Buclin, Pin, Mangin and Giroud 2005, 17).

CBD is an indirect stimulating factor for CB receptors which will lead to elevated anandamide levels, making the theory about CBD's antipsychotic benefits still questionable, although there are clinical studies with great results in lowering psychotic symptoms as well as decreasing side effects of psychiatric medication such as weight gain or prolactin levels increases (Bellocchio and Lafenêtre 2010, 281-283). On the other hand, there is a supposition that could raise important questions about using CBD as an antipsychotic agent. It appears that it is a potent

inhibitor of CYP450 enzymes and that would make difficult for CBD to be used in combination to certain antipsychotic medication (Cipriani and Minichino 2019).

Cannabidiol in depression and anxiety

The antidepressant effect of CBD has been stated by many studies. It is a fact that inhibiting the endocannabinoid system with rimonabant causes depressive symptoms. It is also stated that in animal models, administration of CBD causes immediate anti-depressant effects. The mechanism is yet unclear but it is believed that beyond the endocannabinoid system, CBD has the ability to interact with serotoninergic and glutamatergic neurotransmission and also, to activate synaptogenesis or neurogenesis in the prefrontal cortex or the hippocampus (Ruehle, Rey, Remmers and Lutz 2012, 23-39) There is also the brain derived neurotrophic factor (BDNF) that tends to decrease it's levels in depression. On animal models, it seems that BDNF factor was detected to be as elevated on CBD user group as well as the imipramine (antidepressant) user group (McArthur and Borsini 2006, 436-452).

The presence of CB1 receptors in the amygdala involves them in the mediation of the corticotropin release hormone with possible anxiogenic effect. CBD could decrease anxiety levels by acting on the post-synaptic 5-HT1A receptors. While THC is known to cause anxiety directly proportional with the dosage, CBD has the exact opposite effect even at high dosages. From animal to human studies, the results tend to reveal a good possibility for the usage of CBD by itself or in combination with psychiatric medication with good tolerance and low to none risks of substance addiction (Niesink and van Laar 2013, 130.) The anxiolytic action of CBD and the involvement of endocannabinoid system in sleep and mood regulation, extents the possibility of using it in therapy of posttraumatic stress disorder.

CBD and drug addiction

The endocannabinoid system plays a major role in the neurobiology of addictive behavior. It is believed that it is the underlying network that triggers the rewarding effect of drugs, in the dopamine independent mechanism that drives the motivation to seek drugs but also in the mechanisms of relapse due to environmental exposure to drugs or drug-related factors (Maldonado, Valverde and Berrendero 2006, 225-232). The same study on the CB system inhibiting activity of rimonabant revealed that some patients quit smoking during test which opened a new perspective on the role of endocannabinoids in the substance abuse neuro-mechanism. It would seem that the key to the problem would be inhibiting the endocannabinoid system. But due to the antidepressant and anxiolytic effects of CBD, it would serve as a good adjuvant in regulating the cravings and the drug reward system and it would decrease anxiety and improve stress during anti-addictive therapy. Some studies state that CBD could even have the capacity of disrupting drug memory expression but only conditioned by non-relapsing (Hurd, Spriggs, Alishayev, Winkel, Gurgov, Kudrich, Oprescu, Salsitz 2019).

CBD in neurodegenerative disorders

The endocannabinoid system's action in oxidation, inflammation, cell regeneration, cognition and memory and it's neuroprotective properties, could involve CBD in possible anti-dementia treatments. But neurodegenerative disorders are complex and almost all studies showed that CBD alone has weak benefits. For this reason, research on possible combinations of phytocannabinoids that would enhance the activity of endocannabinoid system were brought into light. For example, a combination between delta 9-THC and CBD has shown a great neuroprotective effect on patients with Huntington's disease (Sativex ® by GW Pharmaceuticals) as well as for Parkinson's disease patients there could be usage for a combination of CBD and delta 9 – tetrahydrocannabivarin (Zuardi 2008, 271-280). CBD alone could have a beneficial

neuroprotective effect in combination with specific medication in patients with Alzheimer's disease or multiple sclerosis and inn the firs case, there might even be a profilactic use possibility as CBD apparently interacts with the aberrant production of beta-amyloid in limbic and association areas, which is the main subsequent pathophysiological process in Alzheimer's disease (Valdeolivas, Satta, Pertwee, Fernández-Ruiz, Sagredo 2012, 406).

CBD and endocannabinoid system in children and adolescents

Regarding inflammatory diseases and immune disorders in children, there are many studies that confirm the strong involvement of eCB system in the pathophysiology of these conditions. There are even case reports of parents using CBD to counteract side effects of chemotherapy or immunomodulatory medication in their children. From the psychiatric point of view, there are some hypotheses about using CBD as an adjuvant in autism or anxiety and behavior disorders in adolescents and although some studies are promising, there are no clearly defined data that could be used at the moment. Possibilities for using CBD or combinations of phytocannabinoids remain opened to research in the field of infantile psychiatry.

Conclusions

The endocannabinoid system has a major involvement in keeping the homeostasis of the human body. Cannabinoid receptors subtypes are spread throughout the central nervous system and also within immune cells making them part of a complex biological and psychological reactions. The endocannabinoid substances that trigger neurologic transmission and receptor activity can be replaced by phytocannabinoids such as cannabidiol or tetrahydrocannabidiol extracted from cannabis strains. Although their molecular structure is somehow similar, their action is different. THC is a direct psychoactive inductor with important intoxicating effects while CBD is an indirect stimulant of the physiological endocannabinoid system.

