

Cannabinoids and their therapeutic applications in mental disorders

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Mental disorders represent a significant public health burden worldwide due to their high prevalence, chronically disabling nature, and substantial impact on quality of life. Despite growing knowledge of the pathological mechanisms that underlie the development of these disorders, a high percentage of patients do not respond to first-line clinical treatments; thus, there is a strong need for alternative therapeutic approaches. During the past half-century, after the identification of the endocannabinoid system and its role in multiple physiological processes, both natural and synthetic cannabinoids have attracted considerable interest as putative medications in pathological conditions such as, but not exclusive to, mental disorders. Here, we provide a summary of cannabinoid effects in support of possible therapeutic applications for major depression, bipolar disorder, anxiety, posttraumatic stress disorder, and schizophrenia. Considering this evidence, highlighted benefits and risks of cannabinoid use in the management of these illnesses require further experimental study.

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Introduction

Mental disorders, including mood and anxiety disorders, posttraumatic stress disorder (PTSD), and schizophrenia, represent an important public health problem, affecting about 9.6% to 27.8% of the general population worldwide. The pathophysiology is complex and not yet completely understood, although genetic, biological, and environmental factors are probably critical for both onset and progression of these disorders. Antidepressants, benzodiazepines, and antipsychotic drugs represent the main pharmacotherapy; however, 40% to 60% of patients do not gain total relief from their impairing symptoms with such treatments. Thus, there is a strong need to develop alternative/complementary treatments. There are several lines of evidence suggesting

that a promising pharmacotherapy may be based on drugs that target the endocannabinoid system, which in itself appears deregulated in psychiatric patients. This system is recognized as a fundamental modulator of a large variety of physiological processes, including neurodevelopment, emotional states, stress responses, and cognition, so much so that a defect in its signaling might play a role in the pathophysiological underpinnings of mental illnesses.

Cannabis has been used for millennia for therapeutic purposes, and there are several anecdotal reports of its consumption as a form of self-medication for the alleviation of psychiatric symptoms (eg, anxiety, depression, and mania). However, epidemiological studies consistently demonstrated that heavy cannabis use is associated with

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occurrence of psychiatric outcomes, especially in people at risk for psychosis or mood disorders. Hence, evidence supporting cannabis-based interventions for the treatment of mental disorders is equivocal, mainly due to the use of extracts from the whole plant. Cannabis contains various phytocannabinoids, among which Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) are the major constituents.

Both induce their pharmacological effect by interacting with the endocannabinoid system. THC is the main psychoactive ingredient responsible for either psychotic or affective mental health outcomes at higher doses; on the other hand, low doses can attenuate the subjective response to psychosocial stress and act as anxiolytics. In contrast, CBD represents the nonpsychoactive component of the plant that has been suggested to possess antipsychotic, antidepressant, anxiolytic, and procognitive properties. When the effects of THC or CBD were investigated in the management of psychiatric patients, preliminary results suggest that they both may have potential efficacy.

Currently, there are several clinical trials registered on ClinicalTrials.gov, all aimed at evaluating the potential therapeutic effects of cannabis and synthetic cannabinoids on mental disorders. Here, we provide a summary evidencing their possible therapeutic efficacy for the treatment of major depression, bipolar disorder, anxiety, PTSD, and schizophrenia. The term “medical cannabis” here refers to the use of cannabis preparations (raw cannabis, magistral preparations, and standardized cannabis preparations) as medical therapy to treat diseases or alleviate symptoms. “Medicinal cannabinoids,” by contrast, refers to medicinal products with marketing authorization: nabilone (synthetic cannabinoid similar to THC), dronabinol (synthetic THC), nabiximols (plant based with approximately equal quantities THC/CBD), and CBD (plant-based).

