adolescents

Review

Evidence for Cannabidiol as a Medication for the Treatment of Neurological, Psychiatric, Behavioral and Substance Use Disorders in Adolescents

Jennifer A. Ross [1,2], William Riccardelli [2], James Robitaille [3] and Sharon Levy [1,2,*]

[1] Department of Pediatrics, Harvard Medical School, Boston, MA 02115, USA; jennifer.ross@childrens.harvard.edu
[2] Department of Pediatrics, Boston Children's Hospital, Boston, MA 02115, USA; wriccardelli@fourwindshospital.com
[3] Research Operations, Boston Children's Hospital, Boston, MA 02115, USA; james.robitaille@childrens.harvard.edu
* Correspondence: sharon.levy@childrens.harvard.edu

Abstract

Cannabidiol (CBD) is a chemical produced by the cannabis plant that acts as an allosteric modulator of cannabinoid receptors resulting in non-competitive receptor antagonism in the central nervous system. This mechanism of action leads to anti-convulsant, anti-anxiety, and analgesic properties with minimal psycho-activity, which has led to significant interest in the use of CBD as a medication. Legislation around cannabis has changed in recent years, with many states permitting the use of CBD-based products as "medication" without approval from the Federal Drug Administration. This has led to a proliferation of products with associated marketing claims that are often unsubstantiated. This review summarizes the evidence for cannabidiol as a medical treatment, focusing on epilepsy, mental health, behavioral and substance use disorders occurring in pediatric and adolescent populations for which information is available. CBD preparations have been approved by the FDA to treat epilepsy in childhood; no other indications currently exist, and the literature remains inconclusive. Few adverse effects related to CBD use have been reported. However, endogenous cannabinoids play an important role in guiding brain development, and the long-term impact of modulating the endocannabinoid system during periods of brain growth during childhood and adolescence is unknown. While there is excitement about the potential for the development of CBD medications, currently, there is very limited information about the long-term safety of CBD, especially in children and adolescents, and caution is recommended regarding the use of unregulated, unapproved CBD preparations that are currently available over the counter.

Keywords: cannabidiol; cannabinoids; cannabis; marijuana; medical cannabis; medical marijuana; pediatrics; adolescents

check for updates

Received: 21 May 2025
Revised: 10 September 2025
Accepted: 25 September 2025
Published: 30 September 2025

Citation: Ross, J.A.; Riccardelli, W.; Robitaille, J.; Levy, S. Evidence for Cannabidiol as a Medication for the Treatment of Neurological, Psychiatric, Behavioral and Substance Use Disorders in Adolescents. *Adolescents* **2025**, *5*, 54. https://doi.org/10.3390/adolescents5040054

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Cannabidiol (CBD) is an exogenous cannabinoid produced by the cannabis plant. Its most well-known effects are as an allosteric modulator of cannabinoid receptors that results in non-competitive receptor antagonism in the central nervous system [1], leading to anti-convulsant, anti-anxiety, and analgesic properties with minimal psycho-activity. CBD has several other cellular targets, including the serotonin 5-HT 1A receptor and the

transient receptor potential cation channel [2], and plays a role in immuno-modulation [3], including reducing neuroinflammation. These effects have led to significant interest in the use of CBD as a medication for a broad spectrum of disorders. Pre-clinical/animal trials and early-stage human studies have been promising [4–8]. While the research base is growing, significant questions regarding the risks and benefits of CBD therapeutics remain, particularly regarding children and adolescents. Endocannabinoids are known to play an important role in brain development [9], and the long-term impact of exogenous cannabinoid exposure on children and adolescents is unknown. This review examines the evidence for the use of CBD as a medication in children and adolescents, focusing on the areas with the most evidence to date: neurological, psychiatric, behavioral, and substance use disorders. The evidence is summarized in Table 1.

Table 1. Summary of study results. Evidence for the use of CBD as a medication in children and adolescents, a summary table of study results.

Epilepsy					
Disorder	**Study Type**	**Study Size**	**Dose of CBD**	**Adverse Effects**	**Results**
Epilepsy	Meta-analysis	*n = 6 published papers*	10–20 mg/kg/day	Somnolence, decreased appetite, diarrhea	Patients who received CBD experienced a 127% greater seizure reduction compared to those who received placebo.
	Review	*n = 36 published papers*	Not specified	Drowsiness, diarrhea, fatigue, appetite changes	Two of the RCTs and 17 open-label trials reported significant reductions in seizure frequency with CBD, with effects more pronounced in pediatric populations.
Dravet Syndrome	Randomized, double-blind placebo-controlled trial	*n* = 120	20 mg/kg oral solution	Diarrhea, vomiting, fatigue, pyrexia, somnolence	Seizure frequency in CBD group decreased from a median of 12.4 to 5.9 seizures per month.
Lennox–Gastaut Syndrome	Randomized double-blind placebo-controlled trial	*n* = 225	20 mg/kg, 10 mg/kg	Somnolence, decreased appetite, diarrhea	Median percent reduction in drop-seizure frequency of 41.9% with 20 mg/kg/day CBD, 37.2% with CBD 10 mg/kg/day, and 17.2% with placebo ($p = 0.005$ for the 20 mg/kg cannabidiol group vs. placebo group, and $p = 0.002$ for the 10 mg/kg cannabidiol group vs. placebo group).
Tuberous Sclerosis Complex	Randomized controlled trial	*n* = 224	50 mg/kg, 25 mg/kg	Diarrhea, somnolence	Both doses of CBD reduced seizures by approximately half from baseline, and patients taking the 25 mg/kg/day dose of CBD had fewer adverse effects.

Table 1. *Cont.*

Epilepsy					
Disorder	**Study Type**	**Study Size**	**Dose of CBD**	**Adverse Effects**	**Results**
Sturge–Weber Syndrome	Open-label clinical trial	*n* = 5	Not specified	Temporary increased seizures, behavioral issues, right eye exotropia, increased aspartate aminotransferase, tiredness	Three of the patients reported a greater than 50% reduction in seizures and an improved quality of life.
Psychiatric and Behavioral Disorders					
Disorder	**Study Type**	**Study Size**	**Dose of CBD**	**Adverse Effects**	**Results**
Psychosis	Randomized, double-blind, placebo controlled trial	*n* = 33	600 mg	Not specified	Participants who received CBD had increased activation in brain regions associated with the pathophysiology of psychosis after a single dose. Participants who received 21 days of CBD treatment had greater reductions in anxiety and distress associated with psychotic symptoms.
Schizophrenia	Randomized, double-blind, placebo controlled trial	*n* = 88	1000 mg	Nausea, diarrhea, abdominal pain, vomiting	Adjunctive treatment with CBD resulted in a modest but significant decrease in positive symptoms of schizophrenia (hallucinations, delusions, bizarre behavior) and in clinician impressions of illness severity.
	Randomized double-blind placebo-controlled parallel-group fixed-dose study	*n* = 36	600 mg	Sedation	No improvements were observed in cognition or psychotic symptoms for those treated with CBD; the study concluded that augmentation with CBD does not improve cognition or psychotic symptoms in outpatients with schizophrenia.
	Randomized, double-blind, active control trial	*n* = 42	800 mg	Not specified	Neurocognitive functioning improved in both groups with no significant difference between treatments. Participants who received CBD treatment had improvements in processing speed, visual memory, visuomotor coordination, and sustained attention.

