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The Potential of Cannabidiol Treatment for Cannabis Users With Recent-Onset Psychosis

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A major factor associated with poor prognostic outcome after a first psychotic break is cannabis misuse, which is prevalent in schizophrenia and particularly common in individuals with recent-onset psychosis. Behavioral interventions aimed at reducing cannabis use have been unsuccessful in this population. Cannabidiol (CBD) is a phytocannabinoid found in cannabis, although at low concentrations in modern-day strains. CBD has a broad pharmacological profile, but contrary to Δ9-tetrahydrocannabinol (THC), CBD does not activate CB1 or CB2 receptors and has at most subtle subjective effects. Growing evidence indicates that CBD acts as an antipsychotic and anxiolytic, and several reports suggest neuroprotective effects. Moreover, CBD attenuates THC's detrimental effects, both acutely and chronically, including psychotogenic, anxiogenic, and deleterious cognitive effects. This suggests that CBD may improve the disease trajectory of individuals with early psychosis and comorbid cannabis misuse in particular—a population with currently poor prognostic outcome and no specialized effective intervention.

Keywords: cannabidiol/cannabis/psychosis/THC/first episode

Cannabis Use Detrimentally Affects Outcome in Individuals With Recent-Onset Psychosis

The prevalence of cannabis misuse is significantly greater in people with schizophrenia (PSZ) than in the general population.[1,2] Cannabis use disorders are especially common in younger patients and patients with first-episode psychosis. Estimates of cannabis use at first break range from one to two thirds of affected individuals.[3–6] The impact on conversion to psychosis has been studied extensively; frequent use doubles the risk of developing schizophrenia[7] and is associated with a younger age at first episode.[8] After the first break, estimates of continued use range from just over 50%[5,9] to 100% of users.[6]

Cannabis use after a first psychotic break is a major predictor of bad prognostic outcome. This is of particular significance given that the early clinical trajectory of psychotic disorders is thought to critically influence long-term outcome.[10–13] Cannabis use, especially heavy use, is associated with more and earlier psychotic relapses.[14] Among users with first-episode psychosis, heavier users tend to experience more, and more severe, psychotic symptoms and show a poorer illness trajectory with regards to functional outcomes.[15] Specifically, cannabis use is associated with more severe symptoms and poorer antipsychotic response in the positive and disorganized dimensions.[16,17] Longitudinally, periods of cannabis use are accompanied by a dose-dependent increase in the odds of relapse to psychosis.[18] Cannabis use is also associated with poorer medication adherence following a first break,[6,19] and, in part related to that, a lower probability of remission during the following year.[6] Effects of cannabis use on cognitive outcome in PSZ are more controversial. Several studies suggest paradoxical positive associations between use history and cognition,[20,21] which may however reflect selection bias due to a role of cannabis in precipitating psychosis despite lower biological vulnerability, and the cognitive challenges associated with obtaining an illicit substance.

The acute effects of cannabis, Δ9-tetrahydrocannabinol (THC), or of the THC analog nabilone in nonpsychotic individuals mimic positive, negative, and cognitive symptoms of schizophrenia,[22–24] as well as neurophysiological phenomena associated with psychosis.[25–28] In PSZ, THC acutely worsens psychotic symptoms and cognitive functions,[29] and there is evidence that individuals with a predisposition for psychosis are more vulnerable to these acute psychotomimetic and cognitive-impairing effects.[30] Chronically, cannabis abuse has detrimental effects on brain morphology specifically in PSZ with continuing consumption after conversion.[31,32]

Behavioral interventions targeted at reducing cannabis use in individuals with first-episode psychosis have been consistently unsuccessful (reviewed by Wisdom et al[9]). An effective treatment framework for this population is

lacking entirely, and many programs available to individuals with early psychosis actively exclude for heavy, unmanaged cannabis abuse. Thus, there is an urgent need for novel treatments that reduce cannabis use or its detrimental consequences in people with recent-onset psychosis.

Cannabidiol

Cannabis contains >100 different cannabinoids; however, the phytocannabinoid THC is the main psychoactive component, thought responsible for the deleterious effects described above. Cannabidiol (CBD) is another phytocannabinoid in cannabis. Contrary to THC, it has at most subtle subjective effects and no euphorogenic properties,[33] and it does not activate CB1 or CB2 cannabinoid receptors. Despite its very low affinity and absence of intrinsic activity, CBD appears to reduce the efficacy of THC and other agonists at CB1 and CB2 receptors.[34–37] CBD antagonizes THC effects also via GPR55 receptors, which are activated by THC and blocked by CBD.[35] CBD's pharmacological profile further includes 5-HT_{1A} receptor activation (in common with antidepressant drugs), adenosine reuptake inhibition,[38–43] antioxidant[44] and anti-inflammatory effects,[45,46] suppression of immunoactivation-induced tryptophan degradation,[47] binding and transient activation of TrpV1 vanilloid receptors,[38] and upregulation of the endocannabinoid anandamide (*N*-arachidonoylethanolamine, AEA), the latter by interacting with fatty acid-binding proteins that mediate AEA's cellular reuptake and transport to its catabolic enzyme fatty acid amide hydrolase (FAAH).[38,48] CBD also inhibits T-type calcium channels,[49] and the conversion of THC to the more psychoactive 11-OH-THC.[36,50] Furthermore, there is evidence that CBD is a partial agonist at dopamine D2High receptors.[51] For an in-depth review of CBD's pharmacological actions, see Gururajan and Malone.[52]