Major depressive disorder

Over the years, clinical evidence led to the hypothesis of a link between defects in the endocannabinoid system and depression. Specifically, under basal conditions, serum levels of the two primary endocannabinoids, anandamide

(AEA) and 2-arachidonoylglycerol (2-AG), were found to be reduced in medication-free women diagnosed with major depression, indicating a deficit in peripheral endocannabinoid activity.^{1,2} Furthermore, the decrease in serum levels of 2-AG was strongly correlated with the duration of the depressive episode, whereas serum AEA levels were negatively correlated with anxiety symptoms. On

the other hand, moderate exercise prescribed to improve mood states (ie, feelings of depression, total mood disturbance, and state anxiety) increased serum levels of AEA and related fatty acid ethanolamides (ie, oleoylethanolamide) in women with major depression.³ Similarly, 2-AG and AEA serum levels were elevated in patients with major depression treated with electroconvulsive therapy relative to baseline.⁴

In human postmortem studies, cannabinoid receptor type 1 (CB_1) density and functionality, as well as CB_1 messenger RNA (mRNA) levels, were elevated in the dorsolateral prefrontal cortex of suicide victims with major depression.⁵⁻⁷ These findings probably represent a compensatory upregulation to counteract endocannabinoid tone lowering in the central nervous system. In contrast, Eggen et al⁸ did not find any change in CB_1 -receptor mRNA and protein levels in the same brain areas of depressed individuals who committed suicide. However, the fact that the expression of CB_1 receptor in the anterior cingulate cortex was decreased in depressed patients treated with serotonin-selective reuptake inhibitors is consistent with the notion of an enhanced receptor density in drug-naïve patients suffering from major depressive episodes.⁹

As for CB_2 receptors, no changes were detected in mRNA levels in the dorsolateral prefrontal cortex of suicide victims with major depression.⁷ However, alterations in gene and protein expression of CB_2 receptor were found in the dorsolateral prefrontal cortex of suicide victims with no clinical psychiatric history.¹⁰ Genetic studies found a significant association between polymorphisms (ie, rs1049353 and rs806368) in the CB_1 -receptor gene (*CNR1*), depression susceptibility, and clinical response to antidepressant medications, particularly in female patients with high comorbid anxiety.^{11,12} Some investigations showed that genetic polymorphisms (ie, Q63R and rs2501432) in the CB_2 receptor

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gene (*CNR2*) seem to be also associated with depression.^{13,14} Finally, the single nucleotide polymorphism rs324420 of the gene encoding for the fatty acid amide hydrolase (*FAAH*), the main enzyme responsible for endocannabinoid degradation, appears to be associated with major depression, mostly in adult individuals who have been exposed to childhood trauma.^{1,11,15}

In spite of this strong evidence for an involvement of the endocannabinoid system in the pathophysiology of depression, no clinical trials have been registered to evaluate the efficacy of medical cannabis/medicinal cannabinoids for the treatment of major depression. Most of the evidence for an antidepressant effect of medical cannabis comes from case reports and observational studies. For example, in a systematic review, Walsh et al¹⁶ identified several cross-sectional investigations in which there was clear evidence for an improvement of mood through medical cannabis. This was corroborated by another recent meta-analytic review in which over 35% of the participants reported self-medication with cannabis to alleviate symptoms of depression.¹⁷ Accordingly, a large-scale epidemiological study reported that occasional or even daily consumption of cannabis lowers depressive symptoms compared with nonusers.¹⁸ On the other hand, another recent systematic review and meta-analysis of randomized controlled trials in which medicinal cannabinoids (eg, dronabinol, nabiximols, and nabilone) were used to treat symptoms related to other medical conditions (eg, chronic pain or multiple sclerosis), highlighted no significant effect on the secondary outcome of depression.¹⁹ Research also showed that the use of medical cannabis to cope with depressive symptoms is associated with cannabis-related problems. For example, Babson et al²⁰ reported that individuals with heightened depression also had heightened cannabis use because of the beneficial effects of cannabis on perceived sleep quality. This suggests that heavy cannabis use may be associated with an increased risk of developing depression as well as with levels of symptom severity.²¹ Accordingly, independent cohort studies investigating cannabinoid effects on depressive symptoms either in psychiatric patients or in the general population, reported that both medicinal and recreational cannabinoids worsened depressive symptoms.^{22,23} From recent research, however, it appears that acute cannabis use induces an immediate positive effect followed by worsening of depressive symptoms after repeated use.²⁴ In addition, a population-based longitudinal study suggests that associ-

ations between cannabis use and a more severe course of major depression should be ascribed to concomitant socio-demographic and clinical factors rather than to cannabis use itself.²⁵ Thus, at present, the evidence for efficacy and safety of medical cannabis or medicinal cannabinoids in major depression is still weak, and additional clinical studies of high methodological quality are needed.

