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Review

# Therapeutic potential of cannabidiol polypharmacology in neuropsychiatric disorders

Olivier J. Manzoni[1], Antonia Manduca[2,3,4], and Viviana Trezza[2,3,*]

**Cannabidiol (CBD), the primary non-intoxicating compound in cannabis, is currently approved for treating rare, treatment-resistant seizures. Recent preclinical research suggests that CBD's multifaceted mechanisms of action in the brain, which involve multiple molecular targets, underlie its neuroprotective, anti-inflammatory, anxiolytic, and antipsychotic effects. Clinical trials are also exploring CBD's therapeutic potential beyond its current uses. This review focuses on CBD's polypharmacological profile and discusses the latest preclinical and clinical findings regarding its efficacy in neuropsychiatric disorders. Existing evidence suggests that CBD's ability to modulate multiple signaling pathways may benefit neuropsychiatric disorders, and we propose further research areas to clarify its mechanisms, address data gaps, and refine its therapeutic indications.**

## Highlights

Recent cellular and rodent studies highlight that cannabidiol (CBD), the main non-intoxicating cannabinoid in cannabis, has multifaceted mechanisms of action in the brain, encompassing multiple molecular targets and resulting in a range of potential beneficial effects on brain function and behavior.

The promising preclinical findings, combined with preliminary clinical reports of CBD's efficacy in patients with various psychiatric conditions, have encouraged recent randomized controlled trials to more thoroughly assess its therapeutic potential in psychiatric disorders, including substance-use disorder, anxiety, psychoses, and autism spectrum disorder.

While CBD is generally well tolerated and shows promise for treating neuropsychiatric conditions, current clinical evidence has limitations, requiring well-designed, properly powered controlled trials to address data gaps and optimize its benefits for patients with neuropsychiatric disorders.

## CBD is often described as a 'promiscuous' molecule due to its ability to interact with multiple molecular targets

CBD, along with delta-9-tetrahydrocannabinol ($\Delta^9$-THC), is one of the most abundant and well-characterized **phytocannabinoids** (see Glossary) found in *Cannabis sativa L.* [1,2]. While both compounds share the same molecular formula ($C_{21}H_{30}O_2$), they differ in chemical structure: $\Delta^9$-THC contains a cyclic ring, whereas CBD has a hydroxyl group. This small structural difference results in markedly distinct pharmacological properties. Notably, CBD lacks the intoxicating effects of $\Delta^9$-THC and demonstrates minimal abuse potential [3–5].

To date, a highly purified oral CBD preparation has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for two rare and severe refractory epileptic syndromes (i.e., **Dravet syndrome** and **Lennox–Gastaut syndrome**) and for **tuberous sclerosis complex**, a rare multisystem disorder frequently associated with seizures [1,4] (Box 1).

While the strongest evidence for the medical use of CBD is for treatment-resistant epilepsies, research performed over the past decade has demonstrated that this phytocannabinoid has neuroprotective, anti-inflammatory, anxiolytic, and antipsychotic effects, significantly broadening its therapeutic potential beyond the currently approved indications [1,2,6]. The scientific evidence supporting these claims largely stems from recent cellular and rodent studies that suggest that CBD's diverse therapeutic effects are mediated by intricate mechanisms of action in the brain, involving multiple molecular targets [2,7–9]. Based on the preclinical evidence, recent controlled clinical trials have explored CBD's efficacy in various medical conditions, including neuropsychiatric disorders. Emerging research also indicates that CBD's effects may vary depending on factors such as age, sex, and individual metabolic differences, which can influence both its efficacy and safety profile [10–12].

[1]INMED, INSERM, Aix-Marseille University, 13273 Marseille, France
[2]Dept. Science, Roma Tre University, Rome, Italy
[3]Neuroendocrinology, Metabolism and Neuropharmacology Unit, IRCCS Fondazione Santa Lucia, Rome, Italy
[4]Dept. Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy

*Correspondence:
viviana.trezza@uniroma3.it (V. Trezza).

Box 1. Approved CBD formulations and medical use

Epidiolex/Epydiolex[iv,v], a highly purified CBD preparation, is approved for the treatment of seizures associated with Lennox–Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients aged 1 year and older in several countries, including the USA, European Union, UK, Australia, New Zealand, Israel, Switzerland, and Canada. It is administered as an oral solution containing 100 mg/ml of CBD. The initial dose is 2.5 mg/kg twice daily, up to a maintenance dose of 10 mg/kg twice daily for patients with Lennox–Gastaut syndrome and Dravet syndrome, and 12.5 mg/kg twice daily for patients with tuberous sclerosis complex. The most common side effects include somnolence and sedation, which typically occur early in treatment (and more frequently when combined with the benzodiazepine clobazam), diarrhea, vomiting, and decreased appetite. Elevations in transaminases, liver enzymes involved in amino acid metabolism, are the most common reason for discontinuing treatment. The risk of elevated transaminases increases when CBD is used concurrently with valproate. When CBD is coadministered with drugs that are CYP3A4/CYP2C19 inducers or CYP2C19 substrates, dose adjustments may be required. Information on long-term safety and effects on pregnancy and lactation is currently unavailable.

Sativex[vi], an oromucosal spray formulation containing both CBD and $\Delta^9$-THC in a 1:1 ratio, has been approved in 29 countries, including the UK, Canada, New Zealand, the European Union, and Australia, but not in the USA. Sativex is indicated as an add-on treatment to improve spasticity in multiple sclerosis. The spray is applied at the onset of muscle contractions to reduce spasticity and pain in patients with multiple sclerosis. A titration period is required to determine the optimal dose, and the number and timing of sprays may vary between patients. Common adverse reactions include changes in appetite, dizziness, disorientation, mood swings, depression, amnesia or memory impairment, somnolence, and blurred vision (1–10% of users). Less common effects (0.1–1% of users) include syncope, anxiety, illusions, paranoia, hallucinations, and delusional beliefs. Coadministration of Sativex with other drugs that are CYP3A4 substrates may increase the plasma concentration of the concomitant drug. Sativex is contraindicated in individuals under 18 years of age, in those with a history of psychoses, and during pregnancy and breastfeeding.

In this review, we discuss CBD's therapeutic potential in neuropsychiatric disorders, with a particular focus on its complex polypharmacological profile, encompassing both receptor- and non-receptor-mediated mechanisms of action. We integrate recent findings from highly translational preclinical models and double-blind **randomized controlled trials** (**RCTs**) that have assessed CBD's efficacy and safety in **substance-use disorder** (**SUD**), anxiety, psychoses, and autism spectrum disorder (ASD), conditions that have attracted significant research interest and demonstrated the most promising results. We aim to navigate the complex and often contradictory recent literature on CBD's use in these neuropsychiatric disorders, while identifying key data gaps and unresolved questions. Furthermore, we address critical concerns related to CBD's use for both medical and non-medical purposes and outline research priorities to optimize its therapeutic potential and safety profile.

## CBD's mechanisms of action involve interaction with several receptors

CBD influences multiple receptor systems through both direct and indirect interactions, including cannabinoid [1], serotonin [13–15], vanilloid [16,17], and opioid [18] receptors, as well as several other molecular pathways [19] (Figure 1 and Table 1).