Table 1. *Cont.*

Psychiatric and Behavioral Disorders					
Disorder	**Study Type**	**Study Size**	**Dose of CBD**	**Adverse Effects**	**Results**
Anxiety Symptoms and Disorders	Retrospective chart review	*n* = 72	25–175 mg	Fatigue, sedation, dry eyes, and one patient with a developmental disorder had to be taken off the CBD regimen because of increased sexually inappropriate behavior.	Patients reported bigger improvements and more sustained response to anxiety symptoms than sleep.
	Open-label trial	*n* = 31	Titrated up to 800 mg	No serious or severe side effects	Anxiety was reduced, and improvement was noted in depressive symptoms and overall functioning.
Social Anxiety	Randomized, double-blind, placebo controlled trial	*n* = 24	600 mg	Not specified	The study concluded that CBD reduced anxiety in patients with social anxiety disorder.
	Randomized, double-blind, placebo controlled crossover trial	*n* = 10	400 mg	Not specified	Use of CBD was associated with significantly decreased subjective anxiety.
	Randomized, double-blind, placebo controlled trial	*n* = 37	300 mg	Not specified	CBD significantly decreased self-reported anxiety using validated measures.
Posttraumatic Stress Disorder	Case Report	*n* = 1	25 mg	No reported side effects	Increased sleep quality and decreased anxiety.
	Retrospective case series	*n* = 11	Unspecified CBD dosage with routine psychiatric treatment	Fatigue, gastrointestinal discomfort	Patients reported decrease in PTSD symptoms using validated measures.
Behaviors Associated with Autism Spectrum Disorder	Open-label trial	*n* = 53	Pharmaceutical-grade unspecified CBD dosage	Somnolence, change in appetite	Patients reported improvement in four behaviors after treatment, though improvements were not statistically greater than improvement rates for already accepted treatments.
	Randomized, double-blind, placebo controlled trial	*n* = 150	Whole-plant cannabis extract (CBD: Δ9-THC 20:1), purified extract (CBD: Δ9-THC 1:1)	Not specified	The study concluded that there were no sleep improvements with either whole-plant cannabis extract or purified extract compared to placebo.

Table 1. *Cont.*

Psychiatric and Behavioral Disorders					
Disorder	**Study Type**	**Study Size**	**Dose of CBD**	**Adverse Effects**	**Results**
Fragile X Syndrome	Randomized, double-blind, placebo controlled trial	*n* = 212	250 mg or 500 mg based on weight	Frequencies of adverse events were similar in placebo and treatment groups. Events included diarrhea, application site pain, gastroenteritis, cough	Participants with >90% methylation achieved statistically significant improvements in scaled scores, representing improvements in social avoidance, social interaction, and irritable behaviors.
	Open-label trial	*n* = 20	50–250 mg	No serious or severe side effects	The study concluded that the CBD preparation was well tolerated and associated with significant improvement in anxiety and mood scores over the 12-week trial.
	Case series	*n* = 3	32–63.9 mg	No observed adverse events	Parents of the participants reported subjective improvements in anxiety levels, social functioning, feeding behaviors, sleep, motor skills, linguistic skills, and panic attacks.
Rett Syndrome	Longitudinal observation study	*n* = 26	15 mg/kg	Somnolence	The study found that 7/10 had reduced seizure incidence, 5/10 had reduced agitation or anxiety, and 4/10 had improved spasticity.
Intellectual Developmental Disorder	Randomized, double-blind, placebo controlled trial	*n* = 88	98% CBD oil (titrated to 20 mg/kg/day in two divided doses; maximum dose 500 mg twice daily)	No serious or severe side effects	Parents of children receiving CBD endorsed a clinically significant positive change in behavior via validated questionnaire.
Substance Use Disorder					
Disorder	**Study Type**	**Study Size**	**Dose of CBD**	**Adverse Effects**	**Results**
Substance Use Disorder	Case Report	*n* = 1	100–600 mg	No observed adverse events	The patient stopped using substances without withdrawal symptoms, assessed with daily clinical evaluations and weekly drug screenings, and had improvement in their depression and anxiety evaluated using screening instruments conducted before CBD treatment and after 8 weeks of CBD treatment.

Table 1. *Cont.*

Substance Use Disorder					
Disorder	**Study Type**	**Study Size**	**Dose of CBD**	**Adverse Effects**	**Results**
Cannabis Use Disorder	Randomized, double-blind, placebo controlled trial	*n* = 82	200 mg, 400 mg, 800 mg	Not specified	Doses of 400 mg CBD and 800 mg CBD were more effective at reducing cannabis use as measured by self-reported days of abstinence and urine cannabis metabolites.
	Open-label trial	*n* = 8	600–1200 mg	Not specified	CBD was well tolerated by all participants, and at 28 days, four participants maintained abstinence from cannabis.
	Open-label trial	*n* = 20	200 mg	No observed adverse events	Patients reported decreased euphoria when using cannabis, reduction in depressive and psychotic-like symptoms, and improvements in cognition.
	Case Report	*n* = 1	300–600 mg	Not specified	Self-reported cannabis withdrawal symptoms decreased to zero by day 6, and depression and anxiety symptoms also improved.
	Case Report	*n* = 1	24 mg titrated to 18 mg	Not specified	Patient reported decreased anxiety, improved sleep, and abstinence from cannabis.
Nicotine Use Disorder	Randomized, double-blind, placebo controlled trial	*n* = 24	Inhaled CBD	Not specified	Participants in the CBD group reduced the number of cigarettes 40% as compared to no change in the placebo group.
	Randomized, double-blind, placebo controlled trial	*n* = 30	800 mg	Headache	Study found that CBD reduced salience to cigarette cues and reduced explicit pleasantness of cigarettes.
Opioid Use Disorder	Randomized, double-blind, placebo controlled trial	*n* = 42	400 or 800 mg	No observed adverse events	CBD reduced salient drug cue-induced craving and anxiety.

2. Epilepsy

The largest body of CBD research has been conducted in patients with epilepsy, and the only Food and Drug Administration (FDA)-approved indication for a CBD formulation is for the treatment of drug-resistant seizures in patients with Lennox–Gastaut syndrome, Dravet Syndrome, and tuberous sclerosis complex. The mechanisms of action that account for anticonvulsant properties are complex and are thought to involve positive allosteric modulation of the GABA receptor [10] and binding to a transmembrane sodium ion channel, resulting in channel inhibition [11]. A 2018 review included 36 individual

studies (six randomized controlled trials (RCTs) and 30 observational) of children and adults (6 months–55 years) with treatment-resistant epilepsy treated with cannabinoids as adjunctive therapy to standard anticonvulsants. Epilepsy diagnoses in subjects enrolled in these studies included Lennox-Gastaut syndrome (two RCTs), Dravet Syndrome (one RCT), and 'mixed' epilepsy syndromes. Two of the RCTs and 17 open-label trials reported significant reductions in seizure frequency with CBD, with effects more pronounced in pediatric populations. A meta-analysis including patients from three of the RCTs found a significant increase in adverse effects (drowsiness with a relative risk (RR) of 2.53, diarrhea with an RR of 2.63, fatigue with an RR of 5.80, and appetite changes with an RR of 5.46) compared to placebo [12]. A more recent meta-analysis that included studies evaluating the impact of CBD on the number of seizures in patients with pharmaco-resistant epilepsy published between March 2014 and January 2024 found that patients who received CBD experienced a 127% greater seizure reduction compared to those who received placebo [13].

