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Cannabidiol and its Potential Evidence-Based Psychiatric Benefits – A Critical Review

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ABSTRACT

The endocannabinoid system shows promise as a novel target for treating psychiatric conditions. Cannabidiol (CBD), a naturally occurring cannabinoid, has been investigated in several psychiatric conditions, with diverse effects and an excellent safety profile compared to standard treatments. Even though the body of evidence from randomised clinical trials is growing, it remains relatively limited in most indications. This review comprises a comprehensive literature search to identify clinical studies on the effects of CBD in psychiatric conditions. The literature search included case studies, case reports, observational studies, and RCTs published in English before July 27, 2023, excluding studies involving nabiximols or cannabis extracts containing CBD and Δ^9-tetrahydrocannabinol. Completed studies were considered, and all authors independently assessed relevant publications.

Of the 150 articles identified, 54 publications were included, covering the effects of CBD on healthy subjects and various psychiatric conditions, such as schizophrenia, substance use disorders (SUDs), anxiety, post-traumatic stress disorder (PTSD), and autism spectrum disorders. No clinical studies have been published for other potential indications, such as alcohol use disorder, borderline personality disorder, depression, dementia, and attention-deficit/hyperactivity disorder. This critical review highlights that CBD can potentially ameliorate certain psychiatric conditions, including schizophrenia, SUDs, and PTSD. However, more controlled studies and clinical trials, particularly investigating the mid- to long-term use of CBD, are required to conclusively establish its efficacy and safety in treating these conditions. The complex effects of CBD on neural activity patterns, likely by impacting the endocannabinoid system, warrant further research to reveal its therapeutic potential in psychiatry.

Introduction

Psychiatric diseases are serious health conditions characterized by clinically significant impairments in various areas, such as disturbances in affect, emotion regulation, perception, thinking, or behaviour. These impairments are usually associated with distress or personal, social, and/or occupational functioning difficulties. As estimated by two different methodological approaches, psychiatric disorders attributed to 125.3 to 418 million disability-adjusted life years (DALYs) in 2019, accounting for 4.9–16 % of the global DALYs [1, 2]. The subsequent economic value was estimated at approximately USD 5 trillion [1].

Despite the burden on individuals with psychiatric conditions, their loved ones, and society, there has been limited progress in developing improved medications with novel mechanisms of action. However, cannabidiol (CBD) shows promise as a novel medication under investigation for various psychiatric conditions.

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CBD is one of two major phytocannabinoids of the plant *Cannabis sativa*. Unlike its structural relative Δ^9-tetrahydrocannabinol (Δ^9-THC), CBD does not pose psychotomimetic effects. To date, CBD has been approved as an orphan drug by the Food and Drug Administration (EPIDIOLEX) and the European Medicines Agency (EPIDYOLEX) as an adjunct treatment for rare forms of childhood epilepsy (Lennox-Gastaut and Dravet syndrome) in treatment resistant-children and to treat tuberous sclerosis complex with other epilepsy treatments in children.

Both CBD and Δ^9-THC interact differently with the endocannabinoid system (ECS) in the human body. The ECS is a complex network of endogenous cannabinoid signalling molecules, cannabinoid receptors type 1 and 2 (CB_1R, CB_2R), transporters, and various enzymes [3, 4]. While the psychotomimetic activity of Δ^9-THC can be explained mainly through its activity on the CB_1R, CBD shows only minimal negative allosteric modulation on the CB_1R [5]. However, the mechanism of action of CBD is not fully understood, and it is likely that more than one mechanism contributes to its suggested anticonvulsant, antipsychotic, antioxidative, anti-inflammatory, antinociceptive, and anxiolytic effects [6]. The anticonvulsant effect of CBD has been attributed to its antagonistic activity at the G-protein coupled receptor GPR55 [7]. Also, direct or indirect activation of the transient receptor potential vanilloid channel [8] or agonistic activation of the nuclear peroxisome proliferator-activated receptor [9] may mediate the anticonvulsive properties of CBD. The antipsychotic effects of CBD appear to be associated with increased levels of the endocannabinoid anandamide [10], suggesting a direct inhibition of the fatty acid amid hydrolase (FAAH) [10], the enzyme responsible for anandamide degradation or of the fatty acid binding proteins [11] responsible for transporting the endocannabinoid to the FAAH enzyme [12]. Furthermore, the agonistic activation or allosteric modulation of the human serotonin receptor ($5\text{-}HT_{1A}$) may mediate the anxiolytic, anti-cataleptic, and anti-nausea effects of CBD [13–16]. However, many other potential cellular targets have been proposed without defining their pharmacological significance [6, 17].

Cannabis consumption, including Δ^9-THC and CBD, has a long history and social acceptance [18], possibly leading to better treatment adherence and success. The diverse biological effects and superior safety profile of CBD make it a promising candidate for new neuropsychiatric treatments.

This critical review focuses on clinical data, intending to provide an overview of evidence-based psychiatric benefits of CBD and the possible lack of clinical evidence in specific psychiatric areas.

Methods

A standardized electronic literature search was performed on PubMed and Web of Science electronic databases. Articles written in English, published before July 27, 2023, and reporting case reports, case report series, observational and clinical studies, and randomised clinical trials (RCTs) investigating the effects of CBD in psychiatric conditions were considered. This article was designed as a critical review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement 2020 [19]. Regarding neurobiological mechanisms of CBD in humans, only technical studies using, e. g., electroencephalography/magnetoencephalography, magnetic resonance imaging (MRI)/functional MRI (fMRI), and positron emission tomography (PET)/single-photon computerized tomography (SPECT) were selected. Studies investigating solely behavioral or neurocognitive effects of CBD in healthy volunteers were not included. Furthermore, we did not include studies on nabiximols (Sativex), which contains almost the same amount of CBD and Δ^9-THC, or cannabis extracts containing both cannabinoids. Notably, only completed studies were considered. The search term "cannabidiol" was combined with "psychiatry", "psychosis", "schizophrenia", "risk mental state", "substance use disorder", "cannabis use disorder", "heroin use disorder", "cocaine use disorder", "alcohol use disorder", "post-traumatic stress disorder", "borderline personality", "anxiety", "mood disorder", "depression", "bipolar", "dementia", "autism", and "attention-deficit/hyperactivity disorder". In addition, an extensive manual search of the reference lists of included studies, was conducted to identify additional relevant publications. Literature searches were performed independently by co-authors ID and CR. Identified studies were assessed based on title and abstract by ID and CR, and accepted publications were verified by FML.

Results

The PRISMA flow chart visualizing the literature selection process is depicted in ▶ **Fig. 1**. The search strategy resulted in a total of 150 publications, of which 54 were included in this review (see ▶ **Table 1–4**). In some cases, several articles were published reporting different aspects of the results of the same study; thus, the publications included are based on 40 separate study populations. Of the 54 publications, 16 studies focused exclusively on the effects of CBD in healthy subjects. Thirty-eight studies investigated CBD as a treatment option in people with a psychiatric condition in the form of a case study (5), case series (2), open-label clinical trial (2), or RCT (29).

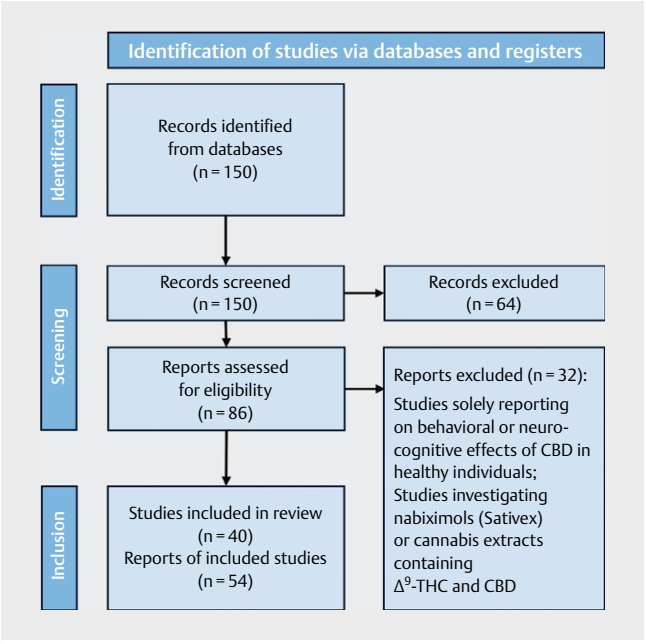
There were no reports on the effects of pure CBD on alcohol use disorder, borderline personality disorder, depression, dementia, and attention-deficit/hyperactivity disorder. In two women with bipolar affective disorder, CBD was ineffective in improving symptoms of a manic phase [20], but apart from this case report, there are no other studies to date.

Of the studies investigating CBD as a treatment option for psychiatric conditions, 20 studies focused on schizophrenia and psychotic disorders or clinically high-risk mental state (CHR) for psychosis, 13 on different types of substance use disorders, 19 on anxiety and post-traumatic stress disorder (PTSD), and 2 on autism spectrum disorder (ASD).