While an early, small-N study suggested that CBD attenuates THC-induced euphoria,[53] a recent investigation did not find that CBD alters the positive reinforcing effects of THC.[54] However, lower appetitive effects of THC-associated stimuli were observed after smoking low-CBD than high-CBD strains of cannabis.[55] Combined, these findings may suggest that chronic treatment with CBD has the potential of reducing cannabis use; however, there are to date no direct tests of this hypothesis.

Evidence that CBD counteracts detrimental effects of cannabis misuse is more plentiful:

CBD Counteracts Deleterious Effects of THC

Given *acutely* to healthy volunteers, oral CBD has been reported to reverse the acute psychotomimetic effects of THC,[56,57] attenuate the anxiogenic and other subjective effects of THC,[58,59] and counteract detrimental effects of THC on delayed episodic recall (but not on immediate recall or digit span)[56] and of the THC analog nabilone on binocular depth inversion.[24] Similarly, inhaled CBD was reported to counteract detrimental effects of THC on prose recall[60] and facial emotion recognition.[61] In parallel, several preclinical reports also suggest reversal of THC-induced cognitive deficits (reviewed by Osborne et al[62]). In an fMRI study, effects of acute CBD on BOLD responses were opposite to acute THC effects in regions including striatum, hippocampus, amygdala, and sensory cortex.[57]

That *chronic* CBD may attenuate psychotogenic effects of chronic THC was suggested by findings that higher levels of CBD in hair samples from cannabis users were associated with lower psychosis-like symptoms.[63,64] Similarly, smokers of cannabis strains known to contain a higher proportion of CBD had lower positive-like symptoms than smokers of low-CBD cannabis.[65] Furthermore, reductions in hippocampal volume and NAA, seen in chronic cannabis users, were not observed in users exposed to larger concentrations of CBD, consistent with neuroprotective effects.[66]

The CBD content of street cannabis has steadily decreased over the last two decades, resulting in a THC:CBD ratio of ~80:1 today, as compared with 14:1 in 1995.[67] Thus, the fact that variation in CBD content of current street cannabis has detectable effects suggests that larger amounts, administered chronically in a controlled manner, may have clear protective effects. Interestingly, evidence was presented at a recent conference that chronic THC use increases striatal D1–D2 dopamine receptor heteromerization,[68] a mechanism suggested to be associated with reduced hedonic value of stimulant drugs and natural rewards, depression, anxiety,[69] and reduced reward learning in cannabis dependence.[70] CBD attenuated the THC-induced increase in D1–D2 heteromerization,[68] suggesting that it may help restore healthy reward processing, a mechanism of high relevance to schizophrenia[71] and substance use disorders.[72] Through this mechanism, as well as through potential attenuation of THC's acute positive reinforcing effects,[53,55] chronic CBD administration may not just reduce the deleterious effects of THC but also cannabis consumption itself, a hypothesis that remains to be tested.

Effects of CBD Alone

CBD appears to also benefit PSZ not using cannabis. In line with preclinical studies suggesting antipsychotic properties of CBD (reviewed by Gururajan and Malone[52] and Schubart et al[73]), a 4-week treatment with CBD (600–800 mg/day p.o.) alleviated psychotic symptoms in otherwise unmedicated PSZ ($N = 21$) to a similar degree as amisulpride ($N = 21$), but with fewer side effects.[74] Symptom reductions were quantified as changes over time relative to a no-drug baseline, without a placebo control, and did not differ between positive and negative

symptom subscales. In a larger trial presented at a recent conference,[75] CBD (1000 mg/day; $N = 43$) or placebo ($N = 45$) was administered p.o. for 6 weeks as adjunct medication to people with schizophrenia-spectrum disorders stably medicated with conventional antipsychotics, but with residual symptoms. This study found significant reductions in positive but not negative symptoms with CBD relative to placebo, over and above the effects of the standard medication, and a near-significant trend toward cognitive improvement as measured with the Brief Assessment of Cognition in Schizophrenia.

