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Cannabis and psychosis: is there a role for Cannabidiol in the treatment of psychosis in young cannabis users ?

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Abstract
Background: Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been the most studied and debated cannabinoids present in cannabis. The last decade has shown a notable increase in literature regarding CBD, recognizing its anti-inflammatory and neuroprotective effects. Although there is limited evidence regarding the use of CBD in psychiatric disorders' treatment, studies so far available have reported therapeutic potential in substance use disorders (SUDs), psychosis and anxiety.
Methods: Literature review, performing a research in MedLine for articles on the subject, written in English and Portuguese, published until 2019, resulting in a total of 108 selected publications.
Results: CBD appears to reduce psychotic symptoms and cognitive impairment associated with cannabis use and decrease the risk of developing psychosis in this context. Early clinical studies using CBD as treatment in patients with psychotic symptoms confirm its potential as an effective antipsychotic compound with negligible side effects, with excellent safety profile and tolerability. Cannabidiol is also capable of modulating the neuronal circuits involved in SUDs, presenting the potential to reduce dependence in these individuals.
Discussion: CBD is currently an emerging therapeutic agent that has shown potential efficacy in the treatment of psychotic disorders and SUDs, and may represent a more easily accepted and tolerable therapeutic agent for this particularly vulnerable population.

Keywords: cannabidiol, cannabis, psychosis, schizophrenia, substance use disorders

1. Introduction

Cannabis (*Cannabis sativa*) is the most consumed, most globally produced, most trafficked and most apprehended illicit substance worldwide, with the prevalence of its use being five times higher than that of other substances. It is also the illegal drug most likely to be tried in any age group, with almost 20% of individuals in the 18-24-year-old age group claiming to have used cannabis in the last year. The United Nations Office on Drugs and Crime (UNODC) reports that about 3.9% of the world's adult population consumes cannabis, totaling about 180.6 million users worldwide [1].

Composed of more than 500 different chemical substances, of the 104 cannabinoids present in cannabis, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been the most studied and debated [2]. THC, actively psychogenic, is especially known for its recreational character, representing a chemical compound that is capable of exerting an agonist action on cannabinoid receptors, producing a mixture of psychomimetic and depressant effects, in addition to several centrally mediated peripheral autonomic effects [2]. On the other hand, and more recently, there has been a growing interest in CBD and its antipsychotic and anxiolytic properties. It is thought that this compound may have an important neuroprotective role, being able to mitigate some of the psychoactive effects of THC, both acutely and chronically, with a view to the cognitive preservation of the user [2]. Thus, the interest in studying the relative percentage of these two components in the consumable forms of cannabis and its derivatives has been renewed, since the potency (concentration of THC) of this drug has increased dramatically over the last few years - by a ratio THC: CBD from 14: 1 in 1995 to approximately 80: 1 in 2014 - which has been shown to have a harmful impact on the health of its users, with a special impact on younger populations [3].

Over the past few decades, the association between cannabis use and the increased risk of developing psychotic disorders such as schizophrenia has been reported through several cross-sectional and prospective epidemiological studies, supported by biological evidence [4, 7]. Thus, interest in the relationship between cannabis use and psychosis has increased dramatically in recent years, partly due to concerns about the increasing availability of cannabis and potential risks to human health and functioning, but also due to the emergence of legalization and decriminalization of its recreational use in several countries, namely in Europe, Canada and the United States of America.

Disorders resulting from cannabis use are especially common in younger patients, and recent studies indicate the presence of concomitant use of cannabis in one to two thirds of individuals with a first psychotic episode [4, 7]. In this population, the challenge of ensuring adequate therapeutic adherence is particularly common, which in most psychotic conditions focuses on the administration of antipsychotic drugs of different classes, including long-acting injectable antipsychotics. The maintenance of regular consumption of cannabinoids is particularly implicated in lower therapeutic adherence, greater number of relapses and readmissions and, consequently, worse prognosis in patients with schizophrenic psychosis [8, 10].

With limited action and often little success in psychotherapeutic interventions, such as Cognitive-Behavioral Therapy (CBT),

there is an urgent need to find new measures to improve the clinical trajectory of these patients.