2.1. Dravet Syndrome [14]

Dravet Syndrome is a congenital seizure disorder resulting from the mutation of a protein that encodes a voltage-gated sodium channel [15]. In 2017, a 14-week randomized, double-blinded placebo-controlled trial examined adding pharmaceutical-grade CBD (20 mg/kg/day oral solution) or placebo to standard antiepileptic medication combinations for 120 pediatric patients (ages 2–18 years) with a diagnosis of treatment-resistant Dravet Syndrome. Seizure frequency in the group receiving CBD decreased from a median of 12.4 to 5.9 seizures a month ($p = 0.01$), and three participants in the intervention group became seizure-free during the study. The study concluded that adding CBD to the standard antiepileptic treatment plans for patients with Dravet Syndrome decreased the frequency of convulsive seizures. More adverse effects, including diarrhea, vomiting, fatigue, pyrexia, and somnolence, were reported in the group receiving CBD, which resulted in greater participant withdrawal.

2.2. Lennox–Gastaut Syndrome [16]

Lennox–Gastaut syndrome is a severe form of epilepsy that begins in childhood. Causes include brain malformations, perinatal asphyxia, head injury, central nervous system infections and genetic mutations. Patients with Lennox–Gastaut syndrome have multiple types of seizures that generally cannot be controlled with a single anticonvulsant [17]. A 2018 phase three randomized double-blinded placebo-controlled trial, involving 225 patients with Lennox–Gastaut Syndrome (ages 2–55 years) who were having two or more drop seizures per week despite standard antiepileptic medication therapy, randomized participants to receive standard therapy plus pharmaceutical-grade CBD 20 mg/kg/day or standard therapy plus pharmaceutical-grade CBD 10 mg/kg/day or standard therapy plus placebo. Drop seizure frequency decreased in both CBD arms of the study, with a median percent reduction in drop-seizure frequency of 41.9% with 20 mg/kg/day CBD, 37.2% with CBD 10 mg/kg/day, and 17.2% with placebo ($p = 0.005$ for the 20 mg/kg cannabidiol group vs. placebo group, and $p = 0.002$ for the 10 mg/kg cannabidiol group vs. placebo group). Eight patients who were treated with CBD became seizure-free during the maintenance phase. The study concluded that adding CBD to standard antiepileptic medication combinations was associated with a significant reduction in frequencies of drop seizures and all seizure types when compared to placebo in patients with Lenno–Gastaut Syndrome. Somnolence, decreased appetite, and diarrhea were the most common adverse effects associated with CBD. Seven patients withdrew from the trial due to adverse effects, with elevated serum aminotransferase concentrations the most common adverse effect in these patients.

2.3. Tuberous Sclerosis Complex [18]

Tuberous sclerosis is a genetic disorder that leads to unregulated cell growth, leading to non-cancerous growths in multiple organs, with growths in the brain leading to early onset of multiple types of seizures [19]. In 2020, a 16-week randomized clinical trial assessing adjunctive CBD for drug-resistant seizures in tuberous sclerosis complex followed 224 patients (ages 1–56 years) with tuberous sclerosis complex treated with 50 mg/kg/day of CBD, 25 mg/kg/day of CBD or placebo. Both dosages of CBD reduced seizures by approximately half from baseline, and patients taking the 25 mg/kg/day dosage of CBD had fewer adverse effects.

2.4. Sturge–Weber Syndrome [20,21]

Sturge–Weber Syndrome is a genetic disorder of the vasculature in the brain, skin and eye that results in cortical dysplasia and impaired cerebral perfusion resulting in seizures [22]. In 2017, five patients (ages 2–19 years) with Sturge–Weber syndrome and treatment-resistant epilepsy received CBD, and three of the patients reported a greater than 50% reduction in seizures and an improved quality of life. The study concluded that CBD may be tolerated as an adjunctive medication for seizure management in patients with Sturge–Weber syndrome. A study that assessed changes in quality of life in 10 patients (ages 3–34 years) with Sturge–Weber Syndrome after 6 months of CBD treatment found significant improvements in neuroscore, patient-reported quality of life, and anxiety and emotional regulation, with one patient withdrawing due to side effects.

3. Psychiatric and Behavioral Disorders

CBD may have therapeutic potential as an antipsychotic medication, an anxiolytic and as an agent to support behavioral regulation in individuals with autism spectrum disorders, though to date, there are no FDA-approved indications for any mental or behavioral health conditions. Clinically relevant studies of CBD for conditions that affect adolescents, including psychosis, schizophrenia, anxiety, post-traumatic stress disorder, and autism spectrum disorders are outlined below.

3.1. Psychosis [23–25] and Schizophrenia [26–29]

Research has indicated that CBD has antipsychotic properties. Its mechanism of action is not fully understood, though likely includes modulation of the endocannabinoid system which stabilizes dopaminergic, glutaminergic and GABAergic systems. Notably, CBD mechanisms are distinct from traditional anti-psychotic compounds whose effects are primarily mediated through dopamine receptor blockade [30]. CBD has been studied in patients at high risk of psychosis (as identified via the Personal Assessment and Crisis Evaluation Clinic criteria [31] or the Comprehensive Assessment of At-Risk Mental States [32]). In a double-blind, placebo-controlled randomized clinical trial, 33 anti-psychotic medication-naïve patients at high risk of psychosis (mean age 22.4–25.4 years) were randomized to receive 600 mg CBD or placebo. Relative to placebo, participants who received CBD had increased activation in brain regions associated with the pathophysiology of psychosis after a single dose. However, high-risk patients who received 7 days of 600 mg/day of CBD did not have significant reductions in anxiety related to an experimental stressor or cortisol levels when compared to high-risk patients receiving placebo. In the same trial, participants who received 21 days of CBD treatment had greater reductions in anxiety and distress associated with psychotic symptoms compared to controls.

An eight-week multicenter double-blinded randomized placebo-controlled parallel-group trial included 88 adult participants (ages 18–65 years) diagnosed with schizophrenia, schizophreniform, schizoaffective or delusional disorders who were evaluated for the use of

CBD as an adjunctive treatment. All participants were randomized to receive 1000 mg CBD daily or placebo along with their previously prescribed antipsychotic regimen. Adjunctive treatment with CBD resulted in a modest but significant decrease in positive symptoms of schizophrenia (hallucinations, delusions, bizarre behavior) and in clinician impressions of illness severity. Overall, CBD was well tolerated, with one participant from the CBD group withdrawing due to adverse gastrointestinal effects (nausea, diarrhea, abdominal pain, and vomiting). A six-week randomized double-blinded placebo-controlled parallel-group fixed-dose study compared 600 mg/day of oral CBD vs. placebo as augmentation therapy in 36 adult patients (ages 18–65 years) with chronic schizophrenia. No improvements were observed in cognition or psychotic symptoms for those treated with CBD. Sedation was reported in 20% of the CBD group (resulting in one participant in the CBD withdrawing from the trial) as compared to 5% of the placebo group. The study concluded that augmentation with CBD does not improve cognition or psychotic symptoms in outpatients with schizophrenia. A four-week parallel-group active-controlled mono-therapeutic double-blind randomized clinical trial enrolled 42 participants (ages 18–50 years) with paranoid schizophrenia who received either up to 800 mg/day of CBD or up to 800 mg/day of amisulpride. Neurocognitive functioning improved in both groups, with no significant difference between treatments. Participants who received CBD treatment had improvements in processing speed, visual memory, visuomotor coordination, and sustained attention.