Schizophrenia and psychotic disorders

Psychosis is a syndrome characterized by the loss of connection to reality and has many underlying conditions [21]. The term schizophrenia describes those severe mental disorders characterized by psychotic symptoms (e. g., altered perceptions, delusional perceptions, hallucinations, diminished emotional expression, motivation, and social withdrawal) and cognitive impairments due to causes that have not yet been identified or ascribed. Approximately 3 % of people worldwide will develop a psychotic disorder at some point in their lives, but less than 1 % will be diagnosed with schizophrenia [22]. The development of antipsychotic medications went along

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▶ **Fig. 1** Adapted Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flowchart [19] illustrating the literature selection process.

with establishing the dopamine hypothesis of schizophrenia, resulting in drugs modulating dopaminergic and serotonergic signalling. However, the success of these medications is restricted by their limited effectiveness in many patients and the common occurrence of (severe) adverse effects [23]. Interestingly, various preclinical and clinical studies suggest a connection between the disease and specific pathological alterations in the ECS, including changes in serum and cerebrospinal fluid endocannabinoid levels and altered expression of CB_1Rs [17, 24]. Therefore, alternative pharmacological interventions modulating the ECS (e. g., CBD) rather than the dopaminergic or serotonergic system have been explored in recent years to provide better treatment options for people with psychotic disorders.

Cannabidiol as a potential antipsychotic medication

The first antipsychotic effects of CBD were reported by Zuardi et al. in 1995 [23] in a single case with schizophrenia, who was treated with up to 1,500 mg CBD per day over 4 weeks, leading to an improvement in psychotic symptoms [25]. This initial positive observation was followed by a case series of three individuals with treatment-resistant schizophrenia [26]. After an initial 5-day placebo treatment, the three young men received up to 1,280 mg of CBD per day for 30 days, followed by another 5-day placebo administration and subsequent treatment with olanzapine for a minimum of 15 days. CBD treatment resulted in only mild symptom relief in one person, while the other two showed no clinical improvement [26]. In six cases with a diagnosis of Parkinson's disease and psychotic symptoms for at least 3 months, open-label CBD treatment (flexible dosing regimen of up to 400 mg/day) resulted in a significant reduction in psychotic symptoms as assessed by the Brief Psychiatric Rating Scale (BPRS) [27]. Although previous case series suggested that patients with a long history of disease would not profit from CBD treatment, a successful case study was recently published [28] of a patient with a 21-year history of treatment-resistant schizophrenia. Seven weeks of CBD treatment (1,000 mg/day) as an adjunct to clozapine and lamotrigine resulted in markedly softened but continuous acoustic hallucinations and reduced negative symptoms. The hallucinations gradually disappeared after another 2.5 weeks with an increased CBD dose (1,500 mg/day). After 8 months, the patient still benefited from continued CBD add-on treatment [28]. However, while open-label case reports may direct research interest, they are very limited in terms of evidence.

Leweke et al. (2012) conducted the first RCT with a parallel-group design, in which 42 acutely psychotic patients received oral CBD or amisulpride (treatment regimen for both compounds: starting dose of 200 mg/day, titrated up to 800 mg/day within 4 days) for 28 days. Both interventions led to similar, significant improvements in positive and negative symptoms of psychosis (assessed by the Positive and Negative Syndrome Scale [PANSS] and BPRS). However, CBD demonstrated a distinctly superior side-effect profile compared to amisulpride treatment. Notably, the clinical improvements were strongly associated with higher serum anandamide levels in patients receiving CBD [10]. An additional secondary outcome analysis reported the effects of CBD and amisulpride on neurocognitive performance [29]. At baseline, both groups showed comparable performance in all neurocognitive tests. Both treatments improved visual memory and processing speed. While CBD enhanced sustained attention and visuomotor coordination, improvements in working memory performance were observed after amisulpride treatment. In 88 individuals with schizophrenia on stable antipsychotic medication, 1,000 mg/day of oral CBD (Epidiolex) as adjunctive therapy for 6 weeks also led to significant improvements in clinical symptoms (evaluated by PANSS and Clinical Global Impression Scale [CGI]) compared to placebo [30]. However, in 36 people with chronic schizophrenia on stable antipsychotic medication, a 6-week treatment with 600 mg/day oral CBD did not improve MATRICS Consensus Cognitive Battery (MCCB) performance or PANSS scores compared to placebo [31]. Similarly, in people with recent-onset schizophrenia (< 5 years), a 4-week treatment with 600 mg/day oral CBD did not affect any clinical assessment (PANSS, Hamilton Depression Scare, Young Mania Rating Scale, CGI, Global Assessment of Functioning Scale, and Social and Occupational Functioning Assessment Scale) or cognitive performance evaluated by the Brief Assessment of Cognition in Schizophrenia [32].

Cannabidiol as an antipsychotic in clinical-high-risk (CHR) mental state for psychosis

Individuals in a CHR mental state for psychosis present with attenuated psychotic symptoms (APS) or brief, limited intermittent psychotic symptoms (BLIPS), as well as more generalized and nonspecific psychiatric symptoms, and often show neurocognitive and functional impairment [33, 34]. To date, no pharmacological treatment has been approved because the condition has long been considered a risk status for psychosis rather than a disorder in its own right [35]. As a result, off-label use of various pharmacological interventions such as antipsychotics or antidepressants is common. However, given the functional impairment of these young people,

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▶ **Table 1** Clinical investigations on CBD for the treatment of schizophrenia and psychosis.

Reference	Study Design	Participants	Treatment	Scales, questionnaires, paradigms	Outcomes
Psychosis					
Zuardi et al., 1995 [25]	Case study	1 individual with SCZ	Up to 1500 mg CBD per day over 26 days	BPRS, IOSPI	Improvement in psychotic symptoms.
Zuardi, 2006 [26]	Case series	3 individuals with TRS	Day 1–5: placebo; day 6–35: CBD (starting at 40 mg/day, titrated up to 1280 mg/day); day 36–40: placebo, followed by a minimum of 15 days of treatment with olanzapine	BPRS	Only mild symptom improvement in one patient.
Zuardi et al., 2009 [27]	Open-label clinical trial	6 Parkinson's patients with psychosis for a minimum of 3 months	150–400 mg/day CBD (dose increased over 4-week treatment period)	BPRS, PPQ, UPDRS, MMSE, FAB, CGI-I	Significant decrease of psychotic symptoms in Parkinson's patients under CBD administration.
Makiol and Kluge, 2019 [28]	Case study	1 patient with TRS	Up to 1500 mg/day CBD as an add-on to clozapine and lamotrigine for 8 months	PANSS	Significant improvement in psychotic symptoms after 2.5 weeks of treatment and after 8 months of ongoing treatment.
*__Leweke et al., 2012__ [10]	RCT, parallel-arm design	39 acutely psychotic patients	800 mg/day CBD (stepwise increase starting at 200 mg/day) or amisulpride for 28 consecutive days	PANSS, BPRS, SAS, EPS	Both interventions led to significant clinical improvement; CBD presented with a clear superior side-effect profile.
*__Leweke et al., 2021__ [29]	RCT, parallel-arm design	39 acutely psychotic patients	800 mg/day CBD (stepwise increase starting at 200 mg/day) or amisulpride for 28 consecutive days	VBM, CPT, LNS, SOPT, DRT, AVLT, ROFT, DSC, TMT, VF	Both interventions improved neurocognitive functioning. CBD and amisulpride both improved visual memory performance and processing speed. CBD additionally improved sustained attention and visuomotor coordination. Amisulpride enhanced working memory performance.
McGuire et al., 2018 [30]	RCT, parallel-arm design	88 SCZ patients treated with standard antipsychotics	1000 mg CBD per day or placebo for 6 weeks	PANSS, BACS, GAF, SANS, CGI-I	CBD administration led to significant clinical improvements without increased occurrence of adverse events compared to placebo.
Boggs et al., 2018 [31]	RCT, parallel-arm design	36 chronic SCZ patients with stable antipsychotic medication	600 mg CBD or placebo for 6 weeks	MCCB, PANSS, several safety assessments for motor side effects	No improvement in MCCB or PANSS scores in patients treated with CBD compared to placebo.
van Boxel et al., 2023 [32]	RCT, parallel-arm design	31 stable recent-onset (<5 years) psychosis patients	600 mg/day CBD or placebo for 28 days	PANSS, HAM-D, YMRS, CGI, GAF, SOFAS, BACS, resting state and reward fMRI, monetary incentive delay task	In the CBD group, decreased positive symptom severity was correlated with diminishing glutamate and N-acetyl-aspartate levels; compared to placebo, CBD treatment affected default mode network functional connectivity.
O'Neill et al., 2021 [49]	RCT, cross-over design	15 psychosis patients, 19 healthy controls	600 mg CBD or placebo, single dose	PANSS, STAI, and fMRI during the verbal paired associate learning task	Patients showed significantly different neural activation compared to healthy controls in a verbal recall task; CBD improved activation patterns but failed to reach the results of the healthy controls.
Clinically high risk (CHR) for psychosis					
Koethe et al., 2023 [36]	Case study	1 antipsychotic-naïve man with CHR	600 mg CBD per day for 4 weeks	PANSS, SPI-A, SIPS, neuropsychological tests, cerebral glucose metabolism	Significant clinical improvement, improved cognitive performance, and increased cerebral glucose metabolism after 4 weeks of treatment.
*__Appiah-Kusi et al., 2020__ [38]	RCT, parallel-arm design	32 CHR patients	600 mg CBD or placebo for 1 week	TSST, STAI, SSDPS, serum cortisol levels	Patients showed significantly different cortisol reactivity compared to healthy controls; CBD administration in patients showed some improvements in anxiety and public speaking stress compared to placebo but did not significantly improve cortisol reactivity.

