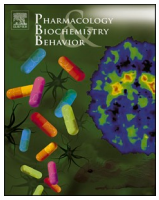
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Review



A systematic review of cannabidiol trials in neurodevelopmental disorders

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ABSTRACT

Cannabis-derived compounds, such as cannabidiol (CBD) and delta-9-trans-tetrahydrocannabinol (THC), are increasingly prescribed for a range of clinical indications. These phyto-cannabinoids have multiple biological targets, including the body's endocannabinoid system. There is growing scientific interest in the use of CBD, a non-intoxicating compound, to ameliorate symptoms associated with neurodevelopmental disorders. However, its suitability as a pharmaceutical intervention has not been reliably established in these clinical populations.

This systematic review examines the nine published randomised controlled trials (RCTs) that have probed the safety and efficacy of CBD in individuals diagnosed with attention deficit hyperactivity disorder, autism spectrum disorder, intellectual disability, Tourette Syndrome, and complex motor disorders. Studies were identified systematically through searching four databases: Medline, CINAHL complete, PsycINFO, and EMBASE.

Inclusion criteria were randomised controlled trials involving CBD and participants with neurodevelopmental disorders. No publication year or language restrictions were applied. Relevant data were extracted from the identified list of eligible articles. After extraction, data were cross-checked between the authors to ensure consistency.

Several trials indicate potential efficacy, although this possibility is currently too inconsistent across RCTs to confidently guide clinical usage. Study characteristics, treatment properties, and outcomes varied greatly across the included trials. The material lack of comparable RCTs leaves CBD's suitability as a pharmacological treatment for neurodevelopmental disorders largely undetermined. A stronger evidence base is urgently required to establish safety and efficacy profiles and guide the ever-expanding clinical uptake of cannabis-derived compounds in neurodevelopmental disorders.

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1. Introduction

Neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), intellectual disability (ID), Tourette's syndrome (TS), and complex motor disorders (CMD), can have a profound negative impact on health and wellbeing. These disorders are phenotypically and pathophysiologically heterogeneous, but also share common phenotypic subdomains. For example, difficulties with attention, social processing, and motor skills are broadly experienced across these disorders. Establishing pharmacological interventions for symptomatology associated with neurodevelopmental disorders is challenging; clear biomarkers are lacking, and outcome measures for clinical trials remain underdeveloped. While the biological substrates of these multifactorial disorders are varied and largely undetermined, the endocannabinoid system (ECS) is increasingly implicated in the pathogenesis of their common symptomology (Zou and Kumar, 2018). Hence, pharmacological interventions that modulate the ECS are attracting increasing attention for their potential to help individuals with neurodevelopmental disorders (Karhson et al., 2016, 2018).

1.1. The endocannabinoid system (ECS)

The ECS is a neuro-modulatory system comprised of functional

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molecules (endocannabinoids) and receptors (including cannabinoid type 1 and type 2 receptors; CB1 and CB2) (Behl et al., 2022). The two most studied endocannabinoids, 2-arachidonoylglycerol (2AG) and anandamide (*N*-arachidonoylethanolamine, AEA), are widespread throughout the body. Involved in emotional regulation and social responsiveness (Zamberletti et al., 2017), the ECS has been strongly implicated in the pathophysiology of ASD (Karhson et al., 2016), ADHD (Centonze et al., 2009; Dawson, 2021), and TS (Müller-Vahl et al., 2020). The ECS has also been hypothesised to function differently in neurodevelopmental disorders, although divergent mechanisms are yet to be substantiated (Ibarra-Lecue et al., 2018; Kerr et al., 2013; Schultz and Siniscalco, 2019; Zamberletti et al., 2017). Hence, pharmacological interventions that modulate the ECS may support associated symptoms (Karhson et al., 2016, 2018).