In laboratory studies employing small sample sizes ($N \leq 15$/group), single oral doses of CBD have been reported to reduce anxiety and associated physiological and BOLD changes in healthy individuals[57,76–78] and in generalized social anxiety disorder.[79] These effects would be of high clinical relevance to individuals with schizophrenia-related disorders given that anxiolytics are frequently prescribed to PSZ, including individuals with first-episode schizophrenia-spectrum disorders,[80] and exposure to benzodiazepines is dose-dependently associated with increased mortality in PSZ.[81] However, anxiolytic effects of chronically administered CBD remain to be confirmed in well-powered clinical trials.

Acute procognitive effects of CBD alone, in the absence of THC-induced impairment, may be suggested by findings of increased sensory cortical responses to visual and auditory stimulation[82] and reduced reaction time[83] in healthy subjects. However, there are also negative findings,[57] and any further evidence to date is lacking. Procognitive effects of CBD when administered chronically may be expected due to its potent antioxidant[44] and anti-inflammatory properties,[46] especially in disorders with an etiology thought to involve oxidative stress and inflammatory processes, such as schizophrenia. Indeed, there is ample preclinical evidence for neuroprotective and procognitive properties of CBD in models of inflammation, ischemia, and excitotoxicity.[50,62] In schizophrenia-spectrum disorder, evidence to date is limited to the trend reported by McGuire et al.[75]

Biological Target Mechanism

As described above, CBD has a broad spectrum of pharmacological actions. Thus, clinical benefits may result from several possible mechanisms:

(*a*) The recent finding that CBD is a partial agonist at dopamine D2High receptors,[51] similar to the antipsychotic aripiprazole, may at least in part account for its antipsychotic effects and for its potential reduction of THC's primary and secondary reinforcing effects. CBD's efficacy as an adjunct to dopamine antagonists[75] may indicate benefits derived from a more even (low) dopaminergic tone, reflecting this partial agonist action. Alternatively, it may point to additional, nondopaminergic mechanisms of CBD's antipsychotic effects—a desirable possibility given that it would open up novel treatment avenues.

(*b*) CBD has been reported to up-regulate concentrations of the endocannabinoid AEA by inhibiting its reuptake and degradation.[38,48] A 4-week treatment with CBD increased AEA serum levels in a small sample of PSZ, and this increase was associated with psychotic symptom reductions.[74] Other studies suggest that anxiolytic effects, too, may be mediated by AEA up-regulation.[84,85] Findings that AEA concentrations are elevated in CSF of acutely psychotic PSZ[86] may reflect a counter-adaptive response because in first-break antipsychotic-naive patients, AEA levels were inversely correlated with psychotic symptoms.[87–89] Similarly, AEA was elevated in CSF of prodromal individuals, and those with higher AEA levels displayed later transition into frank psychosis.[90] Heavy cannabis use is associated with AEA *reduction* in individuals with first-episode psychosis[89] and without psychosis,[91] and lower CSF AEA in the latter group was associated with persistent psychosis-like symptoms.[91] Thus, benefits from AEA up-regulation by CBD may be particularly pronounced in psychosis with comorbid cannabis use.

(*c*) Other pharmacological targets of CBD potentially responsible for its clinical benefits include, but are not limited to, 5-HT_{1A} receptors, GPR55 receptors, and TrpV1 receptors.[52,92] However, any connections drawn between these targets and the clinical effects described above would be speculative at this point in time.

Further research is warranted to determine which, or more likely, which combination of the above mechanisms is responsible for CBD's clinically beneficial actions and attenuation of THC effects. The fact that no single mechanism can to date be denoted as "the" target mechanism should not detract from its clinical potential.

Pharmacokinetics and Safety of CBD

CBD is highly lipophilic and readily crosses the blood brain barrier.[93] It has a long half-life in humans: 18–33 h after i.v. administration,[94] and 2–5 days after chronic oral dosing with ~700 mg/day, with no sex difference.[95] Some CBD metabolites are biologically active and may contribute to CBD's effects profile, although not via action at CB receptors.[96]

Large doses are necessary to compensate for the low bioavailability of oral CBD.[33,54,97] Haney et al[54] found that an 800-mg dose of CBD generated an average peak plasma concentration (C_{max}) of 77.9 ng/ml 3 h (t_{max}) after acute dosing. Inter-individual variability was substantial. Bhattacharyya et al[57] found much lower CBD blood levels

of 17 ± 29 ng/ml 2 h after administration (ie, preceding t_{max}) with a 600-mg dose, and Englund et al[56] reported average blood levels of ~50 ng/ml 3:45 h after oral administration of the same dose. None of the above studies made any reference to the inactive capsule filler. Manini et al[33] administered oral CBD encapsulated and dissolved in corn oil and reported better bioavailability with relatively lower variability: A dose of 800 mg resulted in C_{max} of 221.1 ± 35.6 ng/ml with t_{max} of 3 h, and 400 mg resulted in C_{max} of 181.2 ± 39.8 ng/ml at 3 h.