Looking at the epidemiological description of the substance, it seems counterintuitive that a derivative of Cannabis sativa can present itself as a potential therapeutic agent in psychosis. However, several recent studies have revealed a promising and beneficial impact of the therapeutic use of cannabidiol in different psychiatric pathologies, which has been accompanied by an increasing commercialization of products containing this component all over the world. This article represents a review of the scientific literature on the use of cannabidiol and cannabis with high concentrations of CBD as adjunctive treatment in patients with inaugural psychosis or schizophrenic psychosis already established, through a neurophysiological approach and a particular social and legal contextualization of the use of these substances.

2. Methods

For the review of the specialized literature, a search was carried out in the MedLine / Pubmed databases, which took place between May and September 2019. Only articles written in Portuguese and English, published until 2019, were included.

Considering the *MeSH Database* terms, the keywords used were *Cannabidiol* or *CBD*; *Cannabis* or *Medical Cannabis*; *Schizophrenia*; *Substance-Related Disorders*.

After an initial analysis, the articles and studies related to the therapeutic potential of cannabidiol and medicinal cannabis were selected by the authors, as well as those in which data on epidemiology, physiology, treatment and prognosis of psychotic conditions and substance use disorders were also included, resulting in a total of 108 selected publications.

3. Results

3.1 The Association between Cannabis Use and the Development of Psychosis: From the Human Endocannabinoid System to Cannabis Pharmacokinetics.

The endogenous cannabinoid system is a lipid signaling system that has important regulatory functions in all vertebrates, having been discovered and deeply studied only after the identification of the first receptor for the main psychoactive constituent of *Cannabis sativa*, Δ9-tetrahydrocannabinol (THC) [11].

The complex human endocannabinoid system includes different cannabinoid receptors - of which the most well-understood type 1 (CB1R) and type 2 (CB2R) cannabinoid receptors stand out - endogenous neurotransmitters such as anandamide (AEA) and 2-arachidonylglycerol (2-AG), and the different enzymes responsible for its biosynthesis and degradation, namely the fatty acid amide hydrolase (FAAH) and the monoacylglycerol lipase (MAGL). The interaction between these different components results in the regulation of several neurotransmitter systems, namely the dopaminergic, serotonergic, cholinergic, glutamatergic and gabaergic systems [12].

CB1 receptors represent one of the most common G protein-coupled receptors in the central nervous system, and are preferably found at the presynaptic level in the regions of the neocortex, cerebellum, striatum, amygdala and hippocampus, where they mediate different functions with an impact on cognition, memory, mood or appetite. Its presence in the *Substantia nigra* and mesolimbic dopaminergic pathways also reflects a particular implication in human reward mechanisms. CB1R are also expressed in peripheral tissues, such as in endothelial cells and adipocytes, in which their activation can promote lipogenesis phenomena [12]. The low concentration of CB1 receptors in the spinal cord may also explain the low respiratory and cardiovascular toxicity with the use of cannabinoids [13].

On the other hand, CB2 receptors are mostly expressed at the level of the immune system, which may explain the inhibitory effect of cannabinoids on immune function, thus presenting an important role at the level of immunosuppression, inducing apoptosis, inhibiting proliferation. And suppressing the production of cytokines and chemokines [12].

Endocannabinoids are believed to be released by postsynaptic cells and act as retrograde signals, activating pre-synaptically located CB1 receptors, thus limiting the release of different neurotransmitters. Thus, this system plays an important role in maintaining and determining synaptic plasticity [14]. Through the study of cell models and brain sections, it has been shown that cannabinoids tend to have a blocking action on the release of several neurotransmitters, including GABA, norepinephrine and acetylcholine, thus being able to have both an excitatory and an inhibitory function, depending on the substrate on which act. Cannabinoids also increase the release of dopamine - among other places - in the *nucleus accumbens*, particularly relevant in the processes of addition or learning [15].

The association between cannabis consumption and the development of psychotic symptoms comprises three chronologically distinct events: the acute intoxication that leads to psycho-physiological responses directly due to the pharmacological effects of the substance and which are usually associated with higher doses and potencies, usually having fast resolution and complete recovery; the psychotic disorder induced by cannabis, which occurs during or after its consumption, marked by changes in sensory perception (in the form of delusions or hallucinations), psychomotor disorders and affective disorders; and persistent psychotic disorder in which changes in cognition, personality, affective sphere, or behavior are induced by cannabis and persist beyond the period during which there is a direct effect related to the psychoactive substance [16].