Cannabinoid modulation to the ECS influences numerous physiological processes, including appetite, anxiety, immune response, pain, movement, and memory (Aran et al., 2019b; Lu and Mackie, 2016; Zou and Kumar, 2018). High concentrations of cannabinoid receptors in the cingulate gyrus and prefrontal cortex suggest that the ECS contributes to language, executive, and social functioning; cognitive domains central to ASD, ADHD, and intellectual disability symptomatology (Karhson et al., 2016; Mackie, 2005). The regulatory role of the ECS impacts skills implicated in ASD symptomatology, including social and emotional reactivity, and in ADHD, including learning and memory processes (Bagherzadeh et al., 2012; Rubino et al., 2015; Schultz and Siniscalco, 2019; Trezza, 2015). Recent findings have also linked lower endocannabinoid 'tone' to behaviors that are characteristically divergent in ASD, such as social deficits (Aran et al., 2019b; Kerr et al., 2013).

Endogenous cannabinoid signaling has been examined in both animals and humans, and this has further elucidated the neurobiological underpinnings of neurodevelopmental disorders (Karhson et al., 2016). AEA is a lipid mediator that exerts a modulatory effect on the brain reward circuitry (Ohno-Shosaku and Kano, 2014). Several animal models of ASD with altered ECS functioning have shown improvement in social behavior following AEA manipulation (Melancia et al., 2018; Servadio et al., 2016; Wei et al., 2016), although further studies in humans are needed to determine whether levels of AEA can reflect endocannabinoid tone and indicate social dysfunction phenotype associated with ASD and related disorders (Karhson et al., 2016, 2018). Higher levels of cerebrospinal fluid endocannabinoids, including 2-AG and AEA, have been measured in individuals with TS compared with neurotypical controls (Müller-Vahl et al., 2020).

1.2. Cannabidiol (CBD): mechanisms of action

Cannabidiol, more commonly referred to as CBD, is a phyto-cannabinoid present in the *Cannabis sativa* (*C. sativa*) plant (VanDolah et al., 2019). Like endocannabinoids, which are endogenous compounds naturally produced in mammalian tissues, phyto-cannabinoids interact with the ECS (Zamberletti et al., 2017). While closely related in chemical structure, CBD exerts different pharmacologic outcomes to delta-9-trans-tetrahydrocannabinol (THC), with the latter known for its intoxicating, psychotropic effects (Stout and Cimino, 2014). Possessing a more diverse pharmacological profile, CBD can antagonize the acute effects of THC (Gunasekera et al., 2020) and induces a calming effect on the central nervous system (Shannon et al., 2019).

CBD has multiple targets and mechanisms of action, most of which are still poorly understood (Ibeas Bih et al., 2015), and interacts with various neural receptors, including CB1, CB2, Gpr55, TrpV1, and 5-HT1A (Zuardi, 2017). Unlike THC, which activates cannabinoid CB1 receptors, CBD can act as an antagonist at CB1 receptors through negative allosteric modulation (Laprairie et al., 2015). This action causes a change in the receptor that is likely to mitigate THC's anxiogenic effects (Blessing et al., 2015). CBD has also been shown to increase serum levels of AEA through inhibition of FAAH (Leweke et al., 2012), which increases the release of oxytocin, a neuropeptide that facilitates social attachment (Karhson et al., 2016; Kwan Cheung et al., 2021).

In humans, CBD has been shown to modulate neurochemical activity through several mechanisms (Gunasekera et al., 2020). The ECS is involved in the modulation of GABAergic and glutamatergic neurotransmission, respectively the human brains primary inhibitory and excitatory neurotransmitters (Zamberletti et al., 2017). CBD modulates brain excitation-inhibition (E/I), and has therefore been extensively researched in relation to its anti-seizure properties (Lazarini-Lopes et al., 2021). More recently CBD has been recognised for its ameliorating effects on pervasive ASD symptomatology, including social deficits (Kaplan et al., 2017). The compound has also been established as having a robust safety profile in neuroatypical subgroups (Chin et al., 2020; Heussler et al., 2019; Larsen and Shahinas, 2020) rendering it a viable treatment option in neurodevelopmental disorders.

