

Medical use of cannabis. Cannabidiol: A new light for schizophrenia?

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The medical properties of cannabis have been known for many centuries; its first documented use dates back to 2800 BC when it was described for its hallucinogenic and pain-relieving properties. In the first half of the twentieth century, a number of pharmaceutical companies marked cannabis for indications such as asthma and pain, but since then its use has sharply declined, mainly due to its unpredictable effects, but also for socio-political issues. Recently, great attention has been directed to the medical properties of phytocannabinoids present in the cannabis plant alongside the main constituent Δ^9 -Tetrahydrocannabinol (THC); these include cannabinoids such as cannabidiol (CBD), cannabigerol (CBG), and tetrahydrocannabivarin (THCV). Evidence suggests an association between cannabis and schizophrenia: schizophrenics show a higher use of marijuana as compared to the healthy population. Additionally, the use of marijuana can trigger psychotic episodes in schizophrenic patients, and this has been ascribed to THC. Given the need to reduce the side effects of marketed antipsychotics, and their weak efficacy on some schizophrenic symptoms, cannabinoids have been suggested as a possible alternative treatment for schizophrenia. CBD, a non-psychoactive constituent of the *Cannabis sativa* plant, has been receiving growing attention for its anti-psychotic-like properties. Evidence suggests that CBD can ameliorate positive and negative symptoms of schizophrenia. Behavioural and neurochemical models suggest that CBD has a pharmacological profile similar to that of atypical anti-psychotic drugs and a clinical trial reported that this cannabinoid is a well-tolerated alternative treatment for schizophrenia. Copyright © 2012 John Wiley & Sons, Ltd.

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Introduction

Prejudice, superstition, emotionalism, and even ideology have managed to lead cannabis to ups and downs concerning both its therapeutic properties and its toxicological and dependence-inducing effects.^[1]

Cannabis sativa and *Cannabis indica* have been used for centuries for a variety of medicinal and recreational purposes, but their routine use has been subject to societal and legal sanctions due to psychotropic and addictive effects.

The first documented use of cannabinoids for medical purposes dates back to 2800 BC in the Chinese *herbarium Pen-ts'ao*,^[2] a herbal pharmacopoeia describing many drugs among which cannabis, which was referred to as 'ma', meaning 'chaotic'. *Pen-ts'ao* described the pain-relieving, stupefying and hallucinogenic properties of cannabis and recommended cannabis for constipation, malaria, gout, rheumatism, and menstrual anomalies.

Its therapeutic use was introduced in Western medicine during the first half of the nineteenth century by the Irish physician William Brooke O'Shaughnessy (1809–1889), who studied forensic toxicology and chemistry at the University of Edinburgh in Scotland. He conducted a number of experiments in animals and proved that cannabis was safe even at high doses; thus, he extended the use of cannabis to patients suffering from rheumatism, seizures, and tetanus.^[3]

At the end of the century, a number of pharmaceutical companies were marketing cannabis for asthma and pain relief and as a sedative/hypnotic agent.^[4] It was during the middle of the twentieth century that the therapeutic use of cannabis declined steeply, in part because of its unpredictable individual responses,

but also because of adverse effects (mainly anxiety and cognitive impairment). Legal restrictions in many countries lead to a further reduction in the use of cannabis-derived medicines.^[4]

Nowadays, medical cannabis use is in the midst of socio-political changes, and even with substantial regulatory differences between countries, cannabis extracts are receiving some credit for their medical value.

Recently, the use of cannabis has been linked to an increased risk of schizophrenic-like psychotic episodes; yet, a small population of users prefers to relieve their psychotic symptoms by smoking cannabis. A major issue still to be resolved is what makes cannabis use so multifaceted? *Cannabis spp.* contain several hundred cannabinoids and other components, such as terpenoids, which do not necessarily have the same pharmacological effects on the human body; therefore, scientists started exploring the pharmacology of secondary cannabinoids present in the plant, including cannabidiol (CBD), cannabigerol (CBG), and tetrahydrocannabivarin (THCV).

Among the over 60 cannabinoids present in the *Cannabis* plant, CBD is one of the most abundant along with Δ^9 -tetrahydrocannabinol (THC), but unlike the latter, CBD has no psychotropic activity. Much attention has been directed to this cannabinoid for its numerous pharmacological actions and therapeutic potential.