Bipolar disorder

It is well documented that bipolar disorder is commonly associated with substance use disorders, with cannabis being the most commonly abused drug.²⁶ Some bipolar patients report cannabis use to relieve both manic and depressive symptoms and stated that it was more effective than conventional drugs or helped to relieve the side effects of those medications.²⁷ Also, medical cannabis was associated with better neurocognitive function in these patients.²⁸ As a corollary, smoking cannabis acted to alleviate mood-related symptoms in at least a subset of bipolar patients.²⁹ When evaluating the effects on both mood and neuropsychological performance, Sagar et al³⁰ found that smoking cannabis may result in partial alleviation of clinical symptoms in the short term. However, when two patients diagnosed with bipolar type I disorder were treated with CBD (initial oral dose of 600 mg reaching 1200 mg/day), no effect in attenuating mania was reported.³¹ Moreover, cannabis use might also worsen the occurrence of manic symptoms in those diagnosed with bipolar disorder and might be associated with an increased risk of onset of new manic symptoms.³² When looking at the endocannabinoid signaling, a postmortem study revealed no difference in CB₁-receptor density in the dorsolateral prefrontal cortex of bipolar patients compared with age-matched controls.⁷ Also, no evidence of any alteration in the expression of CB₁ receptor was found in the anterior cingulate cortex of bipolar patients.⁹ On the other hand, the same authors also demonstrated that the administration of a first-generation antipsychotic significantly decreased the expression of CB₁ receptor in the anterior cingulate.⁹ When polymorphisms of *CNR1*, as well as polymorphisms of genes encoding for other components of the endocannabinoid system (eg, N-acyl phosphatidylethanolamine phospholipase D and *FAAH*), were investigated in bipolar patients also in relation to antipsychotic response, no association was reported.^{11,33} On the contrary, a significant association was found between bipolar disorder and a rs41311993 (524C/A) polymorphism of *CNR2*.³⁴

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Taken together, these observations highlight the need to conduct further studies to better clarify the role of the endocannabinoid system as a possible pharmacological target for the treatment of bipolar disorder. In this regard, a randomized clinical trial has been registered to examine CBD (150 to 300 mg/day for a period of 12 weeks) as adjunctive treatment for bipolar disorder (ClinicalTrials.gov identifier: NCT03310593).³⁵ As primary outcome measure, the investigators will evaluate changes in depressive symptoms through the Montgomery-Åsberg Depression Rating Scale. Another trial aimed to evaluate the cognitive and psychophysiological effects of THC (administered through a vaporizer at doses of 2 and 4 mg) in bipolar disorder has been registered but is not yet recruiting (ClinicalTrials.gov identifier: NCT03206463).³⁶ Finally, the effects of dronabinol (one-time oral administration of 5 mg), as well as of CBD (one-time oral administration of 600 mg), on cognitive domains relevant to bipolar disorder, eg, arousal, decision making, cognitive control, inhibition, and temporal perception (sense of timing) will be evaluated in adult patients (ClinicalTrials.gov identifier: NCT04231643).³⁷ As a secondary end point, this study will determine, for the first time, the effects of acute exposure on the cerebrospinal fluid levels of AEA.

Anxiety disorders

As with depression, many anecdotal reports imply that patients with anxiety disorders, as well as subjects with high levels of anxiety, use cannabis for the purposes of self-therapy or coping with anxiety.³⁸ Moreover, approximately two-thirds of patients diagnosed with anxiety disorders decreased their use of anti-anxiety medications after substitution with medical cannabis.³⁹ A small trial conducted by Crippa et al⁴⁰ demonstrated that a single dose of CBD (400 mg) reliably lowered state anxiety on single-photon emission computed tomography (SPECT) scanning in patients with social anxiety disorder. Similarly, in a double-blind clinical trial on drug-naïve subjects with social anxiety disorder, Bergamaschi et al⁴¹ showed that an acute dose of CBD (600 mg) was able to reduce subjective anxiety induced by simulated public speaking. The anxiolytic effects of CBD seem to be related to its predominant actions on limbic and paralimbic cortices (amygdala and the hippocampus, as well as the hypothalamus, the left posterior cingulate gyrus, and the left parahippocampal gyrus), which are widely implicated in the pathophysiology of anxiety.⁴² A double-blind registered clinical trial is currently recruiting patients with anxiety to