1.3. The role of excitatory/inhibitory systems

CBD is understood to regulate glutamate and GABA transmission, thereby influencing the activity of excitatory and inhibitory signaling pathways (Pretzsch et al., 2019a). Increased E/I ratios (i.e., favouring excitation) have been implicated in social processing deficits in ASD specifically, and this imbalance is thought to be driven primarily by dysregulation of the GABAergic system (Canitano and Pallagrosi, 2017; Cochran et al., 2015; Cole et al., 2019; Ford and Crewther, 2014; Gaetz et al., 2014; Gao and Penzes, 2015; Harada et al., 2011; Marsman et al., 2014; Pinkham et al., 2008; Tebartz van Elst et al., 2014). Aberrant E/I, and GABA dysfunction in particular, has also been shown to influence other cognitive processes relevant to ASD and other neurodevelopmental disorders (Canitano and Palumbi, 2021). For example, reduced GABA in the somatosensory cortex has been associated with tactile dysfunction in autistic children (Puts et al., 2017), and GABA dysregulation may be relevant to ASD symptom severity (Brix et al., 2015).

There is increasing evidence supporting the utility of GABA modulation in alleviating core difficulties across neurodevelopmental disorders (Han et al., 2012, 2014; Silverman et al., 2015). However, robust findings are lacking, and many pharmacological interventions for phenotypic subdomains, including social dysfunction, are yet to be approved (Brondino et al., 2016; Selimbeyoglu et al., 2017). The volume of research supporting the importance of reduced GABA transmission in behavioral deficits warrants the commencement of larger clinical trials of GABA-modulating medications (and devices). The potential behavioral and neurophysiological effects of GABA-modulators, such as benzodiazepines (Oblak et al., 2011), CBD (Aran et al., 2019a; Pretzsch et al., 2019b), and cannabidivarin (CBDV) (Pretzsch et al., 2021) require further exploration. In particular, the proposed effects of CBD on E/I balance warrant continued investigation.

1.4. CBD for neurodevelopmental disorders

There are multiple therapeutic methods utilised to target symptom domains associated with neurodevelopmental disorders, including behavioral and pharmaceutical interventions (LeClerc and Easley, 2015), which are individually tailored to address distinct behavioral profiles and specific areas of disability. Personalised intervention plans can sensitively address continuums of severity within each relevant symptom domain, regardless of the primary diagnosis. Pharmacological treatments are often prescribed for symptoms frequently associated with many neurodevelopmental disorders, such as anxiety, depression, rigid behaviors, aggression, and attention deficits (Doyle and McDougle, 2012). These include selective serotonin reuptake inhibitors (SSRIs), psychostimulants, and atypical antipsychotics (Reiersen and Handen, 2011; Sharma and Shaw, 2012). Presently, there are two Food and Drug Administration (FDA) and Therapeutic Goods Administration (TGA)-approved medications used to treat irritability, aggression, and emotion dysregulation associated with ASD; risperidone and aripiprazole

(LeClerc and Easley, 2015; Young, 2020). However, these atypical antipsychotics are often accompanied by unpleasant metabolic and sleep-related side-effects (McCracken et al., 2002; Nurmi et al., 2013; Sharma and Shaw, 2012; Szulc et al., 2005). Methylphenidate, a psychostimulant, is the most prescribed medication for cognitive and behavioral difficulties associated with ADHD and ASD, particularly to improve attention and induce a calming effect (Kolar et al., 2008). However, its benefits are accompanied by significant addictive potential (Chamakalayil et al., 2021) and other adverse effects associated with long-term use, such as elevated risk of psychosis and tics (Krinzinger et al., 2019). For TS, atypical antipsychotics are also commonly prescribed, as well as neuroleptics like haloperidol and pimozide, which are associated with side effects including weight gain and drowsiness (Eddy et al., 2011). Unfortunately, despite the pervasive nature of difficulties often experienced by individuals with neurodevelopmental disorders, there are currently no effective biomedical treatments to alleviate them. This has downstream effects on mental health and wellbeing (Ogundele and Morton, 2022). CBD holds promise as a viable pharmaceutical to treat symptoms associated with neurodevelopmental disorders, such as social and attention deficits, due to its favourable safety profile, exhibiting few adverse side effects (D'onofrio et al., 2020).