As a product of the *Cannabis sativa L.* plant, it is not surprising that CBD is a versatile regulator of the endocannabinoid system. Despite its low affinity for cannabinoid receptors type 1 (CB1R) and type 2 (CB2R), CBD modulates their function, acting as a negative **allosteric modulator** of CB1R [20,21] and as a **partial agonist** of CB2R [20]. However, it can also function as an **inverse agonist** of CB2R [22]. While the precise nature of CBD's direct interaction with CB1R and CB2R remains debated, CBD is also thought to modulate these receptors indirectly by altering endocannabinoid tone. Specifically, CBD inhibits fatty acid amide hydrolase (FAAH) [16], the enzyme that breaks down the endocannabinoid **anandamide** (**AEA**), and binds to fatty acid binding proteins (FABPs) [23], which deliver AEA to FAAH. By competing for FABP binding sites, and by inhibiting FAAH, CBD may increase tonic AEA levels, indirectly activating CB1R and CB2R (for a detailed review on CBD's direct and indirect interactions with the endocannabinoid system, see [1]).

Besides CB1R and CB2R, CBD also directly influences other G-protein-coupled receptors (GPCRs). For example, it is an **antagonist** of GPR55, a GPCR expressed in the immune system,

## Glossary

**Agonist:** a ligand that binds to and activates a receptor, triggering a biological response.
**Allosteric modulator:** a ligand that binds to a receptor at an allosteric site, which is topographically distinct from the primary active (orthosteric) site. Allosteric modulators do not compete with orthosteric ligands for binding. Instead, by influencing receptor conformation, they may enhance (positive allosteric modulators) or diminish (negative allosteric modulators) the binding and/or activity of orthosteric ligands.
**Anandamide (AEA):** the first identified endocannabinoid which mediates its signaling effects through various G-protein-coupled receptors, ion channels, and nuclear receptors in both the central nervous system and peripheral tissues.
**Antagonist:** a ligand that binds to the orthosteric site of a receptor (thereby competing with other orthosteric ligands) but does not influence receptor activity by itself.
**Craving:** a core symptom of substance-use disorder, defined as a strong desire or urge to use a substance. It may be triggered by stressful events or environmental cues.
**Cytochrome P450 (CYP450):** a superfamily of enzymes essential for the metabolism of drugs and other xenobiotics.
**Dravet syndrome:** a rare genetic encephalopathy characterized by infantile-onset intractable seizures, often accompanied by cognitive and motor impairment. Autistic traits are also frequently observed.
**Entourage effect:** a synergistic interaction between multiple cannabis constituents, which together modulate the plant's therapeutic effects.
**Fetal alcohol spectrum disorders:** a range of physical, behavioral, and cognitive impairments caused by prenatal alcohol exposure.
**Fragile X syndrome (FXS):** a genetic disorder caused by the silencing of the fragile X messenger ribonucleoprotein 1 (*FMR1*) gene. It is the most common inherited cause of intellectual disability and autism.
**Inverse agonist:** a ligand that binds to a receptor and decreases its constitutive activity, eliciting a biological response opposite to that of a full or partial agonist.
**Lennox–Gastaut syndrome:** a rare, severe, early-onset epileptic encephalopathy characterized by

gastrointestinal tract, and brain [24]. It acts as a negative allosteric modulator at mu and delta opioid receptors (MOR, DOR) [18], as a positive allosteric modulator at the serotonin metabotropic 5-$HT_{1A}$ receptor (5-$HT_{1A}$R) [13,14], and as a partial agonist at the dopamine D2 receptor (D2R) [25]. Moreover, CBD indirectly activates the adenosine $A_{2A}$ receptor ($A_{2A}$R): it acts as a competitive inhibitor of the equilibrative nucleotide transporter (ENT1), increasing local adenosine levels and thereby leading to indirect $A_{2A}$R activation [26].

CBD also directly modulates the activity of several ionotropic receptors, particularly transient receptor potential vanilloid 1 (TRPV1), serotonin 5-$HT_3$, and GABA-A receptors. It is a weak **agonist** of TRPV1 [16], a non-selective cation channel activated by AEA, heat, protons, nociception and inflammation. *In vitro* studies demonstrate that CBD activates TRPV1 in a dose-dependent manner and rapidly desensitizes it [17]. Other *in vitro* studies have shown that CBD is a negative allosteric modulator of the serotonin ionotropic 5-$HT_3$ receptor [15], potentially reducing serotonin signaling [27]. It also acts as a positive allosteric modulator of the GABA-A receptor, enhancing its activity [28].

Collectively, these findings suggest that CBD's interactions with both metabotropic and ionotropic receptors play a significant role in its therapeutic effects.

## CBD's mechanisms of action involve non-receptor-mediated targets

CBD's pleiotropic effects go beyond receptor interactions and extend to non-receptor-mediated mechanisms, targeting intracellular effectors involved in various cellular and biochemical processes. Key non-receptor-mediated mechanisms of CBD include effects on oxidative stress, mitochondrial function, transcription factors, ion channels, and enzymes.

CBD modulates oxidative stress at multiple levels, leading to a range of downstream effects on cells and tissues [29]. It exhibits intrinsic free radical scavenging properties, reducing reactive oxygen species (ROS) production and protecting cells from oxidative damage [29]. However, pro-oxidant effects of CBD have also been observed in certain experimental systems and at specific doses [29]. Additional factors contribute to CBD's effects on oxidative signaling. First, it affects mitochondrial functions such as intracellular calcium homeostasis, bioenergetic metabolism, apoptosis, and mitochondrial dynamics [30]. The interactions between CBD and mitochondria are complex and involve multiple molecular mechanisms, leading to both neuroprotective and neurotoxic effects, depending on the experimental context [30]. Second, CBD activates peroxisome proliferator-activated receptor gamma (PPAR-γ), a transcription factor that regulates the expression of antioxidant proteins crucial for neuroprotection and neurodegeneration [31]. PPAR-γ activation inhibits nuclear factor kappa B (NF-κB) signaling [31], a pathway associated with neuroinflammation in reactive microglia and astrocytes. Consequently, CBD's neuroprotective effects may be mediated, at least in part, by selective PPAR-γ-dependent inhibition of NF-κB [32].

*In vitro* studies have demonstrated that CBD interacts with neuronal ion channels. It activates the voltage-gated potassium channel Kv7 [33] and inhibits Kv2.1, sodium channels (Nav1.1 to Nav1.7), and neuronal T-type calcium channels [34–36]. These interactions are thought to contribute to CBD's anticonvulsant properties.

Furthermore, CBD inhibits several **cytochrome P450** (**CYP450**) isoforms, including CYP1A2, CYP3A4, and CYP2B6, potentially increasing the effects or side effects of drugs extensively metabolized by these enzymes [37]. Interestingly, while preclinical evidence suggests that CBD may induce specific CYP isoforms, no clinical evidence of such induction has been reported [38].

intellectual impairment, multiple seizure types, and typical electroencephalography abnormalities.
**Partial agonist:** a ligand that binds to a receptor but only partially activates it, eliciting a submaximal biological response.
**Phytocannabinoids:** bioactive terpenoids originally thought to be exclusive to *Cannabis sativa*. They have now also been identified in other flowering plants, liverworts, and fungi.
**Randomized controlled trial (RCT):** the gold standard in clinical research in which participants are randomly allocated to either an experimental group, receiving the treatment, or a control group.
**Substance-use disorder (SUD):** a neuropsychiatric disorder characterized by a problematic pattern of substance use (e.g., legal or illegal drugs, medications). Symptoms include drug cravings, unsuccessful attempts to reduce use, taking more of the substance than intended, and continuing use despite negative consequences that affect health and quality of life.
**Tuberous sclerosis complex:** a rare genetic disorder that causes benign tumors in the brain and other tissues, often associated with neuropsychiatric conditions.