This set of psychoactive and behavioral effects caused by cannabis consumption are essentially due to the action of phytocannabinoid THC, which represents a partial CB1R agonist, acting as an inhibitor of dopamine reuptake at the level of the striated nucleus, causing an increase in tyrosine hydroxylase expression selectively, increasing the capacity for dopamine synthesis and release [17]. This dopaminergic dysfunction is believed to explain the association between cannabis use and the development of psychotic conditions, particularly when combined with its use in adolescence during the maturation of the brain circuits served by the associative striatum, although the biological mechanism by which cannabis increases the risk of psychosis remains poorly understood [17]. Several studies have shown that an increase in the capacity for synthesis and release of dopamine is found in patients with already established psychosis, but that the same increase is also found in individuals who only subsequently developed a frank psychotic disorder [17, 21]. It has also been shown that substances that increase dopamine release are capable of inducing or worsening psychotic symptoms, again

revealing the fundamental role of this neurotransmitter in the pathogenesis of these conditions, as well as the potential therapeutic target that constitutes [17, 21]. It has also been suggested that meso-striatal dopaminergic hyperactivity may be caused by glutamatergic dysfunction in the medial temporal lobe, and that both increased blood flow in the hippocampus and its metabolism have been reported in individuals both at high risk for psychosis and in those with already established psychosis [22].

The adolescence phase is a critical stage in brain development, and is essentially characterized by different processes of maturation and neuronal rearrangement [23]. The endocannabinoid system plays an important role in this process, given its contribution to the proliferation, migration and differentiation of neuronal cells, so that during this specific phase, changes at this level induced by THC can lead to neurobiological changes that can affect brain functions and behavior, through the repeated activation of the endogenous mesolimbic dopaminergic system, which, in turn, can lead to greater sensitization of this system and to the progressive increase of the acquired susceptibility to psychosis [23, 24].

People with schizophrenia are at increased risk of cannabis abuse [25]; in addition, the abuse of this substance has also been proposed as a precipitant of psychotic episodes in people with schizophrenia and capable of anticipating the onset of disease development [26, 28]. A review of the literature on the impact of cannabinoid abuse on the development of schizophrenia found that the use of cannabis causes an increased relative risk of late schizophrenia; however, the authors also concluded that this use "does not appear to be a sufficient or necessary cause for psychosis" [29]. However, it is now well established that this substance is an important agent capable of interacting with other risk factors for the development of psychotic disease, which include the genotype, environmental, social and neurodevelopmental conditions [30].

3.2 CBD *VERSUS* THC Duality

Cannabis potency - expressed by the concentration of Δ9-tetrahydrocannabinol (THC) - and the THC: CBD ratios have increased alarmingly over the past two decades in the United States of America and Europe. It is estimated that there has been an increase in THC concentrations from 4% to 20% and a THC: CBD ratio from 14:1 to 80:1 over the past two decades, through the analysis of apprehended samples [3]. The frequent use of strains of high potency cannabis has been associated with an increase in paranoid symptoms, greater dependence, more frequent use of emergency services, and an increased risk of cannabis-induced psychotic disorder among individuals without a previous psychiatric history [31, 33].

These data, which are of great concern, suggest that the psychoactive properties of cannabis depend on the interaction between the levels of THC and cannabidiol. In fact, cannabis preparations high in THC and apparently free of cannabidiol have been shown to increase the risk of psychosis [34]. With this in mind, it becomes increasingly relevant to know these two phytocannabinoids, apparently so different, and to understand their respective impact on human functioning.

The psychotropic effects of THC are mediated by its agonistic action of CB1R receptors, inhibiting dopamine reuptake at the level of the striated nucleus, selectively increasing the expression of tyrosine hydroxylase, resulting in an increased capacity for synthesis and dopamine release [35, 36]. This increase in dopaminergic activity ends up constituting a possible explanation for the increase in positive psychotic symptoms, namely, paranoid delirium, mistrust, conceptual disorganization, fragmentation of thought, alterations in sensory perception and also a sensation of depersonalization and unrealization. However, slight euphoria, relaxation and a tendency to daydream will be the main desired effects of those who consume cannabis [37].