There are several postulated mechanisms underlying CBD's effects, including inhibition of endocannabinoid degradation (Leweke et al., 2012), modulation of serotoninergic activity (Russo et al., 2005), and anti-inflammatory properties (Burstein, 2015; Vallée et al., 2021). Reliable literature is beginning to reflect the potential for CBD to ameliorate symptoms associated with somatic symptom disorders, as well as psychiatric and neurodevelopmental conditions (Larsen and Shahinas, 2020), such as ASD, ADHD (Cooper et al., 2017), ID (Efron et al., 2021), TS (Abi-Jaoude et al., 2022), and complex motor disorders (Fairhurst et al., 2020). The current evidence regarding its suitability for neurodevelopmental disorder subgroups predominantly comes from open-label studies, retrospective observational studies and anecdotal accounts (Aran et al., 2019a; Aran et al., 2018; Heussler et al., 2022). Amid this research, reliably designed randomised controlled trials (RCTs) in neurodevelopmental populations are steadily emerging.

The primary objective of this systematic review was to assess current evidence for the efficacy of CBD. Considering the widespread anecdotal reports of CBD's therapeutic promise for neurodevelopmental disorders, it is critical to establish a reliable evidence base. RCTs are considered the ideal methodology for measuring causal relationships between interventions and outcomes (Hariton and Locascio, 2018). They utilise randomisation to reduce the bias inherent with other study designs and balance participant characteristics between groups to allow for outcome variation to be attributed to the target intervention. True RCT assessments of causality tend to require concealment of allocation, intention-to-treat (ITT) analysis and when suitable, blinding (Hariton and Locascio, 2018). Identifying multiple comparable RCTs through comprehensive and explicit search methods is a crucial step in ascertaining the current evidence for the efficacy of CBD in relevant clinical populations. This systematic approach allows for our specific research question to be adequately probed, and provides opportunity for common results, strengths, and limitations of the collated RCTs to be identified.

2. Materials and methods

2.1. Search strategy

Studies were identified systematically through searching four databases: Medline, CINAHL complete, and PsycINFO on July 22nd, 2021, and EMBASE on July 26th, 2021. All searches were updated on October 26th, 2022, with one new article identified. No publication year or language restrictions were applied. All search terms were combined with Boolean operators and limited to title and abstract (please see Appendix A and B for the specific search syntax terms used).

Following the initial search of databases and removal of duplicates, titles, and abstracts were independently screened by three authors (NFP, PB, ISB). Due to the high volume of studies yielded from the initial search for title and abstract screening, the primary researcher (NFP) independently screened 100 % of the articles (n = 3510), and two authors (PB, ISB) independently screened 50 % of the articles each (A-K, n = 1755; L-Z, n = 1755). After title and abstract double screening, 100 % agreement was achieved between authors and twenty-seven articles remained for full-text screening. Following full-text screening, 100 % agreement was achieved between three authors (NFP, PGE, TCF) and a total of eight articles remained for inclusion in the review. Following the secondary search, two additional papers were identified for full-text screening and one met eligibility requirements. See Table 1 for eligibility criteria.

2.2. Data extraction

Relevant data were extracted from the identified final list of eligible articles. After extraction, data were cross-checked between the authors to ensure consistency. All qualitative information (i.e., clinical trial type, investigational product/treatment, administration duration, route of administration, and participant characteristics) was then extracted by the primary researcher (NFP).

3. Results

3.1. Included and excluded studies

The literature search is depicted in the PRISMA flowchart below (see Fig. 1) (Moher et al., 2009). The initial database searches yielded 6674 results and secondary searches yielded 699 results. Following removal of duplicates (n = 3415) and screening of titles and abstracts, twenty-nine articles were selected for full-text screening, two of which were acquired from the secondary searches. Full text screening resulted in a final list of nine eligible articles.

3.2. Study characteristics

Study characteristics are reported in Table 2. Five randomised placebo-controlled parallel trials and four randomised placebo-controlled crossover trials were included. All studies were published within the last five years. The studies were conducted in Canada (n = 1), Israel (n = 2), the United Kingdom (n = 6), and Australia (n = 1). Sample sizes ranged from 8 (Efron et al., 2021) to 150 (Aran et al., 2021) (M = 36.5, SD = 44.2). Three trials included predominantly child participants (Aran et al., 2021; Efron et al., 2021; Fairhurst et al., 2020), while the remaining employed adult cohorts (Abi-Jaoude et al., 2022; Pretzsch

Table 1
Eligibility criteria.