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▶ **Table 1** Continued.

Reference	Study Design	Participants	Treatment	Scales, questionnaires, paradigms	Outcomes
***Davies et al., 2022** [39]	RCT, parallel-arm design	33 CHR patients and 19 healthy controls	600 mg/day CBD or placebo for 1 week	CAARMS, STAI, fMRI during fearful-faces task, TSST	Healthy controls showed a significant negative relationship between cortisol levels and parahippocampal activation, which was significantly altered in CHR patients; oral CBD failed to restore this relationship in CHR patients.
***Bhattacharyya et al., 2018** [37]	RCT, parallel-arm design	33 antipsychotic-naïve CHR patients, 19 healthy controls	600 mg CBD or placebo, single dose	fMRI during the verbal paired associate learning task	Significantly decreased neural activation in three brain regions associated with psychosis state in patients compared to healthy controls; CBD increased neural activation in all three brain regions but did not reach the same activation as healthy controls.
***Wilson, 2019** [47]	RCT, parallel-arm design	33 antipsychotic-naïve CHR patients, 19 healthy controls	600 mg CBD or placebo, single dose	fMRI during reward processing tasks, CAARMS	Patients showed an abnormal activation in the left insula / parietal oculum compared to healthy controls, which was reduced by oral CBD administration.
***Davies et al., 2020** [48]	RCT, parallel-arm design	33 antipsychotic-naïve CHR patients, 19 healthy controls	600 mg CBD or placebo, single dose	fMRI during a fearful face-processing task, CAARMS, STAI	Patients showed significantly different neural activation compared to healthy controls; CBD improved activation patterns in patients but failed to match the results of healthy controls.
Healthy volunteers (EEG/MEG, MRI/fMRI, and PET/SPECT studies)					
***Borgwardt et al., 2008** [43]	RCT, repeated measures within-subject design	15 healthy individuals	600 mg CBD, 10 mg Δ^9-THC, or placebo, single dose	VAMS, STAI, AIS, PANSS, physiological measurements, fMRI activation during Go/No-Go Task	Δ^9-THC led to the deactivation of brain regions involved in response inhibition; CBD did not affect those brain regions; Δ^9-THC significantly increased VAMS, AIS, STAI, and PANSS scores compared to placebo; CBD did not affect corresponding ratings.
***Bhattacharyya et al., 2010** [44]	RCT, repeated measures within-subject design	Experiment 1: 15 healthy individuals with minimal previous cannabis exposure; Experiment 2: 6 healthy individuals	Experiment 1: 600 mg CBD, 10 mg Δ^9-THC, or placebo, single dose; Experiment 2: 5 mg i. v. CBD vs. placebo immediately before 1.25 mg i. v. Δ^9-THC, single dose	fMRI measurements during verbal memory, response inhibition, and sensory processing tasks and when viewing fearful faces; PANSS	Opposite effects of Δ^9-THC and CBD on neural activation patterns; CBD administration prevented Δ^9-THC-inducd psychotic symptoms.
***Winton-Brown et al., 2011** [45]	RCT, cross-over design	14 healthy volunteers	600 mg CBD, 10 mg Δ^9-THC, or placebo, single dose	VAMS, STAI, VAIS, PANSS, and physiological measurements; fMRI measurements during sensory stimulation paradigm	No significant symptomatic effects after CBD administration; CBD and Δ^9-THC differentially modulated brain functions in areas related to induced psychosis.
Grimm et al., 2018 [46]	RCT, cross-over design	16 healthy individuals	600 mg CBD, 10 mg Δ^9-THC, or placebo, single dose	EPI, fMRI	CBD administration produced significantly increased fronto-stratial connectivity; Δ^9-THC and placebo showed no effects.

If not stated otherwise, the treatment was administered orally. Studies that refer to the same participants are marked with an asterisk. Abbreviations: AIS = Analogue Intoxication Scale; AVLT = Auditory Verbal Learning Task; BACS = Brief Assessment of Cognition in Schizophrenia; BPRS = Brief Psychiatric Rating Scale; CAARMS = Comprehensive Assessment of At-Risk Mental States; CGI-I = Clinical Global Impression Improvement; CHR = clinically high risk for psychosis; CPT = Continuous Performance Task; DRT = delayed response task; DSC = Digit Symbol Coding; EEG = electroencephalography; EPI = echo-planar imaging; EPS = Extrapyramidal Symptoms Rating Scale; FAB = Frontal Assessment Battery; fMRI = functional magnetic resonance imaging; GAF = Global Assessment of Functioning scale; HAM-D = Hamilton Depression Scale; IOSPI = Interactive Observation Scale for Psychiatric Inpatients; LNS = Letter Number Sequencing; MCCB = MATRICS Consensus Cognitive Battery; MEG = magnetoencephalography; MMSE = Mini-Mental Status Evaluation; PANSS = Positive and Negative Syndrome Scale; PET = positron emission tomography; PPQ = Parkinson Psychosis Questionnaire; PSI = Psychotomimetic Stress Inventory; RCT = randomized controlled trial; ROFT = Rey-Osterrieth complex Figure Task; SANS = Scale for the Assessment of Negative Symptoms; SAS = Social Anxiety Scale; SCZ = schizophrenia; SIPS = Structured Interview for Prodromal Syndromes; SOFAS = Social and Occupational Functioning Assessment; SOPT = Subject Ordered Pointing Task; SPECT = single-photon emission computerized tomography; SPI-A = Schizophrenia Proneness Instrument – Adult; SSDPS = Self-Statements During Public Speaking Scale; STAI = State Trail Anxiety Inventory; TLFB = Timeline Followback; TMT = Trail-Making Task; TRS = treatment-resistant schizophrenia; TSST = Tier Social Stress Test; UPDRS = Unified Parkinson's Disease Rating; VAIS = Visual Analog Intoxication Scale; VAMS = Visual Analog Mood Scale; VAS = Visual Analog Scale; VBM = visual backward masking task; VF = Verbal Fluency; YMRS = Young Mania Rating Scale.

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▶ **Table 2** Clinical investigations on CBD for the treatment of substance use disorder.

Reference	Study Design	Participants	Treatment	Scales, questionnaires, paradigms	Outcomes
Healthy Volunteers					
Lawn et al., 2020 [54]	RCT, repeated measures within-subject design	23 healthy individuals	600 mg CBD or placebo	fMRI measurements during monetary incentive delay task, BDI, AUDIT, FTND, WTAR	CBD administration did not lead to altered reward-related brain activity compared to placebo.
Cannabis Use Disorder					
Crippa et al., 2013 [55]	Case study	1 female (19-year-old) cannabis-dependent patient	Day 1: 300 mg; day 2–10: 600 mg; day 11: 300 mg CBD	WDS, MWSC, BAI, BDI, AIS	Cannabis withdrawal symptoms, anxiety, and dissociative quickly decreased during treatment; relapse of cannabis use at 6-month follow-up, although at a lower frequency.
Shannon et al., 2015 [56]	Case study	1 male cannabis-dependent patient with bipolar disorder	24 mg CBD from oral spray per day, later decreased to 18 mg per day	PSQI, HAM-A	With CBD oil administration, the patient stopped cannabis consumption; positive changes in anxiety and sleep behaviour were noted.
*__Freeman et al., 2020__ [57]	RCT, parallel-arm design	77 cannabis-dependent individuals	200, 400, or 800 mg/day CBD or placebo for 4 weeks	Motivational interviewing, CWS, TLFB, PSQI, BDI, BAI	Cannabis abstinence increased by 0.27 days/week with 800 mg/day CBD treatment.
*__Lees et al., 2023__ [58]	RCT, parallel-arm design	70 cannabis-dependent individuals	200, 400, or 800 mg/day CBD or placebo for 4 weeks	Motivational interviewing, TLFB, CUD symptoms, prose recall, stop signal, trail-making, digit-span, and verbal fluency tasks	No difference in delayed verbal memory measurements between CBD and placebo groups; no significant dose-effect for any secondary outcome.
*__Hua et al., 2023__ [59]	RCT, parallel-arm design	70 individuals with cannabis use disorder	400 or 800 mg/day CBD or placebo for 4 weeks	Plasma anandamide, TLFB, CWS, BAI, BDI	400 mg/day CBD and placebo groups showed a significant reduction in plasma anandamide levels, while concentrations in individuals receiving 800 mg/day CBD did not change over the 28-day intervention.
Cocaine Use Disorder					
de Meneses-Gaya et al., 2021 [60]	RCT, parallel-arm design	31 individuals with crack-cocaine dependence	300 mg/day CBD or placebo, single dose	CCQ-Brief, MCCS, ASSIST, BDI, BAI, VAS, UKU-SERS	CBD administration significantly reduced signs of cravings compared to placebo; no effect on anxiety, depression, or sleep behaviour.
*__Mongeau-Pérusse et al., 2021__ [61]	RCT, parallel-arm design	78 individuals with moderate to severe cocaine use disorder	800 mg/day CBD or placebo, single dose	Drug-cue induced craving, time-to-cocaine relapse, VAS-C, TLFB, cocaine use, SAFTEE	No significant differences in cocaine craving or relapse between CBD and placebo groups.
*__Rizkallah et al., 2022__ [62]	RCT, parallel-arm design	78 individuals with moderate to severe cocaine use disorder	800 mg/day CBD or placebo, single dose	CANTAB: SST, CGT, PRM	No significant differences in cognitive outcomes between CBD and placebo groups.
*__Mongeau-Pérusse et al., 2022__ [63]	RCT, parallel-arm design	78 individuals with moderate to severe cocaine use disorder	800 mg/day CBD or placebo, single dose	Cue-induced craving sessions, relapse prevention group sessions, physiological measurements, VAS-A, BAI	No significant differences in anxiety symptoms and cortisol levels between CBD and placebo groups.
Nicotine Dependence					
Morgan et al., 2013 [64]	RCT, parallel-arm design	24 healthy cigarette smokers	ad libitum CBD or placebo from an inhaler for 1 week	SDS, STAI, BDI, BIS, TCQ, MRS, total cigarettes smoked	Participants inhaling CBD reduced their cigarette consumption by approximately 40 %, while placebo inhalators showed no effect; positive effects of CBD inhalation were maintained throughout the 21-day follow-up appointment.