assess the effect of 1 mL of sublingual CBD tincture (10 mg/mL CBD) administered three times per day (total daily dose of 30 mg) for 4 weeks (ClinicalTrials.gov identifier: NCT02548559).⁴³ Another ongoing multicenter trial will evaluate the efficacy and safety of daily CBD oil capsules (200 mg to 800 mg per day) during an 8-week period on adults diagnosed with generalized anxiety disorder, social anxiety disorder, panic disorder, or agoraphobia (ClinicalTrials.gov identifier: NCT03549819).⁴⁴ Efficacy, tolerability, and safety of CBD oil (150 mg to 300 per day) will also be evaluated in a phase 2 randomized placebo-controlled study design in adults with social anxiety disorder (ClinicalTrials.gov identifier: NCT04086342).⁴⁵ A very recently posted pilot trial (ClinicalTrials.gov identifier: NCT04267679)⁴⁶ will investigate the effect of 25 mg full-spectrum CBD soft gel capsules (up to a total dosage of 100 mg per day) for 12 weeks on individuals with diagnosed anxiety, and the varying anxiolytic effects of cannabis (smoked flower, ingested edible) as a function of the CBD to THC ratio is the subject of another pilot study (ClinicalTrials.gov identifier: NCT03491384).⁴⁷ All these clinical studies have been registered recently and are still in their initiation phase (not yet recruiting), and results cannot be expected until 2021 at the earliest.

It is important to emphasize that cannabis consumption affected anxiety-related behaviors in a dose-dependent manner, with low doses being anxiolytic and high doses inducing increased anxiety and panic.⁴⁸ For instance, a recent double-blind, placebo-controlled study with healthy adults showed that a low dose (7.5 mg) of oral THC significantly reduced self-reported subjective distress after a psychosocial stressor, while high doses (12.5 mg) increased negative mood overall.⁴⁹ At specific doses, neuroimaging studies showed that THC could both increase and decrease negative emotional processing in healthy volunteers.⁵⁰ On the contrary, CBD exerted anxiolytic effects in humans without inducing anxiogenic effects at high doses at baseline.⁵¹ When coadministered, CBD was able to attenuate the anxiogenic effect of high doses of THC, but this has not been confirmed more recently.⁵²

Data underpinning benefits of medicinal cannabinoids on anxiety outcomes were also provided by multiple randomized clinical trials in which they were tested in patients with other medical conditions.¹⁹ However, these effects have not always been consistent since lack of efficacy also has been reported.¹⁹ These conflicting results may pertain to the use

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of varying doses and differences in THC vs CBD content as well as to modes of administration (eg, vaporization, oromucosal sprays, or sublingual preparations). Finally, significant correlation between cannabis use and increased risk for the onset of anxiety disorders, with greater symptom severity and with poorer treatment outcome, have also been found.⁵³ In light of all these results, further clinical studies are needed to better delineate the therapeutic potential of cannabinoids in anxiety disorders.