3.2. Anxiety Symptoms and Disorders [33,34]

CBD induces anxiolytic effects through activation of 5-HT1A receptors [35]. Several studies have evaluated the effects of CBD on anxiety, including blocking anxiety caused by delta-9-tetrahydrocannabinol (Δ^9-THC), in healthy volunteers and patients with anxiety disorders. A retrospective chart review included 72 adult patients (ages 18–72 years) treated with 25–175 mg CBD daily for anxiety or poor sleep. Most patients reported improvements in anxiety symptoms and sleep, with bigger improvements and more sustained response to anxiety symptoms than sleep. In an open-label trial, 31 adolescents and young adults (ages 12–25 years) with an anxiety disorder received CBD titrated up to 800 mg/day. After 12 weeks, overall anxiety was reduced, and improvement was noted in depressive symptoms and overall functioning. There were no serious adverse effects.

3.2.1. Social Anxiety [36–38]

In a double-blind randomized preliminary study, 24 treatment-naïve patients (mean ages 22–24 years) with social anxiety disorder received either 600 mg CBD or placebo 1.5 h prior to a simulation public speaking test. The study concluded that CBD reduced anxiety in patients with social anxiety disorder. A second double-blind study randomized 10 treatment-naïve patients with social anxiety disorder to receive either 400 mg CBD or placebo in a first session, followed by crossover in the second session. Use of CBD was associated with significantly decreased subjective anxiety. Additionally, a double-blind study of 37 young adults (ages 18–19 years) with social anxiety disorder and avoidant personality disorder treated with 300 mg CBD or placebo found that CBD significantly decreased self-reported anxiety using validated measures.

3.2.2. Posttraumatic Stress Disorder (PTSD) [39,40]

Clinical trials are being conducted to analyze CBD for the treatment of PTSD; however, no results are published, and supporting data are limited to case reports. A case report describes a 10-year-old patient with anxiety and insomnia related to a diagnosis of PTSD who used CBD oil, 25 mg per day, later adding sublingual CBD liquid 6–12 mg as needed for anxiety. Using a validated self-report instrument, she was noted to have an increase in sleep quality and a decrease in anxiety without report of side effects. In a retrospective case

series, 10 of 11 adult patients with a diagnosis of PTSD who received CBD in addition to routine psychiatric treatment for 8 weeks reported a decrease in PTSD symptoms using validated measures.

3.3. Autism Spectrum and Intellectual Disability Disorders

There is interest in investigating whether CBD may reduce disruptive behaviors and improve social communication among children with autism spectrum disorders and intellectual disabilities. Several possible mechanisms may underlie these actions, including modulation of the endocannabinoid system [41], activation of 5HT1A receptors [42] and reduced neuroinflammation modulated through TRPV1 receptors [43]. The evidence for use of CBD in children with autism spectrum disorder to treat social, emotional, and cognitive impairments, behavioral dysregulation, anxiety, concentration and Attention-Deficit/Hyperactivity Disorder (ADHD), and sleep problems is anecdotal. Several clinical trials are currently being conducted to evaluate the use of CBD or cannabinoid solutions containing both CBD and Δ^9-THC in children with autism spectrum disorder, and several studies have evaluated the effects of "CBD-rich cannabis" in patients with autism spectrum disorder [44–47].

3.3.1. Behaviors Associated with Autism Spectrum Disorder [48,49]

In an open-label trial of pharmaceutical-grade CBD, parents of children and young adults(ages 4–22 years) with autism spectrum disorder reported improvement in four behaviors (hyperactivity improved in 68%, sleep improved in 71%, anxiety improved in 47%, and self-injury and rage attacks improved in 68%) after treatment, though improvements were not statistically greater than improvement rates for already accepted treatments. A double-blind placebo-controlled study of 150 children and young adults (ages 5–21 years) treated participants for 12 weeks with whole-plant cannabis extract (CBD: Δ^9-THC 20:1), purified extract (CBD: Δ^9-THC 1:1), or placebo. After a washout period, participants crossed over to a predetermined second 12-week treatment. The study concluded that there were no sleep improvements with either whole-plant cannabis extract or purified extract compared to placebo.

3.3.2. Fragile X Syndrome [50–52]

In a randomized controlled trial, 212 patients with Fragile X Syndrome aged 3–17 years received either 12 weeks of CBD (250 mg or 500 mg based on weight) or placebo. Using validated scales, participants with $\geq$90% methylation achieved statistically significant improvements in scaled scores, representing improvements in social avoidance, social interaction, and irritable behaviors. An open-label trial of 20 children and adolescents (ages 6–17 years) with a diagnosis of Fragile X Syndrome evaluated transdermal CBD gel (50–250 mg per day) for 12 weeks. Doses were titrated according to validated anxiety and mood scales. The study concluded that the CBD preparation was well tolerated and associated with significant improvement in anxiety and mood scores over the 12-week trial. CBD was well tolerated with no serious or severe adverse effects. In a case series study, two adults (ages 22 and 26 years) and one child (age 3 years) with diagnoses of Fragile X Syndrome experienced clinical improvement while receiving CBD solutions (32–63.9 mg daily), as reported by parents. Parents of the child reported subjective improvements in anxiety levels, social functioning, feeding behaviors, sleep and motor skills. Parents of the 26-year-old reported improved anxiety and linguistic skills, and the 22-year-old reported decreased anxiety and panic attacks.

3.3.3. Rett Syndrome [53]

A longitudinal observation study of 26 patients (ages 7–32 years) with Rett Syndrome-associated epilepsy included 10 participants treated with CBD, median dose at last follow-up 15 mg/kg/day, for 1–32 months. The study found that 7/10 had reduced seizure incidence, 5/10 had reduced agitation or anxiety, and 4/10 had improvement in spasticity.

3.3.4. Intellectual Developmental Disorder [54]

An eight-week double-blind RCT randomized eight children (ages 11–16 years) to either 98% CBD oil (titrated to 20 mg/kg/day in two divided doses, maximum dose 500 mg twice daily) or placebo. Compared to the placebo group, parents of children receiving CBD endorsed a clinically significant positive change in behavior via validated questionnaire. There were no serious adverse effects.

4. Substance Use Disorder [55]

There are several reports that CBD may have "anti-addictive" action via the regulation of the endocannabinoid, dopaminergic, opioidergic and serotonergic systems which together regulate the reinforcing and motivational properties of psychoactive drugs [56]. Furthermore, antipsychotic, anxiolytic, antidepressant and neuroprotective effects may also benefit patients with substance use disorders. As such, there is significant interest in trials of CBD to treat cannabis, nicotine, opioid and other substance use disorders. In a case report, a 16-year-old with use of cannabis, MDMA, cocaine, and ecstasy, as well as depression, social phobia, and narcissistic personality disorder, received 8 weeks of CBD 100–600 mg/day. The patient participated in a day clinic setting with group therapy, individual psychotherapy, social cognition training, occupational therapy, and physiotherapy. The patient was previously taking sertraline 100 mg daily and discontinued it after 3 weeks of CBD treatment. The patient stopped using substances without withdrawal symptoms, assessed with daily clinical evaluations and weekly drug screenings, and had improvement in their depression and anxiety, evaluated using screening instruments conducted before CBD treatment and after 8 weeks of CBD treatment.