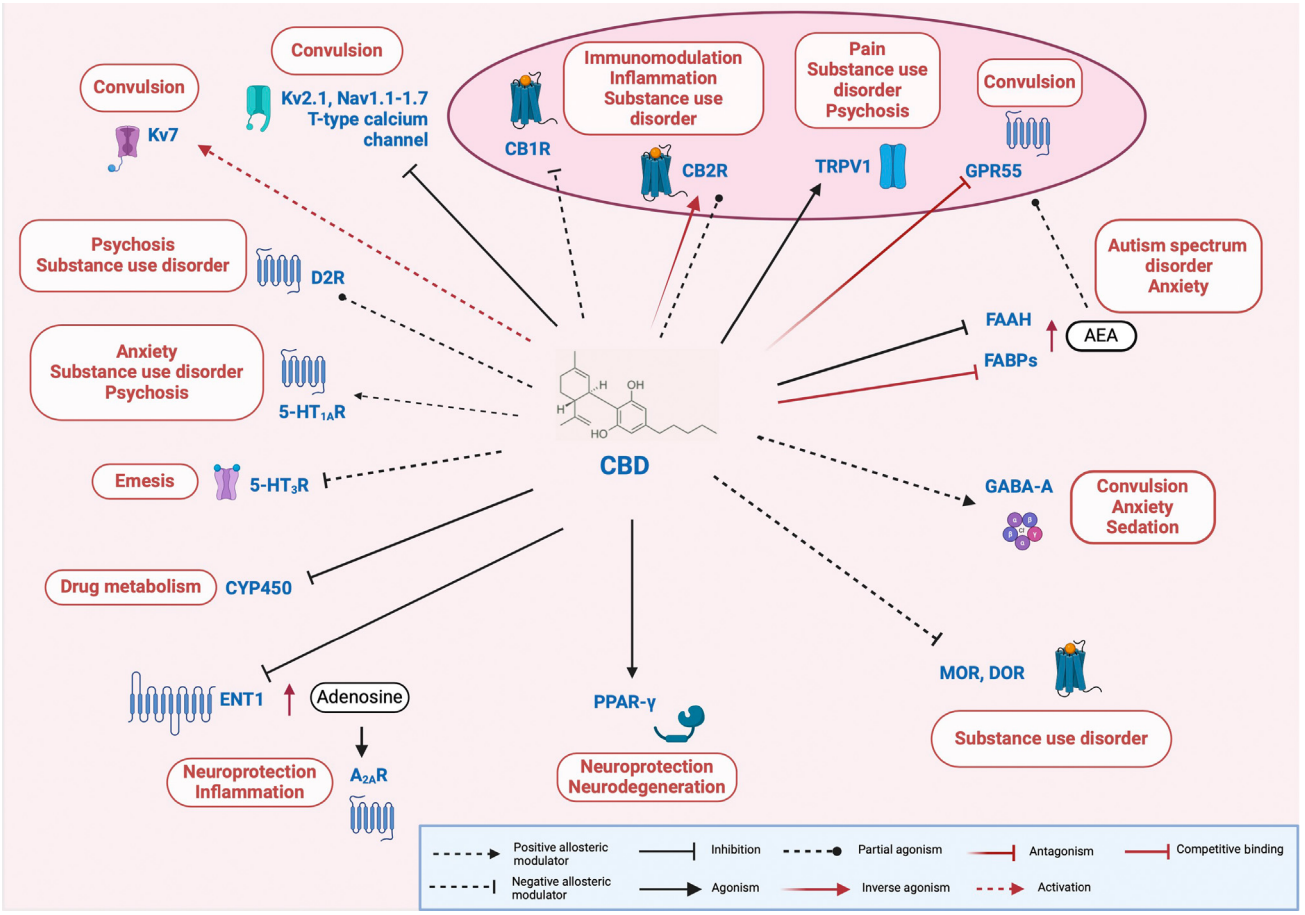


Figure 1. Schematic representation of the main molecular targets of cannabidiol (CBD). CBD is a negative allosteric modulator at type 1 cannabinoid receptors (CB1Rs) [20,21], at mu and delta opioid receptors (MOR, DOR) [18], and at serotonin 5-$HT_3$ receptors (5-$HT_3$R) [15]. CBD has been described to act both as a partial agonist [20] and as an inverse agonist [22] at type 2 cannabinoid receptors (CB2R). It is an agonist at transient receptor potential vanilloid 1 (TRPV1) [16] and peroxisome proliferator-activated receptor gamma (PPAR-γ) [31], a partial agonist at dopamine D2 receptors (D2R) [25], and a positive allosteric modulator at serotonin 5-$HT_{1A}$ receptors (5-$HT_{1A}$R) [14] and GABA-A receptors [28]. Additionally, CBD is an antagonist of G-protein-coupled receptor 55 (GPR55) [24]. CBD may increase anandamide (AEA) levels by competing for fatty acid binding proteins (FABPs) [23] and inhibiting fatty acid amide hydrolase (FAAH) [16], thereby indirectly activating CB1R, CB2R, TRPV1, and GPR55. It also blocks the equilibrative nucleoside transporter (ENT1) transporter [26], leading to the indirect activation of $A_{2A}$ receptors ($A_{2A}$R) by adenosine. Moreover, CBD activates the voltage-gated potassium channel Kv7 [33] and inhibits Kv2.1, sodium channels (Nav1.1 to Nav1.7), and neuronal T-type calcium channels [34,35]. In the liver, CBD inhibits several CYP450 isoforms, potentially leading to drug–drug interactions [38]. Figure created in BioRender.

## CBD efficacy in preclinical models of neuropsychiatric disorders

### SUD

The use of CBD as a pharmacotherapy for SUD is supported by evidence indicating its action on multiple molecular targets and neural circuits involved in addiction [39]. Preclinical studies in well-characterized animal models of SUD have demonstrated its efficacy across different stages of the addiction cycle (e.g., drug-seeking, extinction, reinstatement, and withdrawal) for several classes of addictive substances, including opioids, cannabis, psychostimulants, alcohol, and nicotine [39].

In mice, CBD mitigated behavioral changes associated with heroin withdrawal [40]. This effect was linked to the normalization of tyrosine hydroxylase (TH) and pro-opiomelanocortin gene expression in the ventral tegmental area (VTA). Additionally, CBD restored pro-opiomelanocortin and CB1R gene expression in the nucleus accumbens (NAc) [40]. In rats, CBD was shown to