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▶ **Table 2** Continued.

Reference	Study Design	Participants	Treatment	Scales, questionnaires, paradigms	Outcomes
Hindocha et al., 2018 [65]	RCT, cross-over design	30 non-treatment seeking healthy smokers	800 mg CBD or placebo, single dose	Pleasantness ratings, MPSS, QSU-B, VAS, FTND, STAI, BDI	CBD reversed attentional bias due to tobacco abstinence compared to satiety; CBD reduced the pleasantness of cigarette images; no effect on craving and withdrawal outcomes.
Heroin Use Disorder					
Hurd et al., 2019 [66]	RCT, parallel-arm design	42 drug-abstinent individuals with heroin use disorder	400 or 800 mg CBD or placebo for 3 consecutive days	HCQ, VAS-A, COWS, VAS-C, PANAS, physiological measurements, neutral and drug-related cue sessions, cognitive test sessions	Both doses of CBD significantly reduced cue-induced craving and anxiety compared to placebo; results protracted until the 1-week follow-up.

If not stated otherwise, the treatment was administered orally. Studies that refer to the same participants are marked with an asterisk. Abbreviations: AIS = Athens Insomnia Scale; ARCI = Addiction Research Center Inventory; ASI = Addiction Severity Index; ASI-R = Anxiety Sensitivity Index – Revised; ASSIST = Alcohol, Smoking, and Substance Involvement Screening Test; AUDIT = Alcohol Use Disorders Identification Test; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BIS = Behaviour Impulsivity Scale; BIS-11 = Barrat Impulsiveness Scale; BPI = Brief Pain Inventory; BPRS = Brief Psychiatric Rating Scale; BSI = Brief Symptom Inventory; BTOM-SFS = Brief Treatment Outcome Measure-Social Functioning Scale; CANTAB = Cambridge Neuropsychological Test Automated Battery; CCQ = Cannabis Craving Questionnaire; CGT = Cambridge Gambling Task; CPQ = Cannabis Problems Questionnaire; CUD = Cannabis Use Dependence; CWC = Cannabis Withdrawal Checklist; CWS = Cannabis Withdrawal Scale; DASS = Depression, Anxiety, and Stress Scale; DEQ = Drug Effects Questionnaire; DTS = Distress Tolerance Scale; fMRI = functional magnetic resonance imaging; FTND = Fagerstrom Test for Nicotine Dependence; HAM-A = Hamilton Anxiety Rating Scale; ISI = Insomnia Severity Index; HAM-D = Hamilton Depression Rating Scale; HCQ = Heroin Craving Questionnaire; HDRS = Hamilton Depression Rating Scale; MCCS = Minnesota Cocaine Craving Scale; MCQ = Marijuana Craving Questionnaire; MET/CBT = Motivational Enhancement Therapy and Cognitive Behavioral Therapy; MNWS = Minnesota Nicotine Withdrawal Scale; MPSS = Mood and Physical Symptoms Scale; MRS = Mood Rating Scale; MWC = Marijuana Withdrawal Checklist; MWSC = Marijuana Withdrawal Symptom Checklist; PANAS = Positive and Negative Affect Schedule; POMS = Profiles of Mood States; PRM = Pattern Recognition Memory; PSQI = Pittsburgh Sleep Quality Index; QCQ = Quitting Cannabis Questionnaire; QSU-B = Questionnaire of Smoking Urges – Brief; RCT = randomized controlled trial; SAFTEE = Systematic Assessment for Treatment Emergent Events; SDS = Severity of Dependence Scale; SF-36 Pain Factor = Short-Form-36 Pain Factor; SMHSQ = St. Mary's Hospital Sleep Questionnaire; SST = Stop Signal Task; STAI = State Trail Anxiety Inventory; TCQ = Tiffany Craving Questionnaire; TLFB = Timeline Followback; TQSU = Tiffany Questionnaire of Smoking Urges; UKU-SERS = UKU Side Effects Rating Scale; VAS = Visual Analog Scale: VAS-A = Visual Analog Scale for Anxiety; VAS-C = Visual Analog Scale for Craving; WDS = Withdrawal Discomfort Score; WTAR = Wechsler Test for Adult Reading.

clinical management of individuals with persistent subthreshold psychotic symptoms is indicated.

The first successful treatment with CBD in an antipsychotic-naïve young man with CHR was reported by Koethe et al. [36]. The 4-week CBD treatment (600 mg/day orally) resulted in a significant clinical improvement as evidenced by reduced PANSS scores and improved cognitive performance on various neuropsychological tests. The improvement in clinical symptoms was also accompanied by an increase in cerebral glucose metabolism as assessed by [^{18}F]fluoro-2-deoxyglucose PET. The authors concluded that activation of the ECS via anandamide is likely to enhance the homeostatic effect of this system, the"eby "normal" zing" systemic function and simultaneously upregulating cerebral glucose utilization.

To date, no controlled studies investigating the treatment efficacy of CBD in CHR have been completed.

However, one controlled observational study [37] investigated the effect of a single administration of CBD in a fMRI paradigm. The study results are discussed in more detail in the next chapter of this review. In a subset of the young people with CHR included in this study, Appiah-Kusi et al. [38] examined the cortisol response to social stress (Trier Social Stress Test) in 32 CHR patients receiving either 600 mg oral CBD or a placebo over 1 week, rather than receiving a single dose only, at the level of fluid biomarkers. They compared the results with cortisol reactivity in 26 healthy controls. Although CBD administration led to some improvements in anxiety and the experience of public speaking stress in CHR patients compared to placebo, the effects were not reflected in significant improvements in cortisol reactivity [38]. Similarly, based on data from the same study, Davies et al. reported that 33 people with CHR failed to restore the clear negative relationship between cortisol levels and parahippocampal response seen in healthy controls [39].

Neurobiological background of the antipsychotic effects of cannabidiol

As early as 1932, Kurt Beringer introduced the term 'model psychosis' for psychosis-like symptoms intentionally induced by psychotomimetic drugs [40]. The 'altered states of consciousness' induced in model psychosis, i. e., symptoms of withdrawal from reality often accompanied by perceptual disturbances, thought disorders, delusional ideas, and sometimes hallucinations, are a long-established approach to improving our understanding of certain aspects of schizophrenia [41].

It has been a long-standing clinical observation that both acute and chronic administration of cannabis or Δ^9-THC can induce dose-dependent behavioral, cognitive, or electroencephalographic changes reminiscent of those observed in severe psychiatric disorders, particularly psychosis [41, 42]. Therefore, the Δ^9-THC-induced

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▶ **Table 3** Clinical investigations on CBD for the treatment of social anxiety disorder and PTSD.