In acute terms, the effects of THC at the central level in humans can translate - according to a more subjective character transmitted to us by the consumer - into a feeling of relaxation and general well-being, a sense of refined senses, changes in perception temporal (notion that time passes more slowly), but also paranoid delusional ideation. Of a more objective character, short-term memory changes, decreased motor coordination, catalepsy, hypothermia, analgesia, antiemetic effect and (sometimes marked) increase in appetite are highlighted. With more potent strains or higher doses, it can induce panic attacks, toxic delirium and psychosis. At the peripheral level, the main effects mediated by THC consist of tachycardia, vasodilation (particularly in sclerotic and conjunctiva), decreased intraocular pressure and bronchodilation. The chronic use of this substance, on the other hand, is associated, among other effects, with changes in memory and learning, greater irritability, decreased motivation, lethargy, decreased libido and, of course, more likely to develop an addiction and worsening previous psychiatric symptoms [38].

On the other hand, cannabidiol represents a phytocannabinoid present in *Cannabis sativa* that acts, among others, in the opioid, serotonergic and endocannabinoid systems, having, however, central effects markedly different from those of THC. It represents a non-competitive antagonist of CBR1 (and CBR2) receptors, inhibiting endocannabinoid signaling in a dose-dependent manner, being able to alter the potency of other primary ligands, including endonabinoids and THC, being able to do so in relatively low dosess [39, 40]. This mechanism is also involved in the inhibition of anandamide uptake and metabolism, thus increasing the levels of endogenous cannabinoids [41]. The minimal agonism of CB1 receptors by cannabidiol is probably responsible for its negligible psychoactivity, when compared to THC [42]. Among other mechanisms of action, GPR55 receptor antagonism, 5-HT1A receptor agonism, vanilloid/NMDA receptor modulation, and intracellular calcium regulation stand out [37].

As mentioned, CBD, unlike THC, is devoid of adverse psychoactive effects and its clinical interest comes from its anti-convulsive, analgesic, anxiolytic, anipsychotic, anti-inflammatory, anti-emetic, immunomodulatory, neuroprotective and, potentially, antitumor properties [43].

In order to prove the impact of the relative concentrations of THC and CBD, a study showed that patients with a first psychotic episode were significantly more likely to use strains of high potency, in a more frequent and prolonged manner, when compared with an another control group with cannabis with similar concentrations of THC and CBD (*Di Forti et al*., 2009). In a subsequent study by the same authors, it was possible to conclude that regular consumption of more potent strains would also be associated with the establishment of psychosis at an

earlier age (*Di Forti et al.*, 2014). Over the past decade, several studies that have studied this impact of THC: CBD ratios on the development of psychosis indicate that the use of cannabis with high concentrations of CBD (instead of THC) is associated with significantly less positive symptoms, namely delusions and hallucinations, better cognitive function and lower risk of developing psychosis, as well as a later age of disease onset, when compared to cannabis with low concentrations of CBD. Neuroimaging studies also suggest a correlation between greater concentration of CBD and greater neuronal integrity of the striated nucleus [27, 44].

3.3 "I Have no Disease and Weed Just Relaxes Me!" The Therapeutic Challenge in Young Patients with Psychosis and Cannabis Abuse.

Substance use disorders (SUDs) are estimated to affect around 30 million people worldwide, and are characterized by repeated use of a substance that leads to clinically significant impairment or suffering, making it a serious health problem, with high associated costs [1].

About 70 to 80% of young people with SUDs have at least one concomitant psychiatric disorder [45], and cannabis is involved in approximately 50% of psychosis or schizophrenia of those cases, so there is a growing concern about the deleterious medical and psychiatric consequences of the increase and early initiation of consumption of this substance [46, 48] *Schimmelmann et al*. (2012) described that young people whose cannabis use preceded the onset of psychotic symptoms (and their appropriate treatment), demonstrated to have a longer duration of psychotic symptoms and worse psychosocial functioning when compared to a control group of non-consumers, with greater severity of symptoms, greater academic / employment affect and a greater history of involvement in the criminal system [49].