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Although isolated in the late 1930s, it was not until 1963 that the structure and chemistry of CBD were elucidated by Raphael Mechulam.^[5] Studies focusing on CBD pharmacology were initiated in the 1970s.^[6]

CBD shows a wide range of effects primarily due to a multitude of pharmacological actions.^[7] Pilot studies suggested a low affinity of CBD for cannabinoid receptors,^[8,9] and more recent evidence indicates that at low concentrations it can act as an antagonist against both subtypes of cannabinoid receptor (CB1 and CB2).^[10] In addition, there is evidence suggesting that CBD acts as a cannabinoid receptor inverse agonist^[11] and it decreases anandamide hydrolysis and re-uptake, facilitating endocannabinoid-mediated neurotransmission.^[12] Its effects also involve non-cannabinoid neurotransmission since CBD acts as an agonist at serotonin 5-HT_{1A} receptors *in vitro*^[13] and *in vivo*,^[14] and activates the transient receptor potential cation channel subfamily V member 1 (TRPV1R).^[12] Alternative mechanisms have been proposed to account for the effects of CBD, such as blocking adenosine uptake^[15] and antagonism of the putative cannabinoid receptor G Protein-coupled Receptor 55 (GPR55).^[16]

Whatever its exact mechanisms of action, attention has been focused on the potential use of CBD to treat a number of medical conditions, ranging from the management of Alzheimer's disease (AD) to multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS),^[17] anxiety,^[18,19] bone formation and fracture healing.^[20]

The therapeutic use of CBD in the treatment of symptoms of schizophrenia was initiated in Brazil in the 1980s.^[19,21,22] To date, only one drug containing CBD extracted from plants is available on the market, produced by GW Pharmaceuticals, a British pharmaceutical company which recently launched it under the brand name of *Sativex*, an oromucosal spray containing natural THC and CBD.^[23] Its medical use is recommended as an analgesic for adult patients with advanced cancer, and for the treatment of spasticity and neuropathic pain in patients with MS. Despite the promising data obtained in schizophrenic patients under CBD treatment, the use of *Sativex* is not advised due to the high proportion of THC (each spray delivers a fixed dose of 2.7 mg THC and 2.5 mg CBD), which might induce psychotic episodes *per se*.

Discussion

Briefing the schizophrenia universe

Amongst all psychiatric disorders, schizophrenia is one of the most complex, and possibly the least understood. Patients are likely to experience three categories of symptoms: positive (hallucinations, delusion, thought, and movement disorders), negative (flat affect, anhedonia, apathy, alogia, asociality, avolition), and cognitive symptoms (mainly attention and working memory deficits).

To date, there are no clear-cut theories for schizophrenia physiopathology. The two main hypotheses are the so-called dopaminergic and glutamatergic theories. The dopamine (DA) theory is based on the observation that amphetamine induces behaviour similar to the positive symptoms of schizophrenia, as well as on the fact that antipsychotics with DA receptor antagonism can ameliorate such abnormalities. The DA theory can explain the positive symptoms, but it does not provide an explanation for the negative ones. The glutamate theory seems to explain positive, negative, and also cognitive symptoms. This theory is based on

the observations that the N-methyl D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) induces schizophrenic-like psychosis.^[24] This implies the presence of glutamate dysregulation in schizophrenic patients.

A systematic review of ancient Roman and Greek texts^[25] alluded to some psychiatric ailments, and a general knowledge of psychotic symptoms; however, there were no descriptions of chronic psychotic disorders that would confirm diagnosis of schizophrenia according to contemporary diagnostic criteria, suggesting a lower incidence of this disease in ancient times relative to the present. Pertinently, Canadian philosopher McLuhan suggested that 'schizophrenia may be a necessary consequence of literacy'.^[26]

There is extensive evidence that schizophrenia is a biological disease of the brain, and it is well established that alterations of certain brain structures are indicative of schizophrenia. For example, volume reduction in the ventricles and grey matter, together with an increased amygdala volume are often observed in schizophrenic patients.^[27]

Human studies in schizophrenics support the occurrence of dysfunction in the endocannabinoid system. Schizophrenic patients have significantly higher amounts of anandamide in the blood than healthy subjects,^[28] and significantly higher levels of anandamide have also been detected in the cerebrospinal fluid (CSF) of first-episode schizophrenic patients relative to that documented in healthy volunteers.^[29,30] Dysfunctions of CB1 receptors in schizophrenic patients have been reported, specifically in cortical regions involved in cognition and memory, two functions highly compromised in schizophrenia.^[31–33] The highest densities of CB1 receptors are found in brain regions implicated in schizophrenia, including the cortex, the basal ganglia, and the hippocampus.