Reference	Study Design	Participants	Treatment	Scales, questionnaires, paradigms	Outcomes
Healthy Volunteers					
Spinella et al., 2021 [74]	Open-label RCT, crossover-design	43 healthy individuals	Self-administration of CBD-free hempseed oil or CBD-containing hempseed oil	MAST, CBD belief ratings, NRS for subjective stress, STAI-S-SF, I-PANAS, B-BAES	The expectation of CBD's effects alone led to subjective and physiological anxiolytic responses.
Zuardi et al., 1982 [75]	RCT, cross-over design	8 healthy individuals	Δ^9-THC (0.5 mg/kg), CBD (1 mg/kg), a combination thereof, diazepam (10 mg), or placebo, single dose	STAI, ARCI-Ma, pulse, the analogue self-rating scale for subjective feelings, the self-rating scale of bodily symptoms	CBD addition caused a significant reduction in anxiety, state of intoxication, and subjective effects of Δ^9-THC, while having no effects when administered alone. The physiological effects of Δ^9-THC were not altered by CBD.
Zuardi et al., 1993 [76]	RCT, parallel-arm design	40 healthy individuals	300 mg CBD, 5 mg ipsapirone, 10 mg diazepam, or placebo, single dose	VAMS, STAI, BSS, digital-symbol substitution test, simulated public speaking paradigm	CBD significantly reduced anxiety after a public speaking test, similar to ipsapirone.
Linares et al., 2018 [77]	RCT, parallel-arm design	57 healthy male individuals	150, 300, or 600 mg CBD or placebo, single dose	VAMS, physiological measurements, simulated public speaking test	300 mg CBD significantly reduces subjective anxiety, while 150 mg and 600 mg had no significant effects compared to placebo.
Crippa et al., 2004 [78]	RCT, cross-over design	10 healthy individuals	400 mg oral CBD or placebo 90 minutes before rCBF measurements, single dose	VAMS, SPECT	Significant reduction in subjective state of anxiety and increased mental sedation upon CBD administration compared to placebo; effects were correlated with neural activity in limbic and paralimbic brain regions.
*__Fusar-Poli et al., 2009__ [79]	RCT, cross-over design	15 healthy individuals	10 mg Δ^9-THC, 600 mg CBD, or placebo, single dose	fMRI and SCR measurements during fearful-faces intervention, VAMS, STAI, AIS, PANSS, physiological measurements	Δ^9-THC and CBD showed opposing effects on neural, electrodermal, and symptomatic responses to fearful faces; Δ^9-THC administration led to an increased state of anxiety, while CBD acted anxiolytic.
*__Fusar-Poli et al., 2010__ [80]	RCT, cross-over design	15 healthy individuals	10 mg Δ^9-THC, 600 mg CBD, or placebo, single dose	fMRI and SCR measurements during fearful-faces intervention, VAMS, STAI, AIS, PANSS, physiological measurements	Anxiolytic effects of CBD were correlated to a disruption in the prefrontal-subcortical connectivity, which did not appear after Δ^9-THC administration.
Bloomfield et al., 2022 [81]	RCT, cross-over design	24 healthy individuals	600 mg CBD or placebo, single dose	fMRI measurements during face rating and mental arithmetic tasks, VAS	No significant effects of CBD administration on brain responses, cognitive measures, or experimentally induced anxiety.
Hundal et al., 2018 [86]	RCT, parallel-arm design	32 non-clinical individuals with high-paranoid traits	600 mg CBD or placebo 130 minutes prior to controlled 3D virtual reality scenario, single dose	SSPS, CAPE-state, UMACL, BAI, several cognitive tasks, controlled 3D virtual reality scenario	No impact of CBD on physiological and behavioral symptoms of anxiety and paranoia.
Das et al., 2013 [87]	RCT, parallel-arm design	48 healthy individuals	Inhalation of 32 mg CBD pre- or post-extinction, or placebo, single dose	BDI, STAI, spot-the-word and prose recall tasks, MRS, BSS, fear conditioning, and fear extinction task	Enhanced consolidation of extinction learning upon CBD administration.
Rossi et al., 2023 [85]	RCT, parallel-arm design	17 healthy individuals	600 mg CBD or placebo 90 minutes prior to oral ayahuasca (1 ml/kg) administration, single dose	REFE and empathy tasks	Significant decreases in reaction times, anxiety, sedation, cognitive deterioration, and discomfort in both groups without between-group differences.

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▶ **Table 3** Continued.

Reference	Study Design	Participants	Treatment	Scales, questionnaires, paradigms	Outcomes
Social Anxiety Disorder					
Crippa et al., 2011 [88]	RCT, cross-over design	10 treatment-naïve individuals with SAD	400 mg CBD or placebo, single dose	VAMS, SPECT	Significant improvements in subjective anxiety ratings upon CBD administration were correlated to specific neural signaling patterns.
Bergamaschi et al., 2011 [89]	RCT, parallel-arm design	24 treatment-naïve individuals with SAD, 12 healthy controls	600 mg CBD or placebo, single dose	VAMS, SSPS-N, and physiological measurements during simulated public speaking test	CBD administration significantly reduced anxiety, cognitive impairment, discomfort, and alert levels compared to placebo; results of CBD-treated patients were similar to non-treated healthy controls.
Masataka et al., 2019 [90]	RCT, parallel-arm design	37 late teenagers (18–19 years) with SAD	Oral cannabis oil with 300 mg CBD or placebo for four weeks	FNE, LSAS	CBD administration led to significant decreases in anxiety compared to placebo.
Kwee et al., 2022 [91]	RCT, parallel-arm design	80 treatment-refractory individuals with SAD and panic disorder	300 mg CBD or placebo, single dose	Exposure therapy sessions, FQ, BAI, CGI, BDI-II, SPAI-18, LSAS, motivational interviewing	No effects of CBD administration on treatment outcome.
Berger et al., 2022 [92]	Clinical study, open-label, single-arm	31 treatment-resistant individuals with SAD	CBD titrated from 200 mg/day up to 800 mg/day over the course of 12 weeks	CGI-I, CGI-S OASIS, HARS, QIDS-A, SOFAS	Significant reduction in anxiety severity, as well as significant improvements in depressive symptoms, CGI-severity scores, and functioning.
Post-traumatic Stress Disorder					
Elms et al., 2019 [93]	Case series	11 individuals with PTSD	CBD capsules or oral spray over 8 weeks in a flexible dosing regimen; mean starting dose: 33.18 mg/day: mean final dose: 48.64 mg/day	PCL-5, subjective reports	PTSD symptom reduction upon CBD administration in addition to routine psychiatric care.
***Bolsoni, et al., 2022** [94]	RCT, cross-over design	33 individuals with PTSD	300 mg CBD or placebo before recall of traumatic event, single dose	PCL-5, VAMS, STAI, physiological measurements during trauma recall scenario	No significant effects of CBD on states of anxiety, alertness, and discomfort, or physiological measurements compared to placebo.
***Bolsoni, et al., 2022** [95]	RCT, parallel-arm design	33 individuals with PTSD, separated into sexual and non-sexual trauma groups	300 mg CBD or placebo, single dose	PCL-5, VAMS, physiological measurements during trauma recall scenario	The nonsexual-related PTSD group showed lower anxiety and cognitive impairment when receiving CBD rather than a placebo; no significant effects were found in the sexual-related PTSD group.

If not stated otherwise, the treatment was administered orally. Studies that refer to the same participants are marked with an asterisk. Abbreviations: AIS = Analog Intoxication Scale; ARCI-Ma = Addiction Research Center Inventory for Marihuana Effects; BAI = Beck Anxiety Inventory; B-BAES = Brief Biphasic Alcohol Effects Scale; BDI = Beck Depression Inventory; BSS = Bodily Symptoms Scale; CAPE = Community Assessment of Psychic Experiences; CGI-I = Clinical Global Impressions – Improvement Scale; CGI-S = Clinical Global Impressions – Severity Scale; fMRI = functional magnetic resonance imaging; FNE = Fear of Negative Evaluation Scale; FQ = Fear Questionnaire; HARS = Hamilton Anxiety Rating Scale; I-PANAS = International Positive and Negative Affect Schedule; LSAS = Liebowitz Social Anxiety Scale; MAST = Maastricht acute stress test; NRS = Numerical Rating Scale; OASIS = Overall Anxiety Severity and Impairment Scale; PANSS = Positive and Negative Syndrome Scale; MRS = Mood Rating Scale; PCL-5 = Post-Traumatic Stress Disorder Checklist for the DSM-5; PTSD = Post-Traumatic Stress Disorder; QIDS-A = Quick Inventory of Depressive Symptoms, Adolescent Version; QOL = Quality of Life; rCBF = regional cerebral blood flow; RCT = randomized controlled trial; REFE = Recognition of Emotions in Facial Expressions; SAD = Social Anxiety Disorder; SCR = Skin Conductance Response; SF = short form; SOFAS = Social and Occupational Functioning Scale; SPAI = Social Phobia and Anxiety Inventory; SPECT = single-photon emission computed tomography: SSPS = State Social Paranoia Scale; SSPS-P/N = positive/negative Self-Statements during Public Speaking Scale; STAI = Spielberger's State-Trait Anxiety Inventory; UMACL = University of Wales Mood Adjective Checklist; VAMS = Visual Analog Mood Scale; VAS = Visual Analog Scale.

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▶ **Table 4** Clinical investigations on CBD for the treatment of autism spectrum disorder.

Reference	Study Design	Participants	Treatment	Scales, questionnaires, paradigms	Outcomes
*Pretzsch et al., 2019 [99]	RCT, cross-over design	34 healthy individuals (17 with ASD and 17 neurotypical)	600 mg CBD or placebo, single dose	MRS measurements to determine neurotransmitter concentrations	CBD administration resulted in significantly increased GABA activation in healthy controls, but decreased GABA activation in people with ASD.
*Pretzsch et al., 2019 [100]	RCT, cross-over design	34 healthy individuals (17 with ASD and 17 neurotypical)	600 mg CBD or placebo, single dose	MRI measurements of neural activation	CBD administration resulted in altered fractional amplitude of low-frequency fluctuations and functional connectivity in regions correlated to ASD.