Stimulating the system with exogenous help and without side effects could have important outcomes in a vast number of pathologies giving its involvement in reactions like inflammation response, oxidative mediation, neuroprotective and neurogenesis activity, regulation of metabolism, mood, cognition, memory, sleep and other psychological elements.

In matter of psychiatry, most of the hypotheses regarding the use of CBD were tested on animal models but in the last years, clinical trials advanced rapidly, especially giving the safety in using CBD on different types of patients. Although promising results are revealed at the moment and the prospect of use becomes more defined, there are still debatable data to study, especially in psychiatry.

It is clear that the endocannabinoid system takes part in the neurobiology of most psychiatric disorders and phytocannabinoids might be the key to unlocking the disruptions in the brain chemistry that promote psychiatric symptoms but it is clear that there is still a long way until medical large scale use could be possible. In addition, there is still a public scepticism regarding use of such substances and legal issues for making cannabinoids a part of medical standard therapy is going to be a long process.

References

Bellocchio, L., Lafenêtre, P., Cannich, A., Cota, D., Puente, N., Grandes, P. and Marsicano, G. 2010. "Bimodal control of stimulated food intake by the endocannabinoid system." *Nature neuroscience* 13(3): 281-283.

Buzatu, N.E. 2015. *Fenomenul consumului de substanțe noi cu proprietăți psihoactive ("Etnobotanice"). Aspect penale, criminologice, criminalistice și medicale.* Universul Juridic Publishing House.

Cipriani, A., Minichino, A., Senior, M., Brondino, N., Zhang, S.H., Godwlewska, B.R., Burnet, P.W.J., Lennox, B.R. 2019. "Measuring disturbance of the endocannabinoid system in psychosis: a systematic review and meta-analysis". *JAMA Psychiatry.*

De Souza Crippa, J. A., Zuardi, A. W., Garrido, G. E., Wichert-Ana, L., Guarnieri, R., Ferrari, L., ... and McGuire, P. K. 2004. "Effects of cannabidiol (CBD) on regional cerebral blood flow." *Neuropsychopharmacology* 29(2): 417-426.

Evanson, N.K., Tasker, J.G., Hill, M.N., Hillard, C.J., Herman, J.P. 2010. "Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling." *Endocrinology* 151: 4811–4819. *https://doi.org/10.1210/en.2010-0285*.

Favrat, B., Ménétrey, A., Augsburger, M., Rothuizen, L.E., Appenzeller, M., Buclin, T., Pin, M., Mangin, P., Giroud, C., 2005. "Two cases of "cannabis acute psychosis" following the administration of oral cannabis." *BMC Psychiatry* 5, 17

Hallak, J.E.C., Dursun, S.M., Bosi, D.C., Horta de Macedo, L.R., Machado-de-Sousa, J.P., Abrao, J., et al., 2011. "The interplay of cannabinoid and NMDA glutamate receptor systems in humans: preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects." *Prog. Neuropsychopharmacol. Biol. Psychiatry.*

Henquet, C., & Kuepper, R. 2010. "Does cannabidiol protect against the negative effects of THC?" *The British Journal of Psychiatry* 197(4): 259-260.

Hurd, Y.L., Spriggs, S., Alishayev, J., Winkel, G., Gurgov, K., Kudrich, C., Oprescu, A.M., Salsitz, E. 2019. "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.* https://doi.org/10.1176/appi.ajp.2019.

Ibarra-Lecue, I., Pilar-Cuéllar, F., Muguruza, C., Florensa-Zanuy, E., Díaz, Á., Urigüen, L., ... and Callado, L. F. 2018. "The endocannabinoid system in mental disorders: Evidence from human brain studies." *Biochemical pharmacology* 157: 97-107.

Leweke, F. M., Piomelli, D., Pahlisch, F., Muhl, D., Gerth, C. W., Hoyer, C. and Koethe, D. 2012. "Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia." *Translational psychiatry* 2(3): e94-e94.

Maldonado, R., Valverde, O., and Berrendero, F. 2006. "Involvement of the endocannabinoid system in drug addiction." *Trends in neurosciences* 29(4): 225-232.

McArthur, R., and Borsini, F. 2006. "Animal models of depression in drug discovery: a historical perspective." *Pharmacology Biochemistry and Behavior* 84(3): 436-452.

McGuire, P., Robson, P., Cubala, W. J., Vasile, D., Morrison, P. D., Barron, R., ... and Wright, S. 2018. "Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial." *American Journal of Psychiatry* 175(3): 225-231.

Niesink, R. J., and van Laar, M. W. 2013. "Does cannabidiol protect against adverse psychological effects of THC?" *Frontiers in psychiatry* 4, 130.

Piomelli, D., Giuffrida, A., Calignano, A., and de Fonseca, F. R. 2000. "The endocannabinoid system as a target for therapeutic drugs." *Trends in pharmacological sciences* 21(6): 218-224.

Ruehle, S., Rey, A. A., Remmers, F., and Lutz, B. 2012. "The endocannabinoid system in anxiety, fear memory and habituation." *Journal of Psychopharmacology* 26(1): 23-39.

Valdeolivas, S., Satta, V., Pertwee, R. G., Fernández-Ruiz, J., and Sagredo, O. 2012. "Sativex-like combination of phytocannabinoids is neuroprotective in malonate-lesioned rats, an inflammatory model of Huntington's disease: role of CB1 and CB2 receptors." *ACS chemical neuroscience* 3(5): 400-406.

Zuardi, A. W. 2008. "Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action." *Brazilian Journal of Psychiatry* 30(3): 271-280.