Genetic alterations of the gene encoding for the cannabinoid receptor, the CNR1 gene, have been found to be directly associated with schizophrenia. In a Japanese population^[34] and in a population of the Central Valley of Costa Rica,^[35] individuals with a polymorphism of the CNR1 gene exhibited a 2.3-fold higher susceptibility to the hebephrenic (or disorganized) form of schizophrenia; however, such an association was limited to this subtype of schizophrenia. A polymorphism of CNR1 has been associated with a superior therapeutic effect of antipsychotics.^[36] Noteworthy, the causative relationship between CNR1 mutations and schizophrenia has been questioned.^[37,38]

Does cannabis use induce or ameliorate schizophrenia?

In 1848, a French psychiatrist, Jacques-Joseph Moreau de Tour, began to investigate the effects of cannabis, documenting that marijuana effects were 'many and subtle', and not always discernible to the naked eye. He proposed to test cannabis as an experimental psychotomimetic.^[39] After observing the acute effects that cannabis caused in some of his psychiatric patients, he wrote:

Yes, unquestionably there are modifications (I do not dare use the word lesion) in the organ that is in charge of mental functions, but these modifications are not those one would generally expect. They will always escape the investigations of the researchers seeking alleged or imagined structural changes. One must not look for particular abnormal changes in either the gross anatomical or defined histological structure of the brain; but one must look for an alteration

of its sensibility. That is to say for an irregular, enhanced, diminished, or distorted activity of the specific mechanism upon which depends the performance of mental functions.^[39]

Recent research supports Moreau's observation that THC induces subjective, cognitive, and behavioural changes resembling intrinsic psychosis, and suggests the use of THC as an experimental psychotomimetic drug.^[40]

A number of studies support the hypothesis that cannabis consumption is an important risk factor for schizophrenia, which has been reported to increase with the frequency and dose of cannabis use.^[41–43] Epidemiological studies confirm a high occurrence of schizophrenia in people smoking cannabis,^[44] and chronic cannabis smokers show cognitive deficits similar to those seen in schizophrenic patients.^[45] Moreover, cannabis use is associated with an early onset of schizophrenia; young people with genetic vulnerability to schizophrenia are particularly sensitive to the physical and mental effects of cannabis.^[46]

A seminal 27-year longitudinal study involving more than 50 000 Swedish participants^[41] showed that cannabis use in adolescence was dose-dependently correlated to the risk of developing schizophrenia, with individuals taking cannabis on more than 50 occasions being *ca.* 7 times more likely to develop schizophrenia. The association between cannabis use and schizophrenia was also tested in an Australian cohort.^[47] This study tested four hypotheses proposing that cannabis use may: (1) cause schizophrenia in some patients, (2) precipitate psychosis in vulnerable subjects, (3) exacerbate symptoms of schizophrenia, or (4) be more likely in individuals with schizophrenia. The authors observed that during the last three decades of the twentieth century, cannabis use increased in Australia without a corresponding increase in schizophrenia incidence. Notwithstanding, they also observed that cannabis use exacerbated the course of the disease in schizophrenics, and precipitated its onset in vulnerable subjects.

A dose-response relationship has been established showing occasional cannabis users to have 1.6 times the chance of hospitalization for psychotic episodes, whereas heavy users had 6.2 times that risk,^[48] strengthening the notion that 'the association of cannabis use with psychiatric inpatient treatment is a clear indication of the association of cannabis use with mental illness'.^[48]

Yet, alternatives should not be ignored; for example, the use of cannabis as a self-medication for vulnerable subjects. A recent study showed that four out of six patients reported improved schizophrenic symptoms following synthetic THC administration (Dronabinol).^[49] Spano *et al.* demonstrated that voluntary and passive self-administration of synthetic cannabinoids can ameliorate PCP-induced schizophrenic-like symptoms in rats.^[50] This further supports a potential role of cannabis in ameliorating schizophrenic behaviour. Low doses of cannabis may increase blood flow in cortical areas related with perception, cognition, and mood, possibly mitigating the degree of psychosis.^[51] Unfortunately, to date, there is very little evidence supporting the use of smoking cannabis to medicate schizophrenia.^[41,52–59]

Cannabis use to cure schizophrenia: a matter of ratio

There are 19 clinical trials registered in 2012 for the use of CBD for a variety of medical conditions.^[60] Perhaps no other signalling system (the cannabinoid) discovered during the past 15 years is raising as many expectations for the development of new

therapeutic drugs, encompassing such a wide range of potential strategies for treatments.^[61]

Cannabis use has highly variable physiological effects, but the biochemical basis for this remains a matter of contention. The numerous cannabinoids present in the plant have distinct actions, not all detrimental to mental health. Cannabis effects depend primarily on the content of THC and CBD, and other minor cannabinoids, which in turn depends on the plants' strain, regional origin, and how the plant is processed. For instance, leaves of *Cannabis sativa* (marijuana) have a THC content of 4–6%, whereas the resin (hashish) provides 10–15% THC. Indoor-cultivated plants (skunk) can contain up to 20% THC, while oil formulated as an alcoholic resin extract has up to 60% THC.^[2,62–65]