	Inclusion	Exclusion
Trial design	Randomised controlled trials (parallel/crossover assignment with placebo control) Single/double blinding	Review articles Case reports
Participants	Children (<18 years) or adults (>18 years) Diagnoses of any of the following: ADHD, ASD, TS, ID, syndromic disabilities, CMD	Non-human subjects Participants without neurodevelopmental disorder diagnosis
Intervention	Acute or chronic administration of CBD / CBD and THC / CBDV	Administration of THC-only product
Outcomes	Psychometric measures Neurophysiological measures	
Comparison	Placebo control Neurotypical control group	No comparison group
Publication type	Full articles in peer-review journals Written in English	Abstracts, case studies/series Non-English language articles

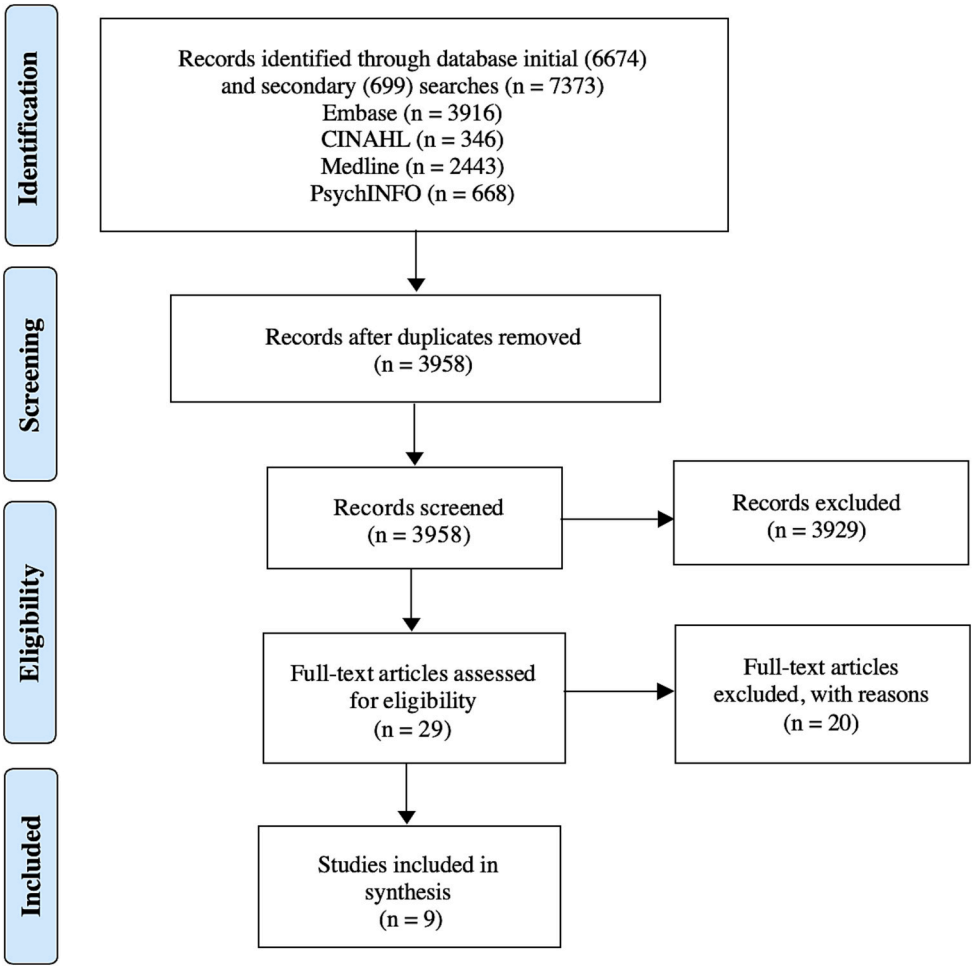


Fig. 1. PRISMA flow diagram of literature search.

et al., 2019a; Pretzsch et al., 2019b; Pretzsch et al., 2019c; Pretzsch et al., 2021). Pretzsch and colleagues included only adults with normal cognitive function (IQ > 70) in their investigation, comprised of four published RCTs (Pretzsch et al., 2021; Pretzsch et al., 2019a; Pretzsch et al., 2019c; Pretzsch et al., 2019b).