Posttraumatic stress disorder

In the last few years, the hypothesis of an involvement of the endocannabinoid system in the pathophysiology of PTSD has become increasingly widespread. For example, a recent CB₁-receptor positron-emission tomography imaging study showed increased CB₁-receptor expression in the brains of individuals with PTSD compared with controls, an increase that was accompanied by a significant reduction in peripheral AEA levels.⁵⁴ Accordingly, AEA levels exhibited a negative relationship with the degree of intrusive symptoms among individuals with PTSD.⁵⁵ Reduced peripheral AEA levels together with a compensatory upregulation of CB₁ receptor suggest a lower endocannabinoid tone in PTSD and warrant the use of both medical cannabis and medicinal cannabinoids as putative treatment options for improving PTSD symptoms.⁵⁶ As reviewed by Hindocha et al,⁵⁷ different cross-sectional studies reported a reduction in PTSD symptomatology in patients assessed on the Clinician-Administered PTSD Scale (CAPS) and using medical cannabis. Also, Roitman et al,⁵⁸ in an open-label study, revealed that, in patients with unremitted PTSD, treatment with sublingual THC (5 mg) twice daily for 3 weeks had beneficial effects on global symptom severity, sleep quality, frequency of nightmares, and PTSD hyperarousal. Moreover, the capacity of nabilone in reducing the intensity of nightmares and improving sleep in patients with PTSD was reported in three different studies.⁵⁷ Finally, a controlled cohort study analyzed retrospective clinical data regarding variable doses of CBD prescribed to 11 psychiatric outpatients diagnosed with PTSD. Ten of these 11 patients reported an overall decrease in PTSD symptom severity.⁵⁹

However, as stated by a commission of the National Academies of Sciences, Engineering and Medicine, the evidence supporting improvement in PTSD symptoms are limited and insufficient.⁶⁰ Randomized clinical trials that have been

registered and are recruiting patients with PTSD to test the efficacy of dronabinol (5 and 10 mg; ClinicalTrials.gov identifier: NCT03008005)⁶¹ and CBD (a fixed dose of 300 mg of a hemp-derived formulation of purified 99.9% CBD oil; ClinicalTrials.gov identifier: NCT04197102)⁶² will provide more evidence on the effect of medicinal cannabinoids in the future. It is also important to point out that 16 US states have listed PTSD as a condition for the use of medical cannabis.

Schizophrenia

Human studies have provided consistent and compelling evidence for heightened endocannabinoid signaling in schizophrenic patients. Elevated levels of AEA were found in blood and cerebrospinal fluid of schizophrenic patients that inversely correlated with psychotic symptoms and normalized after pharmacological treatment with antipsychotics.^{63,64} The results suggest that increased endocannabinoid levels act in a protective manner against psychosis.⁶⁴ Even though results are mixed, alterations in CB₁-receptor density have been detected in postmortem brain tissues of schizophrenic patients specifically in cortical regions that have been linked to schizophrenia, such as dorsolateral prefrontal cortex and anterior cingulate.^{9,65,66} When positron emission tomography (PET) was used to investigate CB₁-receptor availability in vivo in schizophrenic patients, the results were also mixed, with increases in the pons, nucleus accumbens, cingulate, and insular cortex and decreases in the amygdala, caudate, posterior cingulate cortex, hippocampus, hypothalamus, and insula.⁶⁷⁻⁶⁹ These data invite the interpretation that changes in endocannabinoid signaling in schizophrenia is region-specific and related to the specific symptomatology of the patient. Nevertheless, differences in sample size, as well as in methodology used, could account for the variances obtained between studies. Clinical evidence also supports a role for CB₂ receptors with reduced expression in peripheral blood mononuclear cells of treatment-naïve schizophrenic patients with first-episode psychosis, as well as in patients after treatment with olanzapine.^{63,70} Finally, genetic polymorphisms in *CN1R* were implicated in susceptibility to schizophrenia, but there was no consistency for any given association.⁷¹

A meta-analysis conducted on several longitudinal population studies suggests that cannabis use is linked to an increased risk of developing schizophrenia in vulnerable individuals and to precipitate psychotic symptoms in schizophrenic patients.⁷²