In response to treatment with antipsychotic psychiatric drugs, most patients with first psychotic episode (FEP) achieve clinical remission of positive psychotic symptoms [50, 51]; however, the initial course of psychosis is characterized by recurrent recurrences, and it is estimated that up to 80% of patients with FEP will experience a recurrence of psychotic symptoms within 5 years after remission of the initial episode [52]. Each relapse is a potential chronicity factor, contributing to a greater impact on family members and caregivers, and higher costs for health systems. Although reported rates vary considerably between different studies [53], it is estimated that about 26% of patients with psychotic conditions do not adhere to the treatment plan established by the psychiatrist [54], however, especially during the inaugural phases of psychotic disorders, rates of non-adherence to therapy are high (above 50%), and are said to be higher in younger patients [54, 55].

Adherence to treatment can be compromised by the socio-cultural and economic context, characteristics of the disease and the profile of the drugs, as well as individual aspects of the patients. Although the relatively frequent occurrence of side effects of antipsychotic treatment and the lack of insight seem - intuitively - to be the most important contributors to non-adherence, scientific evidence does not always support this association [56, 59]. The concomitant use of psychoactive substances such as cannabis (but also alcohol and other drugs, and these individuals are often polydrug users) also seems to have a particular impact on adherence to therapy in these populations: different recent studies suggest that the use of cannabis may contribute for failure in treatment with antipsychotics, increasing the risk of non-adherence to treatment [60, 62]. However, if cannabis is also a factor that in itself increases the risk of resistance to antipsychotics, it still lacks scientific evidence. In addition to dose-dependent effects on memory as reported by different experimental observational studies, certain positive symptoms demonstrate greater susceptibility to cannabis sensitization, namely delusional paranoid and grandiose ideation, which certainly constitute a difficult obstacle to the existence of criticism regarding the condition morbid and the need for proper treatment [64, 66]. Concomitantly, associated with chronic use and high doses, the so-called cannabis amotivational syndrome has been described, a term that refers to lack of motivation, decline in functioning levels and apathy, a condition with a predominance of negative symptoms, which culminates in a state of neglect and divestment in the individual itself and in its usual activities [67, 68]. Although reversible with long-term abstinence, it is also an important factor that limits correct therapeutic adherence. Chronic use may also be associated with other symptoms that affect the social and occupational spheres, namely easy distractibility, decreased communication skills, introversion, decreased ability to manage interpersonal relationships and even a feeling of depersonalization [38]. Finally, some studies also suggest a dose-response relationship between the severity of substance use and rates of adherence to therapy [69, 71].

It is also relevant to note that the chronic use of cannabis leads to a low synthesis and release of striatal dopamine, with several studies showing that these low levels of dopamine stimulate the craving (desire to consume drugs again) [17, 72]. Antipsychotics, by blocking dopamine, decrease its concentration at the level of the striatum, causing even more marked craving and anhedonia, which also discourages patients from complying with this therapy [73].

It is pertinent to realize that the beginning of the use of cannabis can not only precede or be contemporary to the onset of a psychotic condition, but it can also succeeds it [74]. Several longitudinal studies have also established a reverse causality regarding the association between cannabis use and psychosis, noting that individuals with psychotic pathology seem to have higher rates of newly cannabis use as a way of relieving their symptoms, obviously maintaining consumption for the same reasons in previous consumers [75]. An abrupt interruption of cannabis use after regular and prolonged use is also associated with an withdrawal syndrome, marked by greater anxiety, dysphoria, sleep disorders, irritability and anorexia [76].

4. Discussion

4.1 Therapeutic Potential of Cannabidiol in this Population: a New Look at the Same Plant.

The main therapeutic target in the pharmacological treatment of psychotic disorders (including schizophrenia) is based on dopaminergic block, which is often limited to positive symptoms. Also, about two thirds of patients have a sub-optimal response with treatment with antipsychotics, and these results are even worse when substance use disorders are present [77, 79]. Literature on the treatment of cannabis addiction in individuals with psychotic conditions suggests that psychosocial treatment may

also reduce substance use and mitigate positive symptoms [80, 82]. However, several studies have been carried out that have shown a somewhat limited impact of psychosocial treatment involving adults with SUDs and concomitant schizophrenia (or related disorders), suggesting a limited benefit from the use of psychotherapeutic interventions such as Cognitive-Behavioral Therapy (CBT) and the Motivational Enhancement Therapy (MET) in these individuals [83, 85].