Participants taking stable concomitant medications were included in eight of the nine studies (Abi-Jaoude et al., 2022; Aran et al., 2021; Efron et al., 2021; Fairhurst et al., 2020; Pretzsch et al., 2019a; Pretzsch et al., 2019c; Pretzsch et al., 2019b; Pretzsch et al., 2021). Abi-Jaoude et al. (2022) accepted the continuation of a broad range of concomitant medications throughout their trial. Medication types included stimulants, antipsychotics, atypical antidepressants, benzodiazepines, anticholinergics, calcium channel blockers, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, anticonvulsant, corticosteroids, and antacid elixir medications (Abi-Jaoude et al., 2022). Similarly, Aran et al. (2021) did not exclude any medication types from their trial. Efron et al. (2021) excluded children if they had taken anti-epileptic medications which interact with CBD (e.g., clobazam, topiramate, zonisamide), but did not exclude participants taking other concomitant medications. Fairhurst et al. (2020), report that their participants were often taking multiple medications due to their medical complexity, however, excluded those undergoing treatment with botulinum neurotoxin A in the previous 12 weeks or expected need for concomitant use during the trial. All four studies within the Pretszch et al. investigation (Pretzsch et al., 2021; Pretzsch et al., 2019a; Pretzsch et al., 2019c; Pretzsch et al., 2019b) excluded participants who were taking regular medication known to affect glutamate and GABA neurotransmitter systems, such as benzodiazepines, but those taking other medications were included. In contrast to the eight studies just mentioned, Cooper et al. (2017) excluded participants taking long-acting medications and asked participants to stop their stimulant medication for 1 week before their baseline assessments and for the duration of the study.

3.3. *Treatment characteristics*

Treatment characteristics are reported in Table 2. CBD formulation varied across trials. A CBD:THC ratio of 1:1 was administered by Fairhurst et al. (2020) and Cooper et al. (2017), while Aran et al. (2021) administered a 20:1 ratio. Efron et al. reported their active treatment as 98 % CBD (Efron et al., 2021), 100 mg/ml in grapeseed oil, and Abi-Jaoude et al. (2022) administered two CBD treatments: THC/CBD (9 %/9 %), and CBD 13 %. Finally, Pretzsch et al. (2021, 2019a, 2019c, 2019b), administered single doses of 600 mg of CBDV or CBD, with no reported THC content. All nine studies included a control treatment (placebo). There was also variability in the CBD administration method. Oromusocal spray was used in two trials (Cooper et al., 2017; Fairhurst et al., 2020), six trials administered liquid oral doses of CBD/CBDV (Aran et al., 2021; Efron et al., 2021; Pretzsch et al., 2021; Pretzsch et al., 2019a; Pretzsch et al., 2019c; Pretzsch et al., 2019b), while Abi-Jaoude et al. (2022) administered via vaporizers. Treatment duration was also extremely variable, ranging from acute (single session) administration to chronic administration over 12 weeks.

Table 2
Study characteristics.