Table 1. Affinity and function of CBD on diverse molecular targets and their potential clinical relevance

| Receptor | Affinity | Function | Potential conditions | Refs |
|---|---|---|---|---|
| CB1R | Ki = 1.50 μM<br>$IC_{50}$ > 30 μM<br>Binding free energy = –9.114 kcal/mol | Negative allosteric modulation | Immunomodulation<br>Inflammation<br>Substance-use disorder | [7–9,20] |
| CB2R | Ki = 4.2 ± 2.4 μM<br>$EC_{50}$ = 503 nM<br>$IC_{50}$ > 30 μM<br>Binding free energy = –9.4 kcal/mol | Partial agonism; Inverse agonism | Immunomodulation<br>Inflammation<br>Substance-use disorder | [7–9,20] |
| GPR55 | $IC_{50}$ = 455 nM<br>Binding free energy = –2.39 kcal/mol | Antagonism | Convulsion | [8,9] |
| TRPV1 | $EC_{50}$ = 1 ± 0.1 μM<br>Binding free energy = –10.79 kcal/mol | Agonism | Pain<br>Substance-use disorder<br>Psychosis | [7,8,16] |
| 5-$HT_{1A}$R | Ki = 16 μM | Positive allosteric modulator | Anxiety<br>Substance-use disorder<br>Psychosis | [9,13] |
| 5-$HT_3$R | $IC_{50}$ = 0.6 μM | Negative allosteric modulator | Emesis | [15] |
| PPAR-γ | $EC_{50}$ = 20.1 μM | Agonism | Neuroprotection<br>Neurodegeneration | [9] |
| D2R | Ki = 11 nM at D2R in high-affinity state<br>Ki = 2800 nM at D2R in low affinity state | Partial agonism | Substance-use disorder<br>Psychosis | [25] |
| MOR | Ki = 31.6 μM<br>$IC_{50}$ = 10 μM | Negative allosteric modulator | Substance-use disorder | [9,18] |
| DOR | Ki = 18.4 μM<br>$IC_{50}$ = 10.7 μM | Negative allosteric modulator | Substance-use disorder | [9,18] |
| GABA-A | $EC_{50}$ = 0.9 μM (α4β2γ2)<br>$EC_{50}$ = 1.4 μM (α5β2γ2)<br>$EC_{50}$ = 6.5 μM (α1β2γ2)<br>$EC_{50}$ = 8.2 μM (α6β2γ2)<br>$EC_{50}$ = 10.0 μM (α3β2γ2)<br>$EC_{50}$ = 16.1 μM (α2β2γ2)<br>$EC_{50}$ = 4.4 μM (α2β3γ2)<br>$EC_{50}$ = 17.4 μM (α2β1γ2) | Positive allosteric modulator | Convulsion<br>Anxiety<br>Sedation | [28] |
| Kv7 | $EC_{50}$ = 214 nM | Activation | Convulsion | [115] |
| Kv2.1 | $IC_{50}$ = 3.7 ± 0.8 μm | Inhibition | Convulsion | [34,35] |
| Nav1.1–1.7 | $IC_{50}$ = 1.9–3.8 μM | Inhibition | Convulsion | [34,35] |
| T-type calcium channel | $IC_{50}$ = 5.4–6.1 μM | Inhibition | Convulsion | [36] |
| ENT1 | $IC_{50}$ = 0.12 μM | Competitive inhibition | Neuroprotection<br>Inflammation | [26] |
| FAAH | $IC_{50}$ = 15.2–27.5 μM<br>Binding free energy = –8.3664 kcal/mol | Inhibition | Autism spectrum disorder<br>Anxiety | [8,9,16] |
| FABPs | Ki = 1.690 μM; Binding free energy = –23.64 ± 2.31 kcal/mol (FABP3)<br>Ki = 1.880 μM; Binding free energy = –21.02 ± 0.27 kcal/mol (FABP5)<br>Ki = 1.520 μM; Binding free energy = –22.94 ± 2.25 kcal/mol (FABP7) | Competitive binding | Autism spectrum disorder<br>Anxiety | [23] |
| CYP450 | Ki = 1.9 ±1.2 μM; $IC_{50}$ < 1.0 μM (CYP1A2)<br>Ki = 1.1 ± 0.24 μM; $IC_{50}$ = 1 μM (CYP2B6)<br>Ki = 0.34 ± 0.098 μM; $IC_{50}$ = 1 μM (CYP2E1)<br>Ki = 1.5 ± 0.59 μM; $IC_{50}$ < 1.0 μM (CYP3A4) | Inhibition | Drug metabolism | [37] |

inhibit cue-induced heroin-seeking behavior by normalizing CB1R and AMPA GluR1 expression in the NAc. However, it did not affect heroin self-administration [41].

CBD's negative allosteric modulation of CB1R may have therapeutic potential for cannabis-use disorder [39]. In mice, CBD was shown to reduce behavioral alterations induced by spontaneous [42] but not precipitated [43] cannabinoid withdrawal. Additionally, CBD normalized TH gene expression in the VTA and CB1R, CB2R and MOR gene expression in the NAc [42].

The therapeutic potential of CBD in addressing addiction to psychostimulants, including cocaine and amphetamine, has also been explored in recent preclinical studies. In mice, CBD was shown to prevent priming- and stress-induced reinstatement of cocaine seeking by counteracting cocaine-induced changes in dopamine transporter (DAT) gene expression in the VTA [44]. In another mouse study, CBD attenuated cue-induced reinstatement of cocaine seeking but facilitated stress-induced reinstatement [45]. Both effects were mediated by CB1R [45], suggesting that CBD's influence on CB1R may produce complex effects on the reinstatement of cocaine seeking, potentially limiting its therapeutic utility for cocaine-use disorder [45]. Molecular studies indicate that CB2R, 5-$HT_{1A}$R, and TRPV1 are involved in CBD's ability to reduce cocaine self-administration [46]. In rats, CBD was shown to prevent amphetamine relapse by modulating the expression of D1R, D2R, DAT, and TH in the mesocorticolimbic system [47].

Other studies in both mice and rats suggest that CBD may be effective in treating alcohol addiction. CBD was shown to reduce cue- and stress-induced alcohol seeking and self-administration, withdrawal-induced anxiety and convulsions, and protected rats and mice against alcohol-induced liver and brain damage [48,49]. In a mouse model of **fetal alcohol spectrum disorder**, sex-dependent beneficial effects of CBD were observed [50].

However, in contrast to the promising findings in rodents [48,49], acute and chronic CBD administration at clinically relevant doses did not reduce alcohol seeking or self-administration in baboons [51]. Notably, this study did not assess whether CBD could reduce the reinstatement of alcohol seeking after a period of abstinence or attenuate withdrawal symptoms [51], as seen in rodent models [48,49]. Considering the translational relevance of baboon models in drug abuse research, these findings advise caution in interpreting rodent data regarding CBD's efficacy in treating alcohol addiction.

Recent studies investigating CBD's effects in animal models of nicotine abuse remain limited. In mice, CBD improved cognitive deficits during nicotine withdrawal by reducing microglial reactivity and inflammatory markers in the hippocampus and prefrontal cortex (PFC) [52]. In nicotine-dependent rats, CBD was shown to reduce somatic signs of withdrawal and hyperalgesia [53].

Overall, preclinical studies suggest that CBD may have therapeutic utility in SUD [39–42,44,46–50,52,53]. However, some findings remain controversial [43,45,51]. Further research is needed to confirm the current preclinical evidence, assess the long-term effects of CBD on drug-seeking behavior and withdrawal symptoms, and elucidate the underlying molecular mechanisms, thereby effectively guiding clinical trials.

Note to Table 1:
Abbreviations: CB1R, cannabinoid receptor type 1; CB2R, cannabinoid receptor type 2; CYP450, cytochrome P450; D2R, dopamine receptor 2; DOR, δ opioid receptor; ENT1, equilibrative nucleoside transporter 1; FAAH, fatty acid amide hydrolase; FABPs, fatty acid binding proteins; GABA-A, γ-aminobutyric acid type A receptor; GPR55, G-protein-coupled receptor 55; Kv7 and Kv2.1, voltage-gated potassium (Kv) channels; MOR, μ opioid receptor; Nav1.1-1.7, voltage-gated sodium (Nav) channels; PPAR-γ, peroxisome proliferator-activated receptor gamma; TRPV1, transient receptor potential cation channel of vanilloid type-1; 5-$HT_{1A}$R, serotonin receptor 1A; 5-$HT_3$R, serotonin receptor 3.