4.1. Cannabis Use Disorder [57–61]

In a double-blind placebo-controlled randomized trial, 82 participants (ages 16–60 years) with cannabis use disorder received either 200 mg CBD, 400 mg CBD, 800 mg CBD, or placebo. Compared to placebo, doses of 400 mg CBD and 800 mg CBD were more effective at reducing cannabis use as measured by self-reported days of abstinence and urine cannabis metabolites. There were no severe adverse effects. Eight participants received 600–1200 mg CBD during a seven-day open-label trial in an inpatient medically supervised withdrawal facility. CBD was well tolerated by all participants and at 28 days, four participants maintained abstinence from cannabis. In a 10-week open-label trial, 20 participants (ages 20–46 years) with cannabis use disorder received 200 mg/day of CBD and reported decreased euphoria when using cannabis, reduction in depressive and psychotic-like symptoms, and improvements in cognition. There were no reports of adverse effects. In a case report, a 19-year-old with cannabis use disorder and multiple previous quit attempts associated with significant withdrawal symptoms was treated with CBD (300–600 mg/day) for 11 days. Self-reported cannabis withdrawal symptoms decreased to zero by day 6, and depression and anxiety symptoms also improved. In another case report, a 27-year-old with bipolar disorder and cannabis use disorder received adjunctive treatment with CBD oil (initially 24 mg daily titrated to 18 mg daily). With the addition of CBD treatment, the patient reported decreased anxiety, improved sleep, and abstinence from cannabis.

4.2. Nicotine Use Disorder [62,63]

In a randomized double-blind placebo-controlled study, 24 participants (ages 18–35 years) with cigarette use >10 per day were instructed to use either inhaled CBD or placebo when they had the urge to smoke for 1 week. Participants in the CBD group reduced the number of cigarettes by 40% as compared to no change in the placebo group. In another randomized double-blind crossover study, 30 adults (ages 18–50 years) with nicotine use received either 800 mg CBD or placebo. The study found that CBD reduced salience to cigarette cues and reduced explicit pleasantness of cigarettes.

4.3. Opioid Use Disorder [64,65]

In a preliminary study, CBD reduced subjective cue-induced craving in abstinent participants with opioid use disorder. In a double-blind randomized placebo-controlled trial, 400 or 800 mg CBD or placebo was given daily for 3 days to 42 adult patients (ages 21–65 years) with diagnoses of heroin use disorder who were currently abstinent and found that CBD reduced salient drug cue-induced craving and anxiety.

5. Discussion

CBD is a molecule with multiple cellular targets and significant pharmaceutical potential beyond its established anti-convulsant effects. There is significant interest in developing CBD-based medications and there are several ongoing trials of CBD for numerous mental health, behavioral health and substance use disorders. Several preclinical/animal trials, case reports and open-label trials are promising for the use of CBD as a medication.

To date, the literature regarding the therapeutic benefits of CBD remains inconclusive except for childhood epilepsy, CBD is generally well tolerated but has been associated with several side effects, including nausea, irritability, and sedation, and can have synergistic effects with other sedating drugs. It is metabolized via the cytochrome p450 system and interacts with many medications, including non-steroidal anti-inflammatory medications that can be purchased over the counter [66,67]. Furthermore, the endogenous cannabinoid system plays an important role in guiding brain development, and the long-term risks of the use of CBD in children are unknown.

CBD is available over the counter, and its use is heavily promoted via social media [68]. However, the American Academy of Child and Adolescent Psychiatry discourages the use of CBD in children and adolescents due to the limited evidence base [69,70] and the potential harms associated with use of unregulated, over-the-counter products. The American Academy of Pediatrics opposes the use of all cannabinoids outside FDA regulation [71].

6. Conclusions

Given the therapeutic promise of cannabidiol, we call for additional randomized controlled trials that enroll children, particularly in the areas for which the theoretical underpinnings are greatest: to treat psychosis, anxiety, disruptive behaviors and substance use disorders. Concurrently, we recommend against the use in children of available but unregulated CBD products because of the limited evidence of efficacy and the unknown potential for harm.

Author Contributions: Conceptualization, J.A.R., W.R. and S.L.; writing—original draft preparation, J.A.R. and W.R.; writing—review and editing, J.A.R., W.R., J.R. and S.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: No new data were created.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

CBD	Cannabidiol
FDA	Food and Drug Administration
RCT	Randomized Controlled Trial
RR	Relative Risk
Δ^9-THC	Delta-9-Tetrahydrocannabinol
PTSD	Posttraumatic Stress Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder
GABA	Gamma-Aminobutyric Acid
5-HT1A	Serotonin 1A receptor
TRPV1	Transient Receptor Potential Vanilloid 1