Although the use of psychotropic drugs targeting dopaminergic and glutamatergic neurotransmitter systems has been extensively investigated and applied as therapeutic agents for psychotic pathology, recently there has been a growing focus on the endocannabinoid system as a potential therapeutic target for these disorders.

Currently, CBD is a cannabinoid compound with a wide range of pharmacological effects and a wide spectrum of potential clinical use, and its regulation worldwide is complex and constantly changing; however, this is a product that can easily be purchased online. Thus, although the use of cannabis for medicinal purposes is becoming quite popular, the source of these products is sometimes unknown and their production is not regulated, partly also fueled by dissemination in the most diverse media of the plant itself as a panacea that seems to be a good treatment for all conceivable complaints and diseases [86] – which lacks sustained scientific evidence.

However, the past decade has seen a notable increase in the scientific literature on CBD, largely due to the recognition of its anti-inflammatory and neuroprotective effects [87]. Currently, levels of evidence related to the effectiveness of cannabinoids in the treatment of chronic pain [88], nausea induced by chemotherapy [89] and symptoms of spasticity of multiple sclerosis [90] are well established. These studies have extended its potential therapeutic effect to several other pathologies, including dementia, cerebral ischemia, diabetes, inflammatory and neurodegenerative diseases, nausea and, of course, psychiatric disorders. Currently, there is still limited evidence regarding the safety and efficacy of CBD in the treatment of psychiatric disorders. However, studies available to date have reported potential therapeutic effects for specific psychopathological conditions, including SUDs, chronic psychosis and anxiety [91].

Cannabidiol appears to have the ability to reduce psychotic symptoms and cognitive impairment associated with cannabis use, as well as decrease the risk of developing psychosis in this context. Such action may be due to the opposite effects of CBD and THC on patterns of brain activity in key regions involved in the pathophysiology of schizophrenia, namely the striatum, hippocampus and prefrontal cortex [92]. The first small-scale clinical studies with CBD treatment in patients with psychotic symptoms further confirm the potential of CBD as an effective antipsychotic compound with negligible side effects, with an excellent safety and tolerability profile [93]: doses of up to 1280 mg/day of CBD were administered to humans without toxicity or serious adverse events [94].

In a 4-week study of 42 patients diagnosed with schizophrenia in acute psychotic decompensation, cannabidiol administration in doses 200-800 mg/day showed efficacy comparable to amisulpride (an atypical antipsychotic) in reducing positive and negative symptoms, but being better tolerated. In addition, the authors attributed the improvement in symptoms to the increase in endocannabinoid anandamide, suggesting that cannabidiol can mediate its effect via FAAH inhibition [95]. It is also important to understand that cognitive impairment may precede the onset of other symptoms in schizophrenia and is also associated with low adherence to therapy and a greater tendency to relapse from a first psychotic episode [96]. CBD is particularly interesting as a potential new approach to improve cognition in these conditions, partly due to its strong anti-inflammatory properties [97].

Currently, two randomized clinical studies are being developed that seek to evaluate the effectiveness of CBD in the first psychotic episode (*Leweke et al*., 2018) and in patients in the first 7 years since the onset of psychotic disorder (*Ranganathan et al*., 2018): the first study seeks to study the effectiveness of CBD versus placebo as an adjunct to antipsychotic treatment in a cohort of 180 patients with FEP [98], while the second intends to study the effects of the isolated use of CBD in the described population, evaluating psychotic and cognitive symptoms, but also electrophysiological biomarkers and metabolic parameters [99].

On the other hand, the potential use of cannabidiol in the treatment of SUDs could be due to two mechanisms: first, the CBD agonist activities in 5-HT1A receptors seem to contribute to its anti-craving and relapse reduction effects, regulating the reward system, anxiety symptoms and improving emotional stress management [100]; secondly, CBD acts as a regulator of glutamatergic signaling through the modulation of the serotonergic and endocannabinoid systems. This may play a role in the treatment of addictive behavior, given that the deregulation of glutamatergic transmission has been largely related to drug-seeking behavior and the occurrence of relapses [101].