### Anxiety

Early behavioral studies in mice and rats (reviewed in [54]) demonstrated anxiolytic-like effects of CBD. Recent research has corroborated these findings, showing that CBD reduced stress-induced anxiety-like behaviors in mice [55,56]. Notably, repeated CBD administration prevented anxiety-like behaviors in female mice exposed to early-life stress [56]. Furthermore, in a mouse model of post-traumatic stress disorder (PTSD), CBD not only improved anxiety-like behaviors but also reversed stress-induced changes in the expression of genes related to stress regulation, endocannabinoid signaling, and serotonergic neurotransmission [55]. These effects were significantly potentiated when CBD was combined with the selective serotonin reuptake inhibitor (SSRI) Sertraline [55].

In rats with neuropathic pain, repeated CBD treatment alleviated anxiety-like behaviors through interaction with 5-$HT_{1A}$R [14]. Additional studies in rats have demonstrated that CBD mitigates anxiety-like behaviors induced by $\Delta^9$-THC administration into the PFC [57] or the ventral hippocampus [58]. However, in control rats, CBD administration into the PFC impaired cognitive flexibility and working memory [57]. These findings suggest that, while $\Delta^9$-THC and CBD differentially influence anxiety and cognition, CBD may have adverse cognitive effects when directly targeting the PFC [57].

As discussed earlier, CBD also exhibits anxiolytic-like effects in rodent models of SUD [39,49].

Taken together, these preclinical findings suggest that CBD effectively reduces anxiety-like behaviors across several conditions, including stress-related disorders [55,56], neuropathic pain [14], and SUD [39,49]. However, potential cognitive side effects, particularly involving PFC activity, warrant further investigation [57].

### Psychoses

Recent preclinical studies have provided compelling evidence supporting the antipsychotic effects of CBD in mouse and rat models mimicking specific features of psychotic disorders. In mice, acute CBD administration elicited antipsychotic-like effects [59,60], primarily by modulating DNA methylation in the NAc [59] and engaging 5-$HT_{1A}$R and TRPV1 [60]. Similarly, in another mouse study, repeated CBD administration produced antipsychotic-like effects, primarily mediated through 5-$HT_{1A}$R [61].

Positive outcomes have also been observed in neurodevelopmental models of early-onset schizophrenia. In a rat model induced by late gestational exposure to the antimitotic agent methylazoxymethanol acetate (MAM), repeated CBD treatment during puberty normalized D3R gene expression in PFC, hippocampus and NAc [62]. Another study used maternal immune activation (MIA) during pregnancy to induce schizophrenia-like behavioral and neurochemical alterations in adult rat offspring [63]. In this model, prolonged CBD treatment during adolescence mitigated behavioral deficits in adult female offspring [63]. This effect was associated with modulation of GABAergic tone in the hippocampus and glutamatergic signaling in the PFC [63]. However, the same treatment protocol negatively affected social behavior in control female rats [63], suggesting that CBD may exert adverse effects under non-pathological conditions, particularly during vulnerable neurodevelopmental periods. These findings underscore the need for further research to elucidate the long-term implications of developmental CBD exposure.

### ASD

The therapeutic potential of CBD in ASD and related conditions, such as **fragile X syndrome** (**FXS**), is supported by three primary lines of evidence. First, dysregulation of the endocannabinoid

system has been observed in ASD patients and in mouse and rat models of ASD [64,65]. Second, retrospective and uncontrolled clinical trials using CBD or CBD-enriched cannabis preparations have provided preliminary evidence of efficacy in ASD [66]. Third, studies in a mouse model of Dravet syndrome have demonstrated that CBD's benefits extend beyond seizure control, alleviating comorbid autistic-like traits. Both acute [67] and repeated [68] CBD administration improved social deficits in this model.

Recent preclinical findings further underscore the potential of CBD in ASD. In BTBR $T^{+}Itpr3^{tf}$/J (BTBR) mice, a well-established model of idiopathic ASD, repeated CBD treatment dose-dependently improved behavioral deficits, with low doses effectively targeting social deficits and high doses reducing hyperactivity and repetitive behaviors [69]. These findings suggest that distinct CBD doses may address specific core and comorbid symptoms of ASD, highlighting the need to investigate dose-dependent mechanisms.

Positive outcomes have also been observed in genetic models of ASD. In a mouse model with mutations in the *Cyclin-dependent kinase-like 5* (CDKL5) gene, which causes intellectual disability and autistic-like behaviors, CBD reduced seizure susceptibility as well as cognitive and social impairments [70]. Additionally, in a rat model of FXS, both acute and repeated CBD treatment reversed object recognition memory deficits [71]. These effects were mediated by hippocampal GPR55 [71], the same receptor implicated in CBD's efficacy in the mouse model of Dravet syndrome [67].

Recent preclinical studies have also explored the potential '**entourage effect**' of cannabis constituents in ASD, which is particularly relevant given the increasing popularity of CBD-rich hemp products. In female BTBR mice, the combination of CBD with cannabis-derived terpenes produced stronger prosocial effects than CBD alone [72]. Furthermore, a preparation containing CBD and $\Delta^{9}$-THC in a 20:1 ratio reduced anxiety and repetitive behaviors in the Shank3 mouse model of ASD but did not improve social deficits [73]. Conversely, a low-dose $\Delta^{9}$-THC preparation enhanced social behavior and reduced repetitive grooming in Shank3 mice but had no effect on anxiety [73]. These findings suggest that combining CBD with other cannabis constituents may enhance therapeutic outcomes in ASD, although patient phenotypes must be carefully considered. This intriguing possibility warrants further clinical investigation.

Environmental factors also play a significant role in ASD pathogenesis and are frequently modeled in preclinical research. For instance, environmental manipulations during critical developmental stages, such as prenatal exposure to valproate, induce ASD-like phenotypes in rats and mice. To date, however, only cannabidivarin, the *n*-propyl homolog of CBD, has been tested in this model of ASD [74]. Testing CBD in environmental models of ASD remains a priority for future research.

## Clinical evidence of CBD efficacy in neuropsychiatric disorders

The promising preclinical findings discussed earlier, coupled with preliminary evidence of CBD's efficacy in patients with various psychiatric conditions [3,66], have encouraged recent RCTs to more thoroughly evaluate its therapeutic potential in SUD, anxiety, psychoses, and ASD (Tables 2 and 3).

### SUD

Building on previous research [41], short-term CBD administration reduced cue-induced **craving** and anxiety in heroin-abstinent individuals, with effects persisting for 1 week post-treatment. CBD also reduced stress reactivity to drug cues without impairing cognitive performance [75], supporting its potential in preventing heroin relapse.