References

1. Laprairie, R.B.; Bagher, A.M.; Kelly, M.E.M. Denovan-Wright EM. Cannabidiol is a negative allosteric modulator of the cannabinoid CB $_1$ receptor. *Br. J. Pharmacol.* **2015**, *172*, 4790–4805. [PubMed]
2. de Almeida, D.L.; Devi, L.A. Diversity of molecular targets and signaling pathways for CBD. *Pharmacol. Res. Perspect.* **2020**, *8*, e00682. [CrossRef] [PubMed]
3. Dopkins, N.; Miranda, K.; Wilson, K.; Holloman, B.L.; Nagarkatti, P.; Nagarkatti, M. Effects of Orally Administered Cannabidiol on Neuroinflammation and Intestinal Inflammation in the Attenuation of Experimental Autoimmune Encephalomyelitis. *J. Neuroimmune Pharmacol.* **2022**, *17*, 15–32. [CrossRef]
4. Stark, T.; Di Martino, S.; Drago, F.; Wotjak, C.T.; Micale, V. Phytocannabinoids and schizophrenia: Focus on adolescence as a critical window of enhanced vulnerability and opportunity for treatment. *Pharmacol. Res.* **2021**, *174*, 105938. [CrossRef]
5. Di Bartolomeo, M.; Stark, T.; Maurel, O.M.; Iannotti, F.A.; Kuchar, M.; Ruda-Kucerova, J.; Piscitelli, F.; Laudani, S.; Perkarik, V.; Salomone, S.; et al. Crosstalk between the transcriptional regulation of dopamine D2 and cannabinoid CB1 receptors in schizophrenia: Analyses in patients and in perinatal Δ9-tetrahydrocannabinol-exposed rats. *Pharmacol. Res.* **2021**, *164*, 105357.
6. Stark, T.; Di Bartolomeo, M.; Di Marco, R.; Drazanova, E.; Platania, C.B.M.; Iannotti, F.A.; Ruda-Kucerova, J.; D'Addario, C.; Kratka, L.; Perkarik, V.; et al. Altered dopamine D3 receptor gene expression in MAM model of schizophrenia is reversed by peripubertal cannabidiol treatment. *Biochem. Pharmacol.* **2020**, *177*, 114004. [CrossRef] [PubMed]
7. Stark, T.; Ruda-Kucerova, J.; Iannotti, F.A.; D'Addario, C.; Di Marco, R.; Pekarik, V.; Drazanova, E.; Piscitelli, F.; Bari, M.; Babinska, Z.; et al. Peripubertal cannabidiol treatment rescues behavioral and neurochemical abnormalities in the MAM model of schizophrenia. *Neuropharmacology* **2019**, *146*, 212–221. [CrossRef]
8. Manduca, A.; Buzzelli, V.; Rava, A.; Feo, A.; Carbone, E.; Schiavi, S.; Peruzzi, B.; D'Oria, V.; Pezzullo, M.; Pasquadibisceglie, A.; et al. Cannabidiol and positive effects on object recognition memory in an in vivo model of Fragile X Syndrome: Obligatory role of hippocampal GPR55 receptors. *Pharmacol. Res.* **2024**, *203*, 107176. [CrossRef]
9. Rodrigues, R.J.; Marques, J.M.; Köfalvi, A. Cannabis, Endocannabinoids and Brain Development: From Embryogenesis to Adolescence. *Cells* **2024**, *13*, 1875. [CrossRef] [PubMed]
10. Henley, B.S.; Walsh, R.; Greenhill, S.; Woodhall, G. A GABA-A receptor response to CBD following status epilepticus in the medial entorhinal cortex of the rat. *bioRxiv* **2024**. [CrossRef]
11. Sait, L.G.; Sula, A.; Ghovanloo, M.R.; Hollingworth, D.; Ruben, P.C.; Wallace, B. Cannabidiol interactions with voltage-gated sodium channels. *eLife* **2020**, *9*, e58593. [CrossRef] [PubMed]
12. Stockings, E.; Zagic, D.; Campbell, G.; Weier, M.; Hall, W.D.; Nielsen, S.; Herkes, G.K.; Farrell, M.; Degenhardt, L. Evidence for cannabis and cannabinoids for epilepsy: A systematic review of controlled and observational evidence. *J. Neurol. Neurosurg. Psychiatry* **2018**, *89*, 741–753. [CrossRef]
13. de Oliveira, V.G.; de Almeida, N.B.; Radmann, G.C.; de Oliveira Santos, B.F. The efficacy of cannabidiol for seizures reduction in pharmacoresistant epilepsy: A systematic review and meta-analysis. *Acta Epileptol.* **2025**, *7*, 20. [CrossRef] [PubMed]
14. Devinsky, O.; Cross, J.H.; Laux, L.; Marsh, E.; Miller, I.; Nabbout, R.; Scheffer, I.E.; Thiele, E.A.; Wright, S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *N. Engl. J. Med.* **2017**, *376*, 2011–2020. [CrossRef]
15. Akiyama, M.; Kobayashi, K.; Ohtsuka, Y. Dravet syndrome: A genetic epileptic disorder. *Acta Med. Okayama* **2012**, *66*, 369–376. [PubMed]

16. Devinsky, O.; Patel, A.D.; Cross, J.H.; Villanueva, V.; Wirrell, E.C.; Privitera, M.; Greenwood, S.M.; Roberts, C.; Checketts, D.; Vanlandingham, K.E.; et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. *N. Engl. J. Med.* **2018**, *378*, 1888–1897. [CrossRef] [PubMed]
17. Genetic and Rare Diseases Information Center (GARD). National Institutes of Health. Lennox-Gastaut Syndrome. Available online: https://rarediseases.info.nih.gov/diseases/9912/lennox-gastaut-syndrome (accessed on 24 September 2025).
18. Thiele, E.A.; Bebin, E.M.; Bhathal, H.; Jansen, F.E.; Kotulska, K.; Lawson, J.A.; O'Callaghan, F.J.; Wong, M.; Sahebkar, F.; Checketts, D.; et al. Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex. *JAMA Neurol.* **2021**, *78*, 285. [CrossRef] [PubMed]
19. National Institute of Neurological Disorders and Stroke. Tuberous Sclerosis Complex [Internet]. Available online: https://www.ninds.nih.gov/health-information/disorders/tuberous-sclerosis-complex#:~:text=TSC%20is%20caused%20by%20variants%20(or%20mutations),which%20help%20regulate%20cell%20growth%20and%20division (accessed on 7 September 2025).
20. Kaplan, E.H.; Offermann, E.A.; Sievers, J.W.; Comi, A.M. Cannabidiol Treatment for Refractory Seizures in Sturge-Weber Syndrome. *Pediatr. Neurol.* **2017**, *71*, 18–23.e2. [CrossRef]
21. Smegal, L.F.; Vedmurthy, P.; Ryan, M.; Eagen, M.; Andrejow, N.W.; Sweeney, K.; Reidy, T.G.; Yeom, S.; Lin, D.D.; Suskauer, S.J.; et al. Cannabidiol Treatment for Neurological, Cognitive, and Psychiatric Symptoms in Sturge-Weber Syndrome. *Pediatr. Neurol.* **2023**, *139*, 24–34. [CrossRef]
22. Yeom, S.; Comi, A.M. Updates on Sturge-Weber Syndrome. *Stroke* **2022**, *53*, 3769–3779. [CrossRef]
23. Bhattacharyya, S.; Wilson, R.; Appiah-Kusi, E.; O'Neill, A.; Brammer, M.; Perez, J.; Murray, R.; Allen, P.; Bossong, M.G.; McGuire, P. Effect of Cannabidiol on Medial Temporal, Midbrain, and Striatal Dysfunction in People at Clinical High Risk of Psychosis. *JAMA Psychiatry* **2018**, *75*, 1107. [CrossRef]
24. Appiah-Kusi, E.; Petros, N.; Wilson, R.; Colizzi, M.; Bossong, M.G.; Valmaggia, L.; Mondelli, V.; McGuire, P.; Bhattacharyya, S. Effects of short-term cannabidiol treatment on response to social stress in subjects at clinical high risk of developing psychosis. *Psychopharmacology* **2020**, *237*, 1121–1130. [CrossRef] [PubMed]
25. Bhattacharyya, S.; Wilson, R.; Allen, P.; Bossong, M.; Appiah-Kusi, E.; McGuire, P. 17.3 Effect of Cannabidiol on Symptoms, Distress and Neurophysiological Abnormalities in Clinical High-Risk for Psychosis Patients: A Placebo-Controlled Study. *Schizophr Bull* **2018**, *44* (Suppl. 1), S28. [CrossRef]
26. McGuire, P.; Robson, P.; Cubala, W.J.; Vasile, D.; Morrison, P.D.; Barron, R.; Taylor, A.; Wright, S. Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial. *Am. J. Psychiatry* **2018**, *175*, 225–231. [CrossRef]
27. Boggs, D.L.; Surti, T.; Gupta, A.; Gupta, S.; Niciu, M.; Pittman, B.; Schnakenberg Martin, A.M.; Thurnauer, H.; Davies, A.; D'Souza, D.C.; et al. The effects of cannabidiol (CBD) on cognition and symptoms in outpatients with chronic schizophrenia a randomized placebo controlled trial. *Psychopharmacology* **2018**, *235*, 1923–1932. [CrossRef]
28. Leweke, F.M.; Rohleder, C.; Gerth, C.W.; Hellmich, M.; Pukrop, R.; Koethe, D. Cannabidiol and Amisulpride Improve Cognition in Acute Schizophrenia in an Explorative, Double-Blind, Active-Controlled, Randomized Clinical Trial. *Front. Pharmacol.* **2021**, *12*, 614811. [CrossRef]
29. Leweke, F.M.; Piomelli, D.; Pahlisch, F.; Muhl, D.; Gerth, C.W.; Hoyer, C.; Klosterkotter, J.; Hellmich, M.; Koethe, D. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. *Transl. Psychiatry* **2012**, *2*, e94. [CrossRef] [PubMed]
30. Rasmussen, J.Ø.; Jennum, P.; Linnet, K.; Glenthøj, B.Y.; Baandrup, L. Cannabidiol versus risperidone for treatment of recent-onset psychosis with comorbid cannabis use: Study protocol for a randomized controlled clinical trial. *BMC Psychiatry* **2021**, *21*, 404. [CrossRef]
31. Phillips, L.J.; Yung, A.R.; McGorry, P.D. Identification of Young People at Risk of Psychosis: Validation of Personal Assessment and Crisis Evaluation Clinic Intake Criteria. *Aust. N. Z. J. Psychiatry* **2000**, *34* (Suppl. 2), S164–S169. [CrossRef]
32. Yung, A.R.; Pan Yuen, H.; Mcgorry, P.D.; Phillips, L.J.; Kelly, D.; Dell'Olio, M.; Francey, S.M.; Cosgrave, E.M.; Killackey, E.; Stanford, C.; et al. Mapping the Onset of Psychosis: The Comprehensive Assessment of At-Risk Mental States. *Aust. N. Z. J. Psychiatry* **2005**, *39*, 964–971. [CrossRef]
33. Shannon, S.; Lewis, N.; Lee, H.; Hughes, S. Cannabidiol in Anxiety and Sleep: A Large Case Series. *Perm. J.* **2019**, *23*, 18-041. [CrossRef]
34. Berger, M.; Li, E.; Rice, S.; Davey, C.G.; Ratheesh, A.; Adams, S.; Jackson, H.; Hetrick, S.; Parker, A.; Spelman, T.; et al. Cannabidiol for Treatment-Resistant Anxiety Disorders in Young People. *J. Clin. Psychiatry* **2022**, *83*, 21m14130. [CrossRef] [PubMed]
35. Martínez-Aguirre, C.; Carmona-Cruz, F.; Velasco, A.L.; Velasco, F.; Aguado-Carrillo, G.; Cuéllar-Herrera, M.; Rocha, L. Cannabidiol Acts at 5-HT1A Receptors in the Human Brain: Relevance for Treating Temporal Lobe Epilepsy. *Front. Behav. Neurosci.* **2020**, *14*, 611278. [CrossRef] [PubMed]