The origin of the plant can also make considerable difference in terms of THC content. For example, marijuana produced in the Netherlands in 2008 contained about 16% THC and virtually no CBD, whereas strains imported from Nepal, Afghanistan, or Morocco contained a similar proportion of THC (17%) but also contained 9% CBD.^[64] In 1982, it was found that schizophrenic patients in South Africa experienced an increased frequency of acute psychotic episodes after the use of a variety of *Cannabis sativa* virtually devoid of CBD.^[66] Psychotic effects in some instances are closely related to the THC:CBD ratio: a higher proportion of THC is linked to psychotropic effects, whereas high CBD level is linked to antipsychotic effects. A study conducted by Zuardi *et al.* demonstrated the interactions between THC and CBD in healthy volunteers, with the latter drug inhibiting THC-induced anxiety and subjective alterations.^[67]

In 2008,^[68] it was reported that psychosis and delusions were correlated with the smoked CBD:THC ratio found in hair. Higher levels of anhedonia, hallucinations, and delusions were observed in individuals with only THC in their hair compared with those with both THC and CBD, and those with no cannabinoid. This further supports the concept that the presence of CBD in smoked cannabis counteracts to some extent the psychotropic effects of THC.

High THC and low CBD concentrations have also been associated with a higher risk of a first psychotic episode,^[69] while cannabis with high CBD content was associated with fewer psychotic experiences.^[70] Cognitive deficits emerged in individuals who smoked cannabis with a low-CBD content, whereas high-CBD cannabis smokers tested in memory tasks under acute intoxication performed similarly than when tested in a drug-free state.^[71] Conflicting findings were reported by the same authors in different studies. Zuardi^[72] reported significant improvement of the symptomatology in a 19-year-old schizophrenic girl given increasing doses of oral CBD up to 1500 mg/day for four weeks. However, ten years later the same group reported negative results in three 22–23-year-old boys with treatment-resistant schizophrenia administered CBD monotherapy for four weeks.^[73] The discrepancy may be due to the short CBD treatment and/or to the fact that in the second study the patients were also insensitive to clozapine, an atypical antipsychotic. Even at high doses, CBD was well tolerated and minimal side effects were reported. Intriguingly, psychotic symptoms in acute schizophrenia have been found to be reduced by CBD with a potency similar to amisulpiride, an atypical antipsychotic D2 and D3 receptor antagonist, but with fewer side effects such as extrapyramidal symptoms (movement disorders such as dystonia, pseudo-parkinsonism, akinesia, and akathisia) and weight gain.^[74]

Results reported in the clinical domain were consistent with pre-clinical evidence. CBD reduces stereotypes and hyperlocomotion induced by apomorphine and amphetamine,

respectively, with no undesired effects, such as the extrapyramidal effects induced by classical antipsychotics,^[75–77] thus showing a pharmacological profile resembling that of clozapine. Interestingly, both drugs induce *c-fos* expression (a proto-oncogene commonly employed to detect specific neuronal functional activation) in the lateral septal nucleus and the nucleus accumbens, in which antipsychotics exert some of their effects.^[78] No induction of *c-fos* is seen in motor-related brain areas like the basal ganglia,^[79] explaining the lack of extra-pyramidal motor effects of CBD.

In addition to DA-based models, CBD effects have also been explored in glutamate-based models, as it can reverse the hyperlocomotion induced by the NMDA receptor antagonist ketamine.^[77] CBD also reverses disruption of pre-pulse inhibition induced by NMDA receptor antagonist MK-801 administration.^[80] Moreover, it was reported to restore the deficit in social interactions induced by MK-801.^[81]

The ability of CBD to inhibit the fatty acid amide hydrolase (FAAH, the enzyme that catalyses anandamide degradation) has been suggested as a possible mechanism to explain its antipsychotic effects. Schizophrenic patients have higher levels of anandamide,^[28–30] and the intensity of symptoms is known to be negatively correlated with cerebrospinal levels of anandamide.^[29,82] Accordingly, in animals, the pharmacological blockade of anandamide degradation attenuates psychotic-like behaviours induced by amphetamine and phencyclidine.^[83] Such elevation of anandamide levels observed in schizophrenia has been suggested to reflect a compensatory adaptation to the disease state. Based on this view, the use of FAAH inhibitors has gained growing interest as a possible treatment. Recently, a clinical study conducted by Leweke, suggested that by indirectly enhancing anandamide signalling, CBD alleviates psychotic symptoms in schizophrenic patients.^[84]

The association between improved clinical symptoms and serum anandamide levels observed in CBD-treated schizophrenics, suggests that the ability of CBD to indirectly enhance anandamide signalling might represent a possible mechanism contributing to its antipsychotic properties.