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Furthermore, schizophrenic patients who consume cannabis have lower AEA levels than patients with no cannabis use, thus hindering the protective effect exercised by this endocannabinoid.⁷³ However, the risk enhancement is related to the amount of cannabis used, in particular with the use of high-potency cannabis variants, ie, high THC and low CBD concentrations.⁷⁴ Indeed, smoking cannabis high in CBD content significantly reduced the occurrence and severity of psychotic symptoms.⁷⁵ On the other hand, the high rate of cannabis use in schizophrenic patients was interpreted as an attempt to self-medicate against negative symptoms or to overcome the feeling of depression and anxiety associated with these symptoms.⁷⁶ Accordingly, an open-label case series reported that increasing doses of dronabinol (2.5, 5, and 10 mg) administered for 3 weeks were able to improve schizophrenic symptoms in treatment-refractory patients.⁷⁷ In a randomized controlled clinical trial carried out by Leweke et al,⁷⁸ schizophrenic patients undergoing either CBD or amisulpride treatment for 28 days showed significant improvements in their psychotic symptoms, and no difference in clinical efficacy was detected between the treatments. Moreover, the authors revealed a statistically significant association between the increase in AEA levels and the decrease in psychotic symptoms in patients treated with CBD. A beneficial effect of CBD in patients with schizophrenia was recently confirmed in a multicenter randomized controlled trial.⁷⁹ In this study, patients were randomized to receive CBD (1000 mg) or placebo alongside their existing antipsychotic medication. After 6 weeks of treatment, compared with placebo, the CBD cohort presented with lower levels of positive psychotic symptoms (hallucinations, delusions) and showed greater improvement in cognitive performance. However, a randomized placebo-controlled trial in which stable antipsychotic-treated outpatients with schizophrenia received CBD (600 mg/daily) as adjunct over 6 weeks found no improvement in psychotic symptoms.⁸⁰

The mechanisms underlying the association between cannabis and psychosis in terms of both risk for the development of psychosis and self-medication are not yet fully understood. It is well established that the psychotic outcomes of cannabis are mainly mediated by THC, as its administration in healthy individuals elicits both positive and negative symptoms, as well as cognitive deficits in a dose-dependent manner.⁸¹ Moreover, THC induces a transient exacerbation in psychotic symptoms and cognitive deficits in schizophrenic patients.⁸² Neuroimaging studies showed that THC-induced

psychotic symptoms are associated with the altered activity of several brain areas affected by schizophrenia, including the prefrontal cortex, anterior cingulate cortex, amygdala, and ventral striatum.⁸³ Unlike THC, CBD received growing attention for its antipsychotic properties and in healthy subjects was able to counteract the psychotic symptoms elicited by THC.⁸⁴ Although the mechanism through which CBD exerts its antipsychotic effects is still to be clarified, the majority of studies focused on its ability to indirectly increase AEA levels by inhibiting its reuptake.⁷⁸

Conclusions and future directions

Despite the constant rise of global prevalence rates, many of the current therapeutic options for mental illnesses are far from being ideal in terms of both efficacy and adverse effects. In this scenario, there is an increasing demand, worldwide, for using cannabinoids as a treatment for various mental disorders. Their therapeutic potential is suggested by the fact that the endocannabinoid system on which they act is malfunctioning when evaluated in psychiatric patients. This system plays a fundamental role in a large variety of physiological processes, including neurodevelopment, cognition, emotional states, and stress responses. It is therefore not surprising that its dysregulation may contribute to provoke some of the clinical traits present in patients with mental disorders. Thus, targeting the endocannabinoid system may represent an alternative, or additional, effective approach for their treatment. Although most of the studies reviewed in this article highlight an improvement in psychiatric symptoms, the evidence encouraging the use of cannabinoids in mental disorders is still unconvincing. The few clinical studies done so far have limitations both in the number of patients and in the duration of therapy. Moreover, reliable follow-up information is missing. Furthermore, several investigations evaluating the benefits of cannabinoids on psychiatric symptoms in patients with other medical conditions (eg, chronic pain or multiple sclerosis) have produced mixed results. On the other hand, larger longitudinal studies highlighted harmful consequences associated with regular and heavy cannabis use in psychiatric patients. In light of these facts, high-quality clinical trials will be necessary to confirm the efficacy and safety of cannabinoids specifically in patients diagnosed with a specific psychiatric condition, according to the *Diagnostic and Statistical Manual of Mental Disorders*. It would also be useful for these clinical studies to be integrated with measuring both circulating and

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cerebrospinal endocannabinoid levels and/or by examining differences in endocannabinoid signaling between individuals with psychiatric illness and healthy controls, before and after the treatment with cannabinoids. ■

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