36. Bergamaschi, M.M.; Queiroz, R.H.C.; Chagas, M.H.N.; de Oliveira, D.C.G.; De Martinis, B.S.; Kapczinski, F.; Quevedo, J.; Roesler, R.; Schroder, N.; Nardi, A.E.; et al. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients. *Neuropsychopharmacology* **2011**, *36*, 1219–1226. [CrossRef] [PubMed]
37. Crippa, J.A.S.; Derenusson, G.N.; Ferrari, T.B.; Wichert-Ana, L.; Duran, F.L.; Martin-Santos, R.; Simoes, M.V.; Bhattacharyya, S.; Fusar-Poli, P.; Atakan, Z.; et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report. *J. Psychopharmacol.* **2011**, *25*, 121–130. [CrossRef]
38. Masataka, N. Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers with Social Anxiety Disorders. *Front. Psychol.* **2019**, *10*, 476036. [CrossRef] [PubMed]
39. Shannon, S.; Opila-Lehman, J. Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report. *Perm. J.* **2016**, *20*, 16-005. [CrossRef]
40. Elms, L.; Shannon, S.; Hughes, S.; Lewis, N. Cannabidiol in the Treatment of Post-Traumatic Stress Disorder: A Case Series. *J. Altern. Complement. Med.* **2019**, *25*, 392–397. [CrossRef] [PubMed]
41. Marini, S.; D'Agostino, L.; Mentana, M.; Ciamarra, C.; Gentile, A. Modulation of Excitatory and Inhibitory Systems in Autism Spectrum Disorder: The Role of Cannabinoids. *Int. J. Clin. Stud. Med. Case Rep.* **2023**, *30*, S296–S297. [CrossRef]
42. Resstel, L.B.M.; Tavares, R.F.; Lisboa, S.F.S.; Joca, S.R.L.; Corrêa, F.M.A.; Guimarães, F.S. 5-HT 1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br. J. Pharmacol.* **2009**, *156*, 181–188. [CrossRef] [PubMed]
43. Anand, U.; Jones, B.; Korchev, Y.; Bloom, S.R.; Pacchetti, B.; Anand, P.; Sodergren, M.H. CBD Effects on TRPV1 Signaling Pathways in Cultured DRG Neurons. *J. Pain. Res.* **2020**, *13*, 2269–2278. [CrossRef] [PubMed]
44. Aran, A.; Cassuto, H.; Lubotzky, A.; Wattad, N.; Hazan, E. Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems—A Retrospective Feasibility Study. *J. Autism Dev. Disord.* **2019**, *49*, 1284–1288. [CrossRef] [PubMed]
45. Bar-Lev Schleider, L.; Mechoulam, R.; Saban, N.; Meiri, G.; Novack, V. Real life Experience of Medical Cannabis Treatment in Autism: Analysis of Safety and Efficacy. *Sci. Rep.* **2019**, *9*, 200. [CrossRef]
46. Fleury-Teixeira, P.; Caixeta, F.V.; Ramires da Silva, L.C.; Brasil-Neto, J.P.; Malcher-Lopes, R. Effects of CBD-Enriched Cannabis sativa Extract on Autism Spectrum Disorder Symptoms: An Observational Study of 18 Participants Undergoing Compassionate Use. *Front. Neurol.* **2019**, *10*, 1145. [CrossRef] [PubMed]
47. Bilge, S.; Ekici, B. CBD-enriched cannabis for autism spectrum disorder: An experience of a single center in Turkey and reviews of the literature. *J. Cannabis Res.* **2021**, *3*, 53. [CrossRef] [PubMed]
48. Barchel, D.; Stolar, O.; De-Haan, T.; Ziv-Baran, T.; Saban, N.; Fuchs, D.O.; Koren, G.; Berkovitch, M. Oral Cannabidiol Use in Children with Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities. *Front. Pharmacol.* **2019**, *9*, 1521. [CrossRef] [PubMed]
49. Schnapp, A.; Harel, M.; Cayam-Rand, D.; Cassuto, H.; Polyansky, L.; Aran, A. A Placebo-Controlled Trial of Cannabinoid Treatment for Disruptive Behavior in Children and Adolescents with Autism Spectrum Disorder: Effects on Sleep Parameters as Measured by the CSHQ. *Biomedicines* **2022**, *10*, 1685. [CrossRef] [PubMed]
50. Berry-Kravis, E.; Hagerman, R.; Budimirovic, D.; Erickson, C.; Heussler, H.; Tartaglia, N.; Cohen, J.; Tassone, F.; Dobbins, T.; Merikle, E.; et al. A randomized, controlled trial of ZYN002 cannabidiol transdermal gel in children and adolescents with fragile X syndrome (CONNECT-FX). *J. Neurodev. Disord.* **2022**, *14*, 56. [CrossRef] [PubMed]
51. Heussler, H.; Cohen, J.; Silove, N.; Tich, N.; Bonn-Miller, M.O.; Du, W.; O'Neil, C.; Sebree, T. A phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal cannabidiol (ZYN002) for the treatment of pediatric fragile X syndrome. *J. Neurodev. Disord.* **2019**, *11*, 16. [CrossRef]
52. Tartaglia, N.; Bonn-Miller, M.; Hagerman, R. Treatment of Fragile X Syndrome with Cannabidiol: A Case Series Study and Brief Review of the Literature. *Cannabis Cannabinoid Res.* **2019**, *4*, 3–9. [CrossRef] [PubMed]
53. Desnous, B.; Beretti, T.; Muller, N.; Neveu, J.; Villeneuve, N.; Lépine, A.; Daquin, G.; Milh, M. Efficacy and tolerance of cannabidiol in the treatment of epilepsy in patients with Rett syndrome. *Epilepsia Open* **2024**, *9*, 397–403.
54. Efron, D.; Freeman, J.L.; Cranswick, N.; Payne, J.M.; Mulraney, M.; Prakash, C.; Lee, K.J.; Taylor, K.; Williams, K. A pilot randomised placebo-controlled trial of cannabidiol to reduce severe behavioural problems in children and adolescents with intellectual disability. *Br. J. Clin. Pharmacol.* **2021**, *87*, 436–446. [CrossRef] [PubMed]
55. Laczkovics, C.; Kothgassner, O.D.; Felnhofer, A.; Klier, C.M. Cannabidiol treatment in an adolescent with multiple substance abuse, social anxiety and depression. *Neuropsychiatrie* **2021**, *35*, 31–34. [CrossRef] [PubMed]
56. Navarrete, F.; García-Gutiérrez, M.S.; Gasparyan, A.; Austrich-Olivares, A.; Manzanares, J. Role of Cannabidiol in the Therapeutic Intervention for Substance Use Disorders. *Front. Pharmacol.* **2021**, *12*, 626010. [CrossRef]
57. Freeman, T.P.; Hindocha, C.; Baio, G.; Shaban, N.D.C.; Thomas, E.M.; Astbury, D.; Freeman, A.M.; Lees, R.; Craft, S.; Morrison, P.D.; et al. Cannabidiol for the treatment of cannabis use disorder: A phase 2a, double-blind, placebo-controlled, randomised, adaptive Bayesian trial. *Lancet Psychiatry* **2020**, *7*, 865–874. [CrossRef]