Table 2. Overview of clinical trials published within the last 5 years examining CBD's efficacy in neuropsychiatric disorders (only double-blind RCTs are included)

| Condition | Population | Compound tested | Dose & treatment duration | Outcomes | Main effects | Trial registration number | Refs |
|---|---|---|---|---|---|---|---|
| Opioid-use disorder | 42 drug-abstinent individuals with heroin use disorder | 99.9% pure CBD oral solution | 400 or 800 mg for 3 consecutive days | Acute, short-term, and protracted effects of CBD on drug cue-induced craving and anxiety | CBD 400 mg and 800 mg decreased cue-induced craving and anxiety; these effects persisted one week after the last CBD administration | ClinicalTrials.gov (NCT02539823) | [75] |
| Cannabis-use disorder | 82 individuals with cannabis-use disorder | 99.9% pure CBD oral gelatin capsules | 200, 400 or 800 mg daily for 4 weeks | Cannabis use (assessed as urinary (THC-COOH): creatinine ratio, increased days per week with abstinence from cannabis during treatment) | CBD 400 mg and 800 mg were safe and efficacious at reducing cannabis use | Clinicaltrialsregister.eu (2013-000361-36/GB); ClinicalTrials.gov (NCT02044809) | [76] |
| | 70 individuals with cannabis-use disorder | 99.9% pure CBD oral gelatin capsules | 400 or 800 mg daily for 4 weeks | Anandamide levels from baseline to day 28 and their association with cannabis use, withdrawal, anxiety, depression | CBD 800 mg modulated anandamide levels but this change was not associated with clinical outcomes | Clinicaltrialsregister.eu (2013-000361-36); ClinicalTrials.gov (NCT02044809) | [77][a] |
| | 70 individuals with cannabis-use disorder | 99.9% pure CBD oral gelatin capsules | 400 or 800 mg daily for 4 weeks | Primary and secondary cognitive outcomes | CBD did not affect verbal learning and memory performance | Clinicaltrialsregister.eu (2013-000361-36); ClinicalTrials.gov (NCT02044809) | [78][a] |
| Cocaine-use disorder | 31 individuals with cocaine-use disorder | 99.9% pure CBD powder dissolved in corn oil and packed inside gelatin capsules | 300 mg daily for 10 days | Substance use, craving intensity, anxiety and depression symptoms | CBD did not affect any symptom | Not registered | [79] |
| | 78 individuals with cocaine-use disorder | CBD oral solution (purity not specified) | 800 mg daily for 92 days | Drug cue-induced craving during detoxication and time-to-cocaine relapse | CBD did not reduce cocaine craving or relapse | ClinicalTrials.gov (NCT02559167) | [80] |
| Anxiety | 57 healthy individuals performing a simulated public speaking test | 99.9% pure CBD powder dissolved in corn oil and packed inside gelatin capsules | Single 150 mg, 300 mg or 600 mg dose | Subjective and physiological measures of anxiety | CBD 300 mg reduced subjective ratings of anxiety | Not registered | [83] |
| | 37 individuals with SAD and avoidant personality disorder | CBD oral solution in olive oil (purity not specified) | 300 mg dose daily for 4 weeks | SAD symptoms | CBD significantly reduced SAD symptoms | Japanese Data Inspectorate for clinical trials (JCT0018004564) | [84] |
| | 24 individuals with Parkinson's disease performing a simulated public speaking test | 99.9% pure CBD powder dissolved in corn oil and packed inside gelatin capsules | Single 300 mg dose | Subjective and physiological measures of anxiety; tremor frequency and amplitude | CBD reduced subjective ratings of anxiety and tremor amplitude | Not registered | [85] |

*(continued on next page)*

Table 2. (continued)

| Condition | Population | Compound tested | Dose & treatment duration | Outcomes | Main effects | Trial registration number | Refs |
|---|---|---|---|---|---|---|---|
| | 32 individuals at clinical high risk (CHR) for psychosis and 26 healthy controls subjected to a social stress paradigm | 99.9% pure CBD oral capsules | 600 mg daily for 1 week | Neuroendocrine and anxiety response to social stress | CBD attenuated the abnormal neuroendocrine and psychological stress response in CHR subjects compared to healthy controls | UK Clinical Study Register (ISRCTN46322781) | [86] |
| | 80 individuals with panic disorder with agoraphobia or SAD subjected to exposure therapy | 99.9% pure CBD oral capsules | 300 mg once a week for 8 weeks | Fear response | CBD did not improve fear extinction and the effects of exposure therapy | Clinicaltrialsregister.eu (2014-004094-17) | [89] |
| | 24 healthy individuals performing emotional processing tasks | 99.9% pure CBD oral capsules | Single 600 mg dose | Neuroimaging and cognitive measures as well as subjective response to experimentally induced anxiety | CBD did not produce effects on brain responses to emotional faces and cognitive measures of emotional processing. CBD did not modulate experimentally induced anxiety. | Not registered | [87] |
| | 63 individuals with elevated trait worry | 99.6% pure CBD oral capsules | 50 mg or 300 mg daily for 2 weeks | Worry severity and anxiety symptoms | CBD did not attenuate worry severity and it reduced some anxiety symptoms only following repeated administration | Not registered | [88] |
| | 33 individuals with PTSD | 99.6% pure CBD oral gelatin capsules | Single 300 mg dose | Subjective and physiological symptoms induced by trauma recall | CBD attenuated cognitive impairments during trauma recall. CBD did not reduce anxiety and discomfort induced by trauma recall | Not registered | [90] |
| Psychosis | 13 individuals with stable recent-onset psychosis | 99.9% pure CBD oral gelatin capsules | Single 600 mg dose | Left hippocampal glutamate levels measured by proton magnetic resonance spectroscopy. Symptom severity | CBD increased hippocampal glutamate levels and decreased the severity of psychotic symptoms | Not registered | [94] |
| | 13 individuals with stable recent-onset psychosis | 99.9% pure CBD oral gelatin capsules | Single 600 mg dose | Brain activation measured by functional magnetic resonance imaging (fMRI) while performing a verbal paired associate learning task | CBD partially attenuated mediotemporal and prefrontal dysfunction and altered mediotemporal-striatal connectivity, as well as symptoms, in early psychosis patients | Not registered | [95] |
| | 33 CHR individuals | 99.9% pure CBD oral capsules | Single 600 mg dose | Hippocampal blood flow | CBD partially normalized aberrant hippocampal perfusion | UK Clinical Study Register (ISRCTN46322781) | [97] |

Table 2. (continued)