Authors	Year	Trial location	N of participants	Diagnosis	Age range (years)	Treatment/s	Study Design / Administration	Primary outcome measure
(Abi-Jaoude et al., 2022)	2022	Toronto, Canada	9	Tourette Syndrome	22–54 Mean age 12.3	Vaporized products: - THC 10 % - THC/CBD (9 %/9 %) - CBD 13 % - Placebo (<0.3 % THC, <0.3 % CBD) Vaporiser	Randomised placebo-controlled Crossover Trial Single dose administration: 2-week intervals	Modified Rush Video-Based Tic Rating Scale (MRVTRS)
(Fairhurst et al., 2020)	2020	London, UK Tel Aviv, Israel Prague, Czech Republic	72	Cerebral Palsy or traumatic, non-progressive CNS injury	8–18 Mean age 12.3	Whole-plant cannabis extract 'Nabiximols' (Sativex, THC:CBD, 1:1) Oromucosal Spray	Randomised placebo-controlled Trial 2:1 ratio (Nabiximols: placebo) Chronic administration: 12 weeks	Spasticity Rating on a 0–10 Numerical Rating Scale
(Cooper et al., 2017)	2017	London, UK	30	Attention Deficit Hyperactivity Disorder	18–55 Mean age 36.9	Whole-plant cannabis extract 'Nabiximols' (Sativex, THC:CBD, 1:1) Oromucosal Spray	Randomised placebo-controlled Trial 1:1 ratio Chronic administration:	QbTest of Cognitive Performance
(Efron et al., 2021)	2020	Melbourne, Australia	8	Intellectual Disability	8–16 Mean age 13.5	98 % CBD 100 mg/ml in grapeseed oil Oral	Randomised placebo-controlled Trial 1:1 ratio	Aberrant Behavior Checklist – 2 (ABC-2)
(Aran et al., 2019a)	2021	Jerusalem, Israel	150	Autism Spectrum Disorder	5–21 Mean age 11.8	Whole-plant cannabis extract (CBD:THC, 20:1 ratio) Pure CBD and pure THC (20:1)	Randomised placebo-controlled Trial Chronic administration: 12-week treatment, 4 week washout, 12 week treatment	Home Situation Questionnaire – Autism Spectrum Disorder (HSQ-ASD)
(Pretzsch et al., 2021)	2021	London, UK	13	Autism Spectrum Disorder	20–50 Mean age 30.6	600 mg Cannabidivarin (CBDV)	Randomised placebo-controlled Trial (pseudo-randomised allocation)	Striatal Functional Connectivity
(Pretzsch et al., 2019c)	2019	London, UK	17	Autism Spectrum Disorder	20–50 Mean age 31.2	600 mg Cannabidivarin (CBDV)	Randomised placebo-controlled Trial (pseudo-randomised allocation)	Magnetic resonance spectroscopy (MRS) measures of glutamate and GABA levels
(Pretzsch et al., 2019a)	2019	London, UK	17	Autism Spectrum Disorder	20–50 Mean age 31.2	600 mg Cannabidiol (CBD)	Randomised placebo-controlled Trial (pseudo-randomised allocation)	Magnetic resonance spectroscopy (MRS) measures of glutamate and GABA levels in the DLPFC
(Pretzsch et al., 2019b)	2019	London, UK	13	Autism Spectrum Disorder	20–50 Mean age 30.8	600 mg Cannabidiol (CBD)	Randomised placebo-controlled Trial (pseudo-randomised allocation)	Fractional amplitude of low-frequency fluctuations (fALFF)

3.4. Efficacy and safety outcomes

3.4.1. CBD; effects in tics associated with Tourette Syndrome

A recent crossover RCT examined the efficacy of single doses of three vaporized medical cannabis products and placebo for tics in twelve adults with TS (Abi-Jaoude et al., 2022). Nine participants completed the trial. Participants received single doses (0.25 g) of three distinct medicinal cannabis products: THC 10 %, CBD 9 %/9 %, CBD 13 %, and placebo, administered at 2-week intervals. The primary outcome was the Modified Rush Video-Based Tic Rating Scale (MRVTRS), taken at baseline and at 0.5, 1, 2, 3, and 5 h following product administration. Secondary measures included the Premonitory Urge for Tics Scale (PUTS), Subjective Units of Distress Scale (SUDS), and Clinical Global Impression–Improvement (CGI—I). No product resulted in a statistically significant effect on the MRVTRS. Compared with placebo, significant effects of THC 10 %, and to a lesser extent THC/CBD 9 %9 % where identified on the PUTS, SUDS, and CGI—I. Significant correlations were also recognised between the MRVTRS, PUTS, and SUDS measures and plasma levels of THC and its metabolites.

To address treatment safety and tolerability, participants answered questions regarding adverse events (AEs). The