Preclinical studies suggested that cannabidiol could modulate the neuronal circuits involved in substance use disorders, with the potential to reduce dependence in these individuals [100]. In this sense, there has been a growing interest in the use of products derived from cannabis with a 1: 1 THC: CBD ratio, called nabiximols in the treatment of cannabis addiction - the same products recently approved for the treatment of multiple sclerosis in several European countries and in Canada, administered in the form of mouth spray, which provides a faster onset of action and more favorable pharmacokinetics [102].

Recently, the results of a randomized double-blind clinical trial were published, in which nabiximols (in multiple doses, containing up to 113.4 mg THC/105 mg CBD) or placebo were administered daily for 12 to 40 weeks on cannabis-dependent participants and who sought treatment, with concomitant psychotherapy (CBT/MET), concluding that this resulted in a decrease in cannabis consumption in the study group [103], reinforcing results of previous pilot studies, although its effects at the level of craving are for now only proven in its acute phase [102, 104]. Study participants were unable to differentiate between active medication and placebo treatment, suggesting that intoxication or subjective changes with nabiximols were not perceived to be significantly different from placebo, and therefore did not constitute a risk of creating abuse or dependence even in doses high, as previously described [103, 105]. It should be noted that to date, no studies have been identified that sought to assess the isolated use of CBD in cannabis addiction, although a case report of a 19-year-old woman whose dependence will have been effectively treated with CBD alone has been described [106].

A recent Dutch study found that the use in the smoked form of medicinal cannabis variants with a low THC concentration (0.4% THC and 9% CBD) can sometimes be difficult to accept and effective in treating patients with a psychotic disorder and concomitant SUD, given the abrupt difference in THC concentrations used by these patients, some of whom interrupted the study and resumed consumption of high-potency cannabis species that they would be used to, in search of the euphoric effect or of the feeling of relaxation [107]. Subsequently, a new clinical trial conducted by other Dutch authors concluded that in patients with schizophrenia under antipsychotics and motivated to stop cannabis use, a milder variant containing a minimum THC concentration of 4% (and 8% CBD) can represent an intermediate step to stop these consumptions, having this formulation quite satisfactory acceptance among the participants [108].

A randomized multicenter study (phase 3) was recently published with 128 participants with cannabis dependence who had not previously responded to conventional psychosocial interventions, comparing the administration of nabiximols (each spray of 0.1 ml containing 2.7 mg THC and 2.5 mg CBD, with a maximum of 32 sprays, divided into 4 doses) versus placebo, in combination with six structured sessions of CBT, over 12 weeks. The results reinforced that treatment with cannabinoid agonists, in combination with psychosocial interventions, reduces the illicit use of cannabis, also constituting a safer route of administration (compared to smoked cannabis, associated with chronic respiratory problems) [109].

5. Conclusion

Both substance use and low adherence to treatment are associated with poor outcomes in patients with psychosis.

The risk of relapse after a first psychotic episode is high, placing a substantial burden on health systems worldwide. As the use of cannabis is a potentially preventable risk factor, interventions aimed at improving therapeutic adherence in psychotic conditions, both inaugural and already established, must specifically target the use of this substance, since reducing its consumption can lead to a more favorable course of the disease and at less expensive costs in addressing these pathologies.

Due to the limited number of randomized clinical trials available and the high heterogeneity between the populations studied and the characteristics of the treatment (for example, formulation, dosage or duration), a general interpretation of the role of CBD in psychiatric disorders is far from clear. Large-scale, double-blind, placebo-controlled clinical trials on samples with an adequate number of patients with different psychotic disorders (at different stages) and comorbid substance use are urgently needed in order to establish their clinical utility.

Cannabidiol (CBD) is today an emerging therapeutic agent that has demonstrated potential effectiveness in the treatment of psychotic pathology, substance use disorders, and in the cases of coexistence of these pathologies. The inaugural phases of psychotic conditions constitute a truly critical period of treatment, during which the patient's involvement and adherence to treatment are essential, since the delay in the institution of treatment of psychosis is associated with negative long-term consequences. Cannabidiol may represent a more easily accepted and tolerable therapeutic agent for this particularly vulnerable population.

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