CBD has an extensive record of clinical study in subjects with a variety of conditions, including pain, multiple sclerosis, anxiety, psychosis, and epilepsy, with an excellent safety and tolerability profile, no noticeable psychiatric adverse effects, and no motor impairment (reviewed by Bergamaschi et al[98]). Doses of up to 1280 mg of CBD have been administered to humans without toxicity or serious adverse events.[98–100] Studies assessing cognitive performance did not report any impairment with CBD.[54,56,57,101]

CBD at acute doses of up to 800 mg did not have any effect on heart rate or blood pressure.[33,54,58,79,101,102] Leweke et al[74] reports that a 4-week treatment with 600–800 mg of oral CBD per day did not significantly affect hepatic or cardiac function in PSZ. A 6-week trial in Huntington's disease patients detected no systematic abnormalities specifically associated with CBD treatment (~700 mg/day) in blood chemistry, complete blood count and differential, prolactin levels, and urinalysis.[102] Similarly, the administration of 200–400 mg of CBD to participants with and without epilepsy for 1–4.5 months did not result in any changes in vital signs or labs. A few reports of somnolence may have been due in part to concomitant use of antiepileptic medication.[103] Other studies did not report any subjective effects of CBD (400–800 mg p.o.) other than anxiolytic effects or reversal of adverse effects of THC.[33,54,57,58,61,79,102,104] The only exception is one study reporting a modest increase in self-reported sedation.[105]

Haney et al[54] found that 5 out of 31 study participants reported "gastrointestinal upset" within 72 h of ingesting an 800-mg dose of CBD, as compared with 1, 2, and 1 participants ingesting placebo, 200 and 400 mg, respectively. Similarly, Manini et al[33] reported gastrointestinal side effects in 1 out of 6 participants exposed to an 800-mg dose of CBD. Thus, 800 mg of CBD (p.o.) may be pushing the upper dose limit, although the preliminary report of a trial in PSZ did not mention any such side effects with chronic administration of 1000 mg of CBD per day.[75]

There is no indication of mutagenic effects of CBD.[106] In vitro studies have shown that CBD can suppress production of interleukin 8 and 10[107] and induce lymphocyte apoptosis[108] at micromolar concentrations; thus, there is a theoretical risk of immunosuppression. However, other results suggested a potential biphasic response, with stimulatory action at nanomolar concentrations.[43,98] CBD in the micromolar range also exhibited inhibitory effects on P-glycoprotein efflux and ATPase activity.[98] The extent to which in vitro effects of these concentrations are predictive of potential side effects at the nanomolar concentrations found in human serum after CBD administration is unclear.

CBD acutely inhibits the cytochrome P450 2B, 2C, and 3A subfamilies in vitro, with potential induction after long-term exposure.[98] Again, concentrations associated with these interactions were in the micromolar range and significantly higher than found in human blood.[109] However, the possibility of an altered bioavailability of compounds that are primarily metabolized by these cytochromes has to be considered. Such compounds include (but are not limited to) alprazolam, bupropion, carbamazepine, citalopram, clozapine, diazepam, imipramine, sertraline, valproic acid, and zolpidem. Importantly, a recent trial testing 1000 mg of CBD per day vs placebo in PSZ treated with conventional antipsychotics reported no adverse effects specifically associated with the CBD arm,[75] which suggests that CBD may be a safe adjunct medication.

Summary: Potential Benefits of CBD for Cannabis Users With Recent-Onset Psychosis

The antipsychotic, anxiolytic, and potential procognitive effects of CBD, in the absence of side effects typically seen with conventional medication, would constitute a desirable effects profile for individuals with any schizophrenia-spectrum disorder. In particular, however, its reversal of psychotogenic, anxiogenic, and cognitive-impairing effects of THC, both acutely and chronically, would suggest CBD as a tailored intervention for individuals with psychosis and comorbid cannabis misuse, who constitute a large proportion of patients in the early stages of schizophrenia-related disorders. By potentially dampening the positive reinforcing effects of THC and restoring healthy reward processing, CBD may even reduce cannabis use itself. It has to be emphasized, however, that most of these suggested benefits are based on laboratory studies, in part employing small sample sizes, and confirmation by well-powered randomized clinical trials is largely pending. Clearly, this field is at an early stage, with expectations at risk of overtaking evidence. To date, there are promising leads warranting larger trials to confirm or test CBD's efficacy in reducing positive symptoms, anxiety, cognitive deficits, and cannabis misuse. The combination of these beneficial effects, initiated early in the disease course, would hold the promise to substantially improve the clinical trajectory and long-term outcome of individuals with psychosis and comorbid cannabis misuse, in particular, a population with currently poor prognosis and no specialized effective intervention.

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