58. Pokorski, I.; Clement, N.; Phung, N.; Weltman, M.; Fu, S.; Copeland, J. Cannabidiol in the Management of In-Patient Cannabis Withdrawal: Clinical Case Series. *Future Neurol.* **2017**, *12*, 133–140.
59. Solowij, N.; Broyd, S.J.; Beale, C.; Prick, J.A.; Greenwood, L.M.; van Hell, H.; Suo, C.; Galettis, P.; Pai, N.; Fu, S.; et al. Therapeutic Effects of Prolonged Cannabidiol Treatment on Psychological Symptoms and Cognitive Function in Regular Cannabis Users: A Pragmatic Open-Label Clinical Trial. *Cannabis Cannabinoid Res.* **2018**, *3*, 21–34. [CrossRef]
60. Crippa, J.A.S.; Hallak, J.E.C.; Machado-de-Sousa, J.P.; Queiroz, R.H.C.; Bergamaschi, M.; Chagas, M.H.N.; Zuardi, A.W. Cannabidiol for the treatment of cannabis withdrawal syndrome: A case report. *J. Clin. Pharm. Ther.* **2013**, *38*, 162–164. [PubMed]
61. Shannon, S.; Opila-Lehman, J. Cannabidiol Oil for Decreasing Addictive Use of Marijuana: A Case Report. *Integr. Med.* **2015**, *14*, 31–35.
62. Morgan, C.J.A.; Das, R.K.; Joye, A.; Curran, H.V.; Kamboj, S.K. Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings. *Addict. Behav.* **2013**, *38*, 2433–2436. [CrossRef]
63. Hindocha, C.; Freeman, T.P.; Grabski, M.; Stroud, J.B.; Crudgington, H.; Davies, A.C.; Das, R.K.; Lawn, W.; Morgan, C.J.A.; Valerie Curran, H. Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal. *Addiction* **2018**, *113*, 1696–1705. [CrossRef] [PubMed]
64. Hurd, Y.L.; Yoon, M.; Manini, A.F.; Hernandez, S.; Olmedo, R.; Ostman, M.; Justras-Aswad, D. Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage. *Neurotherapeutics* **2015**, *12*, 807–815. [CrossRef]
65. Hurd, Y.L.; Spriggs, S.; Alishayev, J.; Winkel, G.; Gurgov, K.; Kudrich, C.; Oprescu, A.M.; Salsitz, E. Cannabidiol for the Reduction of Cue-Induced Craving and Anxiety in Drug-Abstinent Individuals with Heroin Use Disorder: A Double-Blind Randomized Placebo-Controlled Trial. *Am. J. Psychiatry* **2019**, *176*, 911–922.
66. Brown, J.; Winterstein, A. Potential Adverse Drug Events and Drug–Drug Interactions with Medical and Consumer Cannabidiol (CBD) Use. *J. Clin. Med.* **2019**, *8*, 989. [CrossRef]
67. Balachandran, P.; Elsohly, M.; Hill, K.P. Cannabidiol Interactions with Medications, Illicit Substances, and Alcohol: A Comprehensive Review. *J. Gen. Intern. Med.* **2021**, *36*, 2074–2084. [CrossRef]
68. Khilji, O.; Leiner, M.; Pathak, I. Social Media Information About Cannabidiol (CBD) Products Use Among Children: Are the Messages Presented Suggesting They Are Safe for Children? *Pediatrics* **2021**, *147*, 110–111. [CrossRef]
69. American Academy of Child & Adolescent Psychiatry. Marijuana and Teens. 2023. Available online: https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Marijuana-and-Teens-106.aspx (accessed on 24 September 2025).
70. American Academy of Child & Adolescent Psychiatry. The Use of Medical Marijuana in Children and Adolescents with Autism Spectrum Disorder for Core Autism Symptoms or Co-Occurring Emotional or Behavioral Problems. 2019. Available online: https://www.aacap.org/aacap/Policy_Statements/2019/Use_of_Medical_Marijuana_in_Children_and_Adolescents_with_Autism_Spectrum_Disorder_for_Core_Autism_S.aspx (accessed on 24 September 2025).
71. Committee on Substance Abuse and Committee on Adolescence. The impact of marijuana policies on youth: Clinical, research, and legal update. *Pediatrics* **2015**, *135*, 584–587. Available online: http://pediatrics.aappublications.org/content/early/2015/01/20/peds.2014-4146 (accessed on 4 January 2022).

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.