If not stated otherwise, the treatment was administered orally. Studies that refer to the same participants are marked with an asterisk. Abbreviations: ASD = Autism Spectrum Disorder; CBD = Cannabidiol; GABA = γ-Aminobutyric Acid; MRI = Magnetic Resonance Imaging; MRS = Magnetic Resonance Spectroscopy; RCT = Randomized Clinical Trials.

model psychosis is often used to study the neurobiological basis of the antipsychotic properties of CBD.

Several fMRI studies have visualized the fundamentally different neurobiological effects of CBD and Δ^9-THC. Borgwardt et al. [43] conducted a pseudo-randomized controlled trial with within-subject repeated measures in 15 healthy volunteers receiving either 10 mg Δ^9-THC, 600 mg CBD, or placebo before a Go/No-Go task. Δ^9-THC administration led to reduced activation of brain regions mediating response inhibition (right inferior frontal and anterior cingulate gyrus), while CBD administration had similar effects on the left temporal cortex and insula, two brain regions usually not involved in response inhibition. In the same participants, CBD and Δ^9-THC also showed opposing effects compared to placebo on several regional brain functions measured by blood-oxygen-level-dependent (BOLD) hemodynamic responses during the verbal recall condition of a verbal memory task, response inhibition (Go/No-Go task), sensory processing after visual and auditory stimulation, and viewing of fearful faces [44]. During auditory and visual processing tasks in the same healthy volunteers, 600 mg CBD and 10 mg Δ^9-THC also resulted in differential activation of brain regions associated with induced psychotic symptoms [45]. Compared to placebo, Δ^9-THC reduced activation in the temporal cortex during auditory processing and the secondary visual cortex during visual stimulus processing. In addition, Δ^9-THC increased the activation in occipital cortex areas (primary visual cortex). Decreased right temporal cortex activation and increased occipital cortex area activation correlated with increases in PANSS total and PANSS positive scores, respectively. In contrast, CBD increased temporal cortex and right occipital lobe activation during auditory and visual processing, respectively. The direct comparison showed that Δ^9-THC and CBD had opposite effects, particularly in the right posterior superior temporal cortex, the right-sided homolog of Wernicke's area.

In another cross-over RCT [46], an acute dose of 600 mg CBD increased fronto-striatal resting-state connectivity in healthy individuals compared to placebo. This network is relevant to executive function, decision-making, salience generation, and motivation. However, Δ^9-THC administration (10 mg, orally) showed no effects. The authors concluded that the plasma levels achieved before the fMRI scan (75 min after study drug intake) had not reached sufficient concentration.

Wilson et al. [47] investigated the effects of acute CBD administration in 33 antipsychotic-naïve CHR individuals in an fMRI study on reward processing, which is commonly dysregulated in psychosis. Compared to 19 healthy controls, the individuals with CHR showed abnormal activation of the left insula/parietal operculum, which was alleviated by the acute oral CBD administration (600 mg, n = 16) but not by placebo (n = 17) [47]. Bhattacharyya et al. [37] showed in the same participants that individuals with CHR have differential BOLD responses in three brain regions associated with psychosis disease states – the striatum (during a verbal encoding task), the mediotemporal lobe, and the midbrain (during verbal recall). Acute CBD administration attenuated the activation patterns without reaching the BOLD response levels observed in healthy controls [37]. Furthermore, in a fearful face processing paradigm, these CHR individuals showed significantly increased activation in the left lingual gyrus and bilateral parahippocampal gyri and attenuated activation in the striatum compared to healthy controls when treated with a placebo. Again, acute CBD administration partially normalized the activation patterns but did not reach the levels seen in healthy controls [48].

O'Neill et al. [49] supported these results found in CHR in 15 individuals with psychosis on standard antipsychotic treatment (RCT with within-subject, cross-over design). Compared to the 19 healthy controls, the psychosis individuals showed altered prefrontal and mediotemporal BOLD responses and greater mediotemporal-striatal functional connectivity during a verbal recall task. The altered activation was normalized in parts after acute CBD intake (600 mg) but did not reach the same BOLD response levels as those observed in healthy controls [49]. In 31 people with recent-onset psychosis, van Boxel et al. [32] found a significant alteration in default mode network connectivity after 28 days of CBD treatment (600 mg/day) adjunctive to standard antipsychotic medication. The authors suggested that the therapeutic effects of CBD may be based on the observed changes in default mode network connectivity [31].

Substance use disorder (SUD)

SUD is a chronic medical condition characterized by recurrent and compulsive substance use despite adverse consequences. It encompasses a range of substance-related problems, impacting various aspects of the life and well-being of an individual [50]. The ECS

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has been shown to play a critical role in mediating rewarding effects by modulating neurotransmission in key areas of the mesocorticolimbic system involved in the initiation and maintenance of drug use and in the development of the compulsions and loss of behavioral control that occur during drug dependence [51]. Despite the definitive addictive potential of cannabis, CBD itself does not pose a risk of developing dependence or tolerance, as has been concluded in clinical interventions [52, 53].

However, in an RCT with a repeated-measures design involving 23 healthy volunteers performing a monetary incentive fMRI task, acute oral CBD administration (600 mg) had no effects on neural correlates of reward expectancy and feedback compared to placebo [54].

Cannabis use disorder (CUD)

The first case report on the possible beneficial effects of CBD on CUD and associated withdrawal symptoms was published in 2013 by Crippa et al. [55]. A 19-year-old female with severe cannabis withdrawal syndrome was treated with oral CBD for 11 days (day 1: 300 mg, day 2–10: 600 mg, day 11: 300 mg), resulting in no symptoms of withdrawal, anxiety, or dissociation during the detoxification process. Therefore, CBD was considered effective against withdrawal symptoms. However, at a 6-month follow-up, the young woman reported a relapse of cannabis use, albeit at a lower frequency of once or twice a week compared to daily use before CBD treatment. A man diagnosed with bipolar disorder and a severe CUD was treated with daily administration of a low CBD dose (24 mg) as an oral spray [56]. The dose was gradually tapered to 18 mg over 2 months. He reported being able to avoid smoking cannabis while on CBD oil treatment and experienced improvements in anxiety, sleep, and social and occupational functioning.

A larger RCT partially confirmed these two anecdotal observations in 82 individuals with CUD [57]. In the initial trial phase, 48 participants received 200, 400, or 800 mg oral CBD or placebo for 4 weeks during a cessation attempt. An interim analysis showed that the two higher doses, but not 200 mg CBD, were more effective than placebo in reducing cannabis use [57]. Therefore, in the second phase of the study, new participants (n = 34) were randomized to receive 400 or 800 mg CBD or placebo. Compared to placebo, CBD doses of 400 and 800 mg decreased the THC-COOH:creatinine ratios by 94.21 ng/mL and 72.02 ng/mL, respectively, and increased average cannabis abstinence by 0.48 and 0.27 days per week, respectively [57]. The results suggest that doses > 200 mg (400–800 mg/day) are required for adequate cannabis withdrawal support. However, results for secondary endpoints were mixed and dose-dependent [57]. While 400 mg CBD reduced the number of cigarettes smoked per week compared to placebo, the same CBD dose increased Pittsburgh Sleep Quality Index scores, indicating poorer sleep quality in participants taking CBD. On the other hand, the higher CBD dose (800 mg) had no effect on these outcomes but reduced cannabis withdrawal symptoms and showed anxiolytic effects on the Beck Anxiety Inventory. In the same study, CBD administration did not affect delayed verbal memory scores and other cognitive outcomes (400 or 800 mg/day), except for the backward digit span, which increased following 800 mg CBD [58]. Therefore, the authors concluded that 800 mg/day may improve working memory performance in people with CUD. A recent publication based on the same RCT reported that anandamide levels decreased over time in CUD individuals taking a placebo during the cessation attempt, while there was no change in anandamide levels in the 800 mg CBD group [59]. No evidence was found for a similar effect of 400 mg CBD compared to placebo. However, the serum anandamide concentrations were not correlated with overall improvement of anxiety, depression, cannabis use, or withdrawal symptoms [59].

Cocaine use disorder

The potential benefits of CBD in treating SUDs have also been investigated in cocaine use disorder. An exploratory, placebo-controlled, double-blind study in 31 individuals with crack-cocaine dependence [60] found no CBD-specific effect. Although 300 mg of oral CBD for 10 days significantly reduced craving, no differences were found between the CBD and placebo groups. Furthermore, indicators of anxiety, depression, and sleep alterations did not differ between the groups. In a long-term intervention in 78 adults with moderate to severe cocaine use disorder, oral CBD administration (800 mg/day for 92 days, oral solution) did not reduce cocaine craving or relapse cases compared to placebo [61]. Separate analyses of the same trial also found no differences in cognitive outcomes [62] or anxiety symptoms and cortisol levels [63].

Nicotine dependence

Chronic tobacco smokers typically experience intense withdrawal symptoms when attempting to reduce their dose or quit smoking altogether. In a double-blind RCT [64], 24 smokers receiving ad libitum CBD or placebo via an inhaler were monitored for their subsequent tobacco self-administration, craving (assessed using the Tiffany Craving Questionnaire), and sedation, depression, and anxiety status (Mood Rating Scale). CBD consumption significantly reduced cigarette smoking by approximately 40 % during the 1-week intervention, and the effect was maintained at the 21-day follow-up visit, while placebo inhalers showed no impact on cigarette smoking [64]. However, CBD did not affect craving or sedation, depression, and anxiety scores [64].

A double-blind, placebo-controlled, cross-over study investigated the potential of a single oral dose of 800 mg CBD to target processes relevant to smoking cessation in 30 non-treatment-seeking, dependent cigarette smokers [65]. Following overnight cigarette abstinence, CBD reversed the attentional bias to cigarette cues so that it was no different from the attentional bias when the participants were allowed to smoke before the test. The authors concluded that this reduction in the implicit salience of drug cues may be the potential underlying mechanism by which CBD exerts its anti-addictive effects [65]. Furthermore, CBD reduced the pleasantness of cigarette cues compared to placebo without affecting craving and withdrawal symptoms or cardiovascular measures.

Heroin use disorder

Hurd et al. tested the short-term effects of oral CBD (Epidiolex, 400 or 800 mg/day) versus placebo in 42 drug-abstinent individuals with heroin use disorder [66]. Compared to placebo, acute CBD administration significantly reduced craving and anxiety induced by salient drug cues compared to neutral cues. In the 3-day intervention, participants also experienced significant reductions in cue-induced craving and anxiety when treated with either dose of CBD

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compared to placebo. The positive effects persisted through the 7-day follow-up.

Anxiety and post-traumatic stress disorder

PTSD and anxiety are distinct but somehow related mental health conditions with significant implications for affected individuals. PTSD arises after experiencing or witnessing a traumatic event, leading to intrusive memories, avoidance behaviours, negative mood changes, and increased arousal. Anxiety disorders involve heightened arousal, fear, and nervousness, affecting daily functioning and overall quality of life. Both conditions can manifest with physical symptoms, further exacerbating distress and impairing coping abilities. Timely recognition, appropriate treatment, and ongoing support are crucial in managing PTSD and anxiety, facilitating recovery, and enhancing overall well-being. Standard treatment methods for PTSD and anxiety include, e. g., cognitive-behavioral therapy and antidepressants, modulating serotonin, and norepinephrine reuptake in the neurons [67]. The ECS is important in modulating emotional behaviours and regulating fear, anxiety, and stress-coping processes by modulating synaptic activity at many 'nodes' of the neural circuits involved [68, 69]. In addition, alterations of eCBs and respective lipid levels in serum [70], plasma [71], and hair [72] of individuals with PTSD as well as elevated CB_1R availability [73] detected in PET scans suggest an involvement of the ECS in the pathology of PTSD.

Anxiolytic effects of cannabidiol in healthy individuals

First, the importance of controlled studies must be emphasized, as the mere expectation of the effects of CBD led to significant physiological and subjective anxiolytic effects [74]. In a cross-over RCT, all participants always received sublingual CBD-free hempseed oil but were informed that they would self-administer CBD-free hempseed oil in one session and CBD-containing hempseed oil in the other. Although no systematic changes in subjective stress or anxiety were observed concerning the expected condition, the expected CBD condition was associated with increased sedation and a different pattern of heart rate variability, indicating reduced anticipatory stress. Notably, participants who were a priori convinced that CBD has anxiolytic properties reported a significant decrease in anxiety in the CBD expectancy condition [74].

The first report on the possible anxiolytic effects of CBD was published in 1982 by Zuardi et al. [75]. The authors administered oral Δ^9-THC (0.5 mg/kg), CBD (1 mg/kg), a combination of the two, diazepam (10 mg), or placebo to 8 participants in an RCT (cross-over design) before several physiological and behavioral examinations. CBD administration had no anxiolytic effect per se but appeared to reduce anxiety and other subjective alterations triggered by Δ^9-THC. Notably, the authors did not observe any CBD-related changes in the physiological effects of Δ^9-THC, suggesting that CBD does not block the activity of Δ^9-THC but rather acts through separate mechanisms to alleviate the unpleasant effects associated with cannabis use [75]. A simulated public speaking test in 40 healthy individuals showed comparable anxiolytic effects (assessed using the Visual Analog Mood Scale [VAMS] and State-Trait Anxiety Inventory [STAI]) of CBD and ipsapirone, an antidepressant and anxiolytic compound commonly used in RCTs as an active comparator [76]. To establish the dose-response curve for the anxiolytic effect of CBD, they later tested three different doses (150 mg, 300 mg, and 600 mg) versus placebo in 57 healthy male subjects [77]. Notably, the previously established dose of 300 mg proved effective again in a simulated public speaking test, while the two alternative doses did not show significant changes in subjective anxiety ratings (VAMS), thus representing an inverted U-shaped dose-response curve for the anxiolytic effects of CBD [77].

Crippa et al. investigated the effects of CBD on regional cerebral blood flow (rCBF) measured by SPECT in an RCT with a cross-over design. SPECT is a neuroimaging technique involving tracer injection, which, according to the authors, often leads to increased anticipatory anxiety in subjects compared to during or after image acquisition [78]. Compared to placebo, 10 healthy volunteers reported decreased subjective anxiety and increased mental sedation following a single oral ingestion of 400 mg CBD before the SPECT scan started. In addition, CBD modulated resting-state activities in limbic and paralimbic cortical brain areas commonly implicated in the pathophysiology of anxiety. However, changes in rCBF did not correlate with subjective anxiety scores [78]. Compared to Δ^9-THC (10 mg, oral), CBD administration (600 mg, oral) showed opposite effects on neural, electrodermal, and symptomatic responses to fearful faces in 15 healthy subjects [79]. However, while Δ^9-THC also increased feelings of anxiety, CBD only tended to reduce anxiety levels. The authors hypothesized that the alternation between neutral and fearful faces in the fMRI paradigm elicited only a transient anxious response to each stimulus without producing sustained changes in subjective anxiety levels [79]. However, a separate analysis of the same data showed that CBD attenuated the amygdalar response to fearful faces, an effect that correlated with the trend level of anxiolytic effect for CBD [44]. Later, dynamic causal modelling (DCM), a method for assessing effective connectivity in neuroimaging data, was used to re-evaluate these fMRI data and led to the suggestion that the potential anxiolytic effects of CBD may be neurophysiologically based on a disruption of prefrontal-subcortical connectivity [80].

In contrast, in 24 healthy individuals receiving either 600 mg CBD or placebo, no effects of acute CBD administration were found on emotional processing (using an fMRI paradigm based on neutral, fearful, and happy faces), cognitive activity (using a mental arithmetic task to measure emotional responses to stress and a face rating test with neutral, angry and happy expressions), and subjective response to experimentally induced anxiety [81]. The negative outcomes has been suggested to result from insufficient CBD blood concentrations, as CBD was administered in a fasted state, and several pharmacokinetic investigations indicate that the bioavailability of CBD without any food consumption is extremely low [82–84]. When combined with the psychoactive brewed drink ayahuasca, known for its anxiolytic and antidepressant effects, both CBD (600 mg) and placebo administration in 17 healthy individuals resulted in significantly decreased reaction times in a computerized facial expressions recognition task and a multifaceted empathy test, and a reduction in subjective anxiety, sedation, cognitive deterioration, and discomfort ratings [85]. Thus, a CBD-specific effect was not observed.

Furthermore, 32 non-clinical individuals with high paranoid traits did not benefit from a single oral dose of 600 mg CBD (Epidiolex) before a controlled 3D virtual-reality scenario as measured

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by levels of anxiety (Beck Anxiety Inventory), cortisol, blood pressure, and heart rate [86].

In summary, studies investigating acute subjective and objective anxiolytic effects of CBD in healthy volunteers show conflicting results. Nevertheless, CBD may still be an interesting compound for treating anxiety disorders when combined with specific therapies.

In a Pavlovian fear conditioning paradigm assessing extinction and consolidation of conditioned fear memory in 48 healthy subjects, inhalation of 32 mg CBD after the extinction task (post-extinction) attenuated fear responses rated by shock expectancy compared to placebo. Both pre- and post-extinction CBD inhalation tended to reduce skin conductance responses during the reinstatement task. These results indicate that CBD can potentiate the consolidation of extinction memory [87]. Of note, the attenuation of fear responses following CBD inhalation after the extinction task was not associated with reduced anxiety. Therefore, the authors concluded that CBD may be a valuable adjunct to extinction-based therapies for anxiety disorders [87].

Results in people with social anxiety disorder (SAD)

To test the anxiolytic effect of CBD in SAD, 15 treatment-naïve people with SAD received a single oral dose of CBD (400 mg) or placebo in a cross-over RCT. As predicted, CBD also attenuated the rCBF in the left parahippocampal gyrus and hippocampus and increased it in the right posterior cingulate gyrus. However, subjective anxiety ratings were not correlated with these specific neural signalling patterns [88]. The anxiolytic properties of CBD were also confirmed in an anxiety-provoking simulated public speaking test in 24 treatment-naïve individuals with SAD who received either a single oral dose of 600 mg CBD or placebo [89]. Furthermore, 4 weeks of treatment with 300 mg CBD per day significantly reduced anxiety scores on the Fear of Negative Evaluation questionnaire and the Liebowitz Social Anxiety Scale compared to placebo in 37 adolescents with SAD [90]. In contrast, in 80 individuals with treatment-refractory SAD or panic disorder, the acute oral administration of 300 mg CBD before eight separate exposure therapy sessions did not improve treatment outcomes compared to placebo [91]. Therefore, in the absence of an adequate control group, the significant anxiety reduction, as well as improvements in depressive symptoms, CGI-severity scores, and functioning in 31 young individuals with treatment-resistant SAD that were measured after a 12-week open-label intervention with add-on CBD administration (starting dose: 200 mg/day; titrated up to 800 mg/day) could also be attributed to the fact that the participants were informed about the treatment and simply expected the intervention to be effective [92].