Alternatively, CBD's ability to bind TRPV1Rs has also been suggested as a possible alternative mechanism to explain its anti-psychotic-like effects using a model of impaired sensory gait (pre-pulse inhibition) induced by the glutamate receptor antagonist MK801.^[81]

Whether CBD may alleviate psychotic symptoms through complementary or alternative mechanisms, including interactions with serotonin 5-HT_{1A} receptors,^[13,14] and GPR55 receptors^[17] should also be taken in consideration, and at present awaits further clarification.

CBD effects have been investigated mainly focusing on positive and negative symptoms of schizophrenia, yet little is known about its potential effects on cognitive symptoms. This is of great interest as schizophrenics are cognitively impaired, primarily in attention, working memory, and executive functions. Unfortunately, currently prescribed anti-psychotics have limited efficacy in ameliorating these cognitive deficits, increasing the scientific and clinical interest on possible CBD effects on these symptoms.

The high density of cannabinoid receptors in the hippocampus suggests that the endocannabinoid system is involved in superior cognitive functioning; hence, it is reasonable to expect some modification of cognitive symptoms following cannabinoid pharmacological manipulation. CBD increases *c-fos* expression in brain areas often impaired in schizophrenia and involved in attention processes (including medial pre-frontal cortex and the

cingulate gyrus),^[85] indicating increased activity in these regions. Hence, there is a rationale to believe that CBD treatment might be beneficial for cognitive symptoms; however, initial pre-clinical and clinical results have not been promising. For instance, in schizophrenic patients treated with 300 or 600 mg CBD, no beneficial effects were documented in the *Stroop Color Word Test* attentional task, and the highest dose being even detrimental.^[86]

In one animal study, a CBD-rich extract was found to be ineffective in a spatial memory task in animals treated with MK801 and scopolamine;^[87] however, this extract also contained a significant concentration of THC, which could have counterbalanced the positive effect of CBD. In previous work, the same group showed that CBD-enriched extracts had no effects on working and short-term memory, and that at high doses it antagonizes THC-induced memory deficit.^[88] This suggests that CBD could counteract memory deficits induced by cannabinoids, but not cholinergic or glutamatergic disruption. CBD effects on cognitive function are currently under investigation in a phase II clinical trial,^[89] in which CBD is administered together with anti-psychotics to treat cognitive symptoms in schizophrenic patients.

These studies indicate that CBD possess anti-psychotic properties, but whether they extend to the cognitive domain awaits further investigation.

Conclusion

In conclusion, there is mounting evidence supporting the therapeutic use of CBD to treat schizophrenic symptoms; however, medical use of cannabinoid extracts is met with opposition in many countries based on legislation, and social traditions.

The unpredictability of the physiological effects of cannabis promotes the perception that there is a potential risk of anti-social behaviour. The fact that cannabis effects also depend upon endogenous cannabinoid tone may account for such variability between users, along with the variety of cannabis strains, provenance, and THC:CBD content. All these variables certainly render the endorsement of cannabis for medical use a conundrum.

Research offers an overwhelming body of data supporting its therapeutic value. Undeniably, the habitual use of cannabis increases the risk of developing schizophrenia, especially in vulnerable subjects, but evidence suggests that this may be largely attributed to THC. Conversely, preclinical and clinical studies suggest a potential anti-psychotic activity of CBD, with a pharmacological profile resembling that of atypical anti-psychotics. Being devoid of psychotropic activity, CBD could represent a reliable medication for schizophrenia, especially in view of its lack of extra-pyramidal side effects.

Particular attention should be paid, however, when supporting the idea of using 'cannabinoids to treat schizophrenia'. This could lead to the misconception, especially among adolescents, that smoking cannabis is always good for you.

'In terms of harm reduction, users should be made aware of the higher risk of memory impairment associated with smoking low cannabidiol strains of cannabis like 'skunk' and encouraged to use strains containing higher levels of cannabidiol'.^[71]

It might sound somewhat idealistic, but I value Morgan's statement. According to the definition of Catullo, cannabis inspires a feeling of *Odi et Amo* (hate and love). I feel that balanced information should be favoured within the media to inform the cannabis-smoking community (especially adolescents), of both the *good* and the *bad* aspects of cannabis.

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