| Condition | Population | Compound tested | Dose & treatment duration | Outcomes | Main effects | Trial registration number | Refs |
|---|---|---|---|---|---|---|---|
| | 33 CHR individuals | 99.9% pure CBD oral capsules | Single 600 mg dose | Functional magnetic resonance imaging during a fearful face-processing paradigm | CBD modulated brain function in regions implicated in psychosis risk and emotion processing | UK Clinical Study Register (ISRCTN46322781) | [98] |
| | 33 CHR individuals | 99.9% pure CBD oral capsules | Single 600 mg dose | Functional magnetic resonance imaging during a reward-processing paradigm | CBD attenuated insular activation during reward processing | Not registered | [99] |
| | 31 individuals with stable recent-onset psychosis | 99.9% pure CBD oral capsules | 600 mg daily for 4 weeks | Resting state functional connectivity; prefrontal metabolite concentrations; brain activity patterns during reward processing; symptomatology | CBD attenuated impaired resting state functional connectivity and reduced positive symptom scores. No effect on prefrontal metabolite concentrations or brain activity during reward processing | Not registered | [96] |
| Autism spectrum disorder | 150 children and adolescents with ASD | Cannabis extract with CBD and THC (20:1) dissolved in olive oil solution for sublingual drops | Escalating dose till maximum 420 mg CBD and 21 mg THC per day per 12 weeks | Improvement in behavioral problems; social responsiveness; parental stress | Cannabis extract improved disruptive behaviors and caregiver-reported symptom severity | ClinicalTrials.gov (NCT02956226) | [100] |
| | 60 children with ASD | Cannabis extract with CBD and THC (9:1) administered in drops | Escalating dose till maximum 420 mg CBD and 21 mg THC per day per 12 weeks | Caregiver-reported symptom severity | Cannabis extract improved social interaction, psychomotor agitation, number of meals, anxiety, and concentration | Brazilian Registry of Clinical Trials (10743) | [101] |
| | 17 individuals with ASD and 17 neurotypical controls | 99.9% pure CBD oral solution | Single 600 mg dose | Spontaneous regional brain activity measured by state fMRI | CBD altered functional connectivity between brain regions involved in ASD | ClinicalTrials.gov (NCT03537950) | [102] |
| | 17 individuals with ASD and 17 neurotypical controls | 99.9% pure CBD oral solution | Single 600 mg dose | Glutamate and GABA levels measured by magnetic resonance spectroscopy | CBD modulated glutamate-GABA levels, but prefrontal GABA levels responded to CBD differently in ASD patients compared to controls | ClinicalTrials.gov (NCT03537950) | [103] |
| | 212 children and adolescents with FXS | 4.2% CBD transdermal gel | 250 mg or 500 mg daily for 12 weeks | Social avoidance | Significant improvement observed only in a subset of patients with ≥ 90% methylation of *FMR1* | ClinicalTrials.gov (NCT03614663) | [104] |

Abbreviation: CHR, clinical high risk.
[a]Data recorded as secondary outcomes in a larger RCT of CBD for cannabis-use disorder [76].

Table 3. Overview of ongoing[a] clinical trials[b] for CBD in neuropsychiatric disorders registered in US[i], European[ii], and Australian and New Zealand[iii] databases

| Condition | N° of trials & estimated participants | Registered on | Registration number | Status |
|---|---|---|---|---|
| Opioid-use disorder | 6 (*n* = 729) | https://clinicaltrials.gov/ | NCT06206291<br>NCT05299944<br>NCT04567784<br>NCT04587791<br>NCT06544291<br>NCT03813095 | 4 recruiting, 2 not yet recruiting |
| Cannabis-use disorder | 3 (*n* = 498) | https://clinicaltrials.gov/ | NCT06107062<br>NCT05885542<br>NCT06569394 | Recruiting |
| | 2 (*n* = 280) | https://anzctr.org.au/ | ACTRN12623000526673<br>ACTRN12616001001482 | Recruiting |
| Alcohol-use disorder | 4 (*n* = 502) | https://clinicaltrials.gov/ | NCT05613608<br>NCT06512389<br>NCT05860699<br>NCT05159830 | 3 recruiting, 1 not yet recruiting |
| | 1 (*n* = 152) | https://www.clinicaltrialsregister.eu/ | 2019-004740-30 | Ongoing |
| Nicotine-use disorder | 2 (*n* = 170) | https://clinicaltrials.gov/ | NCT05445804<br>NCT06218056 | 1 recruiting, 1 not yet recruiting |
| Anxiety | 12 (*n* = 1173) | https://clinicaltrials.gov/ | NCT05571592<br>NCT02548559<br>NCT05649059<br>NCT06290063<br>NCT05283382<br>NCT06123702<br>NCT06266611<br>NCT03549819<br>NCT05753007<br>NCT06261502<br>NCT04482244<br>NCT04878627 | 6 recruiting, 4 not yet recruiting, 2 ongoing-not recruiting |
| | 2 (*n* = 137) | https://www.clinicaltrialsregister.eu/ | 2020-003739-62<br>2020-004294-48 | Ongoing |
| | 3 (*n* = 300) | https://anzctr.org.au/ | ACTRN12624000236594<br>ACTRN12623000803695<br>ACTRN12621001659897 | Not yet recruiting |
| Psychosis | 4 (*n* = 580) | https://clinicaltrials.gov/ | NCT04411225<br>NCT04105231<br>NCT02926859<br>NCT02088060 | 3 recruiting, 1 ongoing-not recruiting |
| | 1 (*n* = 86) | https://www.clinicaltrialsregister.eu/ | 2007-002245-20 | Ongoing |
| | 2 (*n* = 493) | https://anzctr.org.au/ | ACTRN12622001112752<br>ACTRN12621000349842 | Recruiting |
| Autism spectrum disorder | 3 (*n* = 167) | https://clinicaltrials.gov/ | NCT05015439<br>NCT04517799<br>NCT04520685 | 1 recruiting, 2 ongoing-not recruiting |
| | 1 (*n* = 204) | https://www.clinicaltrialsregister.eu/ | 2021-002542-33 | Ongoing |
| | 1 (*n* = 34) | https://anzctr.org.au/ | ACTRN12622000437763 | Ongoing-not recruiting |

[a]As of October 2024.
[b]Only double-blind RCTs are included.

Positive outcomes have also been reported in cannabis-use disorder. CBD reduced cannabis consumption in these patients [76], potentially by modulating plasmatic AEA levels [77]. Importantly, verbal learning and memory performance remained unaffected [78].

In contrast, CBD demonstrated no effect on cocaine craving, relapse, anxiety, or cortisol levels in individuals with cocaine-use disorder [79,80], despite preclinical evidence suggesting its efficacy in modulating cocaine-related behaviors [44–46].

Clinical evidence for CBD in alcohol and nicotine addiction is sparse. A preliminary placebo-controlled study found minimal effects of CBD on subjective responses to alcohol in heavy drinkers [81]. Although no recent RCTs have evaluated CBD for nicotine-use disorder, ongoing and planned trials (Table 3) may provide further insights.

Overall, while many preclinical studies suggest that CBD may counteract the addictive properties of commonly abused drugs, clinical evidence supports its efficacy primarily in opioid and cannabis-use disorders. Larger studies with extended follow-up periods and biomarker analyses are needed to confirm these findings.

### Anxiety

Early small-scale RCTs reported that CBD reduced social anxiety symptoms in healthy volunteers undergoing anxiogenic public speaking tasks and in patients with social anxiety disorder (SAD), likely by modulating brain regions implicated in SAD [3,82]. More recent studies have confirmed these findings, reporting anxiolytic effects of CBD in social contexts among healthy individuals [83], patients with SAD [84], individuals with Parkinson's disease [85], and those at high risk of psychosis [86].

CBD's effects on emotional processing, defined as the cognitive interpretation of emotion-related information, have also been explored. In healthy individuals, CBD did not affect brain responses to emotional faces or cognitive measures of emotional processing [87]. It also failed to reduce worry severity in individuals with high trait worry [88], or improve fear extinction and exposure therapy outcomes in treatment-refractory anxiety patients [89]. However, CBD attenuated cognitive impairments during trauma recall in PTSD patients, although it did not reduce the anxiety or discomfort associated with recalling traumatic events [90].

In conclusion, CBD appears promising for treating SAD. However, further research should focus on optimizing dosing, evaluating long-term safety, and exploring sex-specific differences in therapeutic response.

### Psychoses

Preliminary clinical findings indicated that CBD may have antipsychotic effects, particularly in individuals at high risk for psychosis or in the early stages of the disorder [3]. Higher doses of CBD, either as monotherapy [91] or adjunctive therapy [92], have proven more effective than lower doses [93].