Implications for individuals with post-traumatic stress disorder

A retrospective, open-label case series of 11 adults with PTSD who received low-dose oral CBD capsules or spray (flexible dosing regimen; mean starting dose: 33.18 mg/day; mean final dose: 48.64 mg/day [range: 2–100 mg]) for 8 weeks in addition to routine psychiatric interventions (with frequent changes in concurrent psychiatric medications for the study) resulted in improved PTSD symptoms in 10 out of 11 participants, as indicated by a 28 % reduction in PTSD Checklist for the DSM-5 scores [93]. In a recent RCT, a single dose of 300 mg oral CBD administered to 33 individuals with PTSD before being exposed to playbacks of their own recall of traumatic experiences had no effect compared to placebo [94]. However, when the participants were divided into two groups based on whether they had experienced sexual or non-sexual trauma, the non-sexual trauma group showed significantly reduced levels of subjective anxiety and cognitive impairment (both assessed by the VAMS) when given CBD versus placebo, while the sexual trauma group did not benefit from treatment [95].

Autism spectrum disorder

ASD is a neurodevelopmental condition characterized by challenges in social communication and repetitive patterns of behaviour, interests, or activities. Individuals with ASD can exhibit a wide range of abilities and differences in their interactions with the world around them [96]. While there is no cure for ASD, early intervention, and tailored therapies, such as behavioral interventions, speech and language therapy, occupational therapy, and social skills training, can significantly improve the quality of life and functioning of individuals with ASD [97]. Since children with ASD appear to have lower plasma levels of anandamide than healthy children [98], raising anandamide levels (e. g., by using CBD) may be a promising treatment alternative.

However, to date, only one observational single-dose study has been conducted, investigating the effects of a single oral CBD dose (600 mg) or placebo in 17 people with ASD and 17 neurotypical controls [99, 100]. Magnetic resonance spectroscopy scans revealed that CBD shifted the levels of both the excitatory (glutamate and glutamine) and inhibitory (γ-aminobutyric acid (GABA) and macromolecules [GABA +]) neurotransmitters in both groups. While CBD increased glutamine levels in the basal ganglia and decreased them in dorsomedial prefrontal cortex (DMPFC) in both groups, it had opposite effects on GABA + in each participant group. More specifically, CBD decreased GABA + in both brain regions analysed (basal ganglia and DMPFC) in ASD and increased it in healthy controls, with the effect being significant only in the DMPFC [99]. In the same observational study, the authors found a significant increase in the "fractional amplitude of low-frequency fluctuations" (fALFF) and functional connectivity in regions associated with ASD [100]. This increase was most pronounced in ASD and not significant in controls.

Discussion

This critical review found that despite the considerable interest in the ECS and CBD, only 38 studies have investigated CBD as a treatment option in people with a psychiatric condition, including 29 publications on RCTs based on 18 distinct clinical trials. Notably, only nine of these clinical trials, as well as seven case reports and two open-label studies, investigated the effects of multiple doses of CBD (3 days to 6 weeks in RCTs and up to 8 months in a case report), demonstrating that the acute effects of CBD have been primarily studied to date. However, to understand the therapeutic impact and long-term safety, more RCTs are urgently needed where patients with psychiatric conditions are treated with multiple, sufficient doses of CBD for a duration appropriate for the respective condition.

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The potential efficacy of CBD and the underlying neurobiological processes have been primarily investigated in schizophrenia or associated psychotic disorders (e. g., schizophrenia, CHR, or model psychosis) (for references, see ▶ **Table 1**). Distinct neurobiological effects from Δ^9-THC suggest the potential benefits of CBD in modulating brain regions associated with psychosis. Notably, RCT results suggest the efficacy of CBD at a dose of ≥ 800 mg/day to treat psychosis successfully [10, 30].

The studies now available on SUDs - particularly CUD - and anxiety and stress-related disorders (SAD and PTSD) report conflicting results (▶ **Table 2,3**). While some studies show promising effects of CBD, others have not been able to prove its efficacy.

For SUDs (▶ **Table 2**), oral doses of ≥ 400 mg appear to be necessary to successfully facilitate cessation [57]. In both cannabis and nicotine dependence disorders, CBD reduced consumption and the pleasantness of drug stimuli but not subjective craving. In contrast, a significant reduction in craving was observed in heroin use disorder [66]. However, no beneficial effects of CBD were found in cocaine use disorder. The lack of efficacy in these studies may be driven by insufficient daily dosages of CBD.

CBD does not appear to have anxiolytic properties per se but may reduce anxiety in anxiety-provoking situations, including Δ^9-THC administration, simulated public speaking tests, or examinations such as SPECT, which are associated with increased anticipatory anxiety (▶ **Table 3**). One study in healthy volunteers suggested that CBD may improve the consolidation of extinction memory and concluded that CBD may be a beneficial adjunct treatment during extinction-based therapy [87]. On the other hand, experimentally induced anxiety-provoking situations must not be mistaken as elaborated models of anxiety disorders. Therefore, using CBD as an anxiolytic is not backed by sufficient evidence [101]. The potential of CBD to enhance extinction memory consolidation may also be key for treating PTSD. However, a single-dose study suggests that only people with PTSD who have not experienced sexual trauma may benefit from CBD treatment [95]. Of note, there is no research yet on whether prolonged CBD treatment is also beneficial for people with PTSD associated with sexual trauma. Interestingly, CBD doses of 300–600 mg may be effective (▶ **Table 3**), indicating that the molecular mechanisms involved in the antipsychotic effect of CBD and its stress/anxiety-reducing effects may differ. Again, the limited number of studies, the limited treatment duration, and the lack of dose-finding studies, make it difficult even to consider this evidence-based.

In ASD (▶ **Table 4**), CBD affected neurotransmitter levels, the fALFF, and the functional connectivity in certain brain regions differently between ASD individuals and healthy controls [99, 100], but further RCTs are required to assess the potential benefits of CBD in ASD.

Although no clinical trials have been conducted to date, the preclinical evidence for the potential benefits of CBD in other neuropsychiatric conditions, like alcohol use disorder [102–105], ADHD [106], and depression [107], as well as its generally mild side effect profile [108, 109], provide a reason to vigorously pursue research in this area, whereby particularly RCTs on subacute and chronic CBD administration are needed. Specifically, due to the insufficient and unsatisfying treatment options available for many people living with chronic psychiatric conditions, who often experience a wide range of side effects or a lack of treatment efficacy [110–112], more research is needed to find alternative treatment approaches to ultimately allow people to live with and manage a diagnosis that often equates to life-long psychiatric care and medication.

Seeing the broad spectrum of psychiatric conditions that CBD might positively affect is interesting. One approach to explaining the complex mode of action of CBD and its effects on neural activity patterns is its impact on the ECS. The complexity of the ECS and the wide range of bodily functions and pathways it is involved in have yet to be understood. However, we do have some idea of its effects on the immune system [113], metabolic functions [114], inflammatory pathways [115], and the central nervous system [116]. In some psychiatric conditions, an imbalance in some aspects of the ECS has also been shown to be associated with the disease state [17, 24, 70, 71, 73, 98, 117–120]. Whether this imbalance represents a pathophysiological, causal mechanism, or results of respective disease pathologies requires further investigation, as this will contribute to understanding the spectrum and potential use of targeting the ECS in different conditions.

This critical review provides a comprehensive overview of the existing literature on the use of CBD in psychiatric conditions and highlights the limitations of the published data, the potential benefits, and the limitations of CBD in clinical practice. In summary, while the review suggests promising aspects of CBD in treating certain psychiatric conditions, it emphasizes the need for more extensive and rigorous research, including long-term studies and RCTs, to establish its potential effectiveness, safety, and mechanisms of action in various clinical settings.

Conclusion

The review identifies the promise of CBD as a mechanistically different antipsychotic treatment and suggests potential roles in treating cannabis, nicotine, and heroin use disorders, as well as SAD and PTSD under specific circumstances. However, the need for further controlled studies and clinical trials, particularly on mid- to long-term use of CBD, is underscored. This information is urgently needed to establish its efficacy and safety in various psychiatric conditions conclusively. The limitations outlined, including conflicting results and insufficient dosages, demonstrate that more extensive research efforts are required to comprehensively understand the therapeutic potential of CBD. For a wider use of CBD in clinical practice, marketing authorization for indications fulfilling registration criteria will be necessary to guarantee both efficacy and safety in certain disorders, as well as constant pharmaceutical quality, sufficient bioavailability, appropriate dosages, and general availability of standardized CBD medications.

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Conflict of Interest

FML is a shareholder of curantis UG (Ltd.) and received a research grant from Endosane Pharmaceuticals GmbH. CR is a shareholder of lero bioscience UG (Ltd). CR and ID are currently employed by Endosane Pharmaceuticals GmbH.

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