Recent RCTs substantiate these findings. In patients with recent-onset psychosis, a single CBD dose reduced the severity of psychotic symptoms [94], increased hippocampal glutamate levels [94], and modulated hippocampal–striatal connectivity [95]. Long-term adjunctive CBD treatment in these patients attenuated impairments in resting state functional connectivity [96]. In individuals at clinical high risk for psychosis, acute CBD partially normalized abnormal hippocampal perfusion [97], modulated mediotemporal and striatal function during fear processing [98], and reduced insular activation during reward-processing tasks [99]. Collectively, these findings highlight CBD's ability to modulate brain activity patterns associated with psychosis. Ongoing RCTs aim to further clarify its therapeutic potential in this context (Table 3).

### ASD

CBD is approved for the treatment of Dravet and Lennox–Gastaut syndromes, which are often associated with autistic traits (Box 1). However, despite positive preliminary reports [66] and promising preclinical data [64], clinical evidence supporting CBD's efficacy in ASD remains limited.

Two recent RCTs in ASD patients reported improvements in some behaviors, but they used CBD-rich cannabis extracts (i.e., with low $\Delta^9$-THC content) [100,101] rather than pure CBD. Another study in adults with and without ASD found that acute CBD altered functional connectivity in ASD-related brain regions, but did not assess clinical outcomes [102]. Moreover, CBD had opposite effects on GABAergic neurotransmission in prefrontal and subcortical regions of adults with and without ASD [103].

CBD's potential in FXS has also been explored. Transdermal CBD demonstrated efficacy in FXS patients with ≥90% methylation of the *Fragile X Messenger Ribonucleoprotein 1* (*FMR1*) gene, who typically exhibit more severe symptoms [104]. However, this study was limited to children and adolescents, and the subset of patients with high gene methylation was small, highlighting the need for larger studies to validate these findings.

## Critical issues related to CBD use

Both earlier clinical findings and recent studies indicate that CBD is generally well tolerated [3]. However, potential adverse effects warrant careful consideration, including significant drug–drug interactions due to CBD's modulation of CYP450 enzymes [37,38,105]. Individual factors such as underlying health conditions, sex, dosage, product quality, and the presence of other phytocannabinoids may also influence CBD's neuropsychiatric effects [105]. For example, while CBD is often thought to mitigate psychotic symptoms induced by acute $\Delta^9$-THC exposure [106], a recent metanalysis found no consistent evidence supporting this effect [107]. Emerging studies indicate that CBD can increase plasma levels of $\Delta^9$-THC and its psychoactive metabolite 11-OH- $\Delta^9$-THC, potentially amplifying their psychoactive effects [108,109]. Notably, this pharmacokinetic interaction has been observed at CBD doses as low as 30 mg [109]. These findings raise concerns about the non-medical use of CBD. In several countries, low-dose CBD products are marketed as dietary supplements, cosmetics, and food items. However, both animal and human studies suggest that CBD may have toxicological effects at certain doses [105]. Consequently, regulatory agencies such as the FDA and European Food Safety Authority (EFSA) have expressed concerns regarding the widespread use of non-pharmaceutical CBD products, identifying data gaps and uncertainties surrounding CBD intake for non-medical purposes [110,111].

Pregnancy and breastfeeding are areas of particular concern. Like $\Delta^9$-THC, CBD crosses the placenta, potentially influencing fetal development. CBD also accumulates in breast milk, posing potential risks to breastfeeding infants. Animal studies indicate that prenatal CBD exposure can produce sex-specific adverse effects on brain development at the molecular, cellular, synaptic, and behavioral levels, with both short- and long-term consequences [112–114]. Therefore, CBD use during pregnancy and breastfeeding should be approached with caution.

Adolescence represents another sensitive developmental window, given the extensive brain maturation occurring during this period. However, data on the long-term effects of CBD exposure during adolescence remain limited (for a detailed review on the effects of cannabinoids, including CBD, in children and adolescents, see [66]). This underscores the urgent need for further research on the developmental implications of CBD use.

## Concluding remarks and future perspectives

This review highlights the broad therapeutic potential of CBD in treating neuropsychiatric disorders. Unlike conventional medications that typically target specific receptors, CBD interacts with a wide range of molecular targets. This 'promiscuous' activity allows CBD to modulate multiple signaling pathways simultaneously, potentially restoring homeostasis in dysregulated cells or neuronal circuits. These multitarget mechanisms may underlie its diverse therapeutic effects, including anxiolytic, antiepileptic, antipsychotic, and anti-addictive properties. However, this mechanistic complexity poses significant challenges in fully elucidating CBD's mechanisms of action. The relative contribution of individual pathways to its therapeutic effects remains poorly understood.

Preclinical studies provide compelling evidence of CBD's efficacy, yet several critical questions remain unanswered. Research is needed to determine its impact on brain function during sensitive developmental windows, evaluate the long-term consequences of chronic use, and investigate sex-specific outcomes (see Outstanding questions).

Clinical data also underscore CBD's therapeutic potential, particularly in treating social anxiety, opioid-use disorder, and cannabis-use disorder. However, many existing studies face limitations, such as small sample sizes, inconsistent dosing regimens and product purity, comorbidities, concurrent use of psychiatric medications, and short treatment durations. Rigorous, well-powered RCTs are essential to validate these findings and establish optimal treatment protocols.

The placebo effect poses another challenge in neuropsychiatric research, where psychological and biological factors intersect. Many studies rely heavily on self-reported outcomes, which are susceptible to variability and bias. Controlled methodologies are crucial for distinguishing true pharmacological effects from placebo responses. At the same time, it is important to acknowledge that placebo effects may contribute to overall treatment efficacy.

Addressing these challenges will require substantial resources and collaboration among researchers, industry stakeholders, and regulatory agencies. Such efforts are justified. Current evidence suggests that CBD's broad molecular effects could provide significant benefits for various neuropsychiatric disorders, particularly in patients unresponsive to conventional therapies or requiring more effective treatment options. By deepening our understanding of CBD's mechanisms of action and refining its clinical applications, we can maximize its therapeutic potential and advance innovative strategies to enhance mental health and well-being.

### Outstanding questions

Will innovative molecular tools and preclinical models clarify CBD's specific molecular targets and mechanisms of action, dissecting those responsible for therapeutic effects from those that contribute to side effects?

Is CBD's therapeutic potential primarily due to interactions with specific receptors or signaling systems, or does it require a broader multitarget modulation?

How does CBD's multitarget pharmacological profile affect its safety, particularly during critical developmental windows (e.g., pregnancy, lactation, adolescence)?

What are the long-term effects of CBD treatment on brain function and neurobehavioral outcomes?

Can research elucidate how CBD modulates the acute psychotomimetic effects of THC, and if so, what are the implications for therapeutic use?

Does CBD's impact on brain processes and neurobehavioral outcomes vary by sex?

How will preclinical and clinical research shape and influence the regulatory landscape for CBD products?

Will changes in regulatory classification of CBD affect scientific research and patient access to CBD-based medications?

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### Resources

[i] www.clinicaltrials.gov/

[ii] www.clinicaltrialsregister.eu/

[iii] https://anzctr.org.au/

[iv] www.ema.europa.eu/en/documents/product-information/epidyolex-epar-product-information_en.pdf

[v] www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf

[vi] https://pdf.hres.ca/dpd_pm/00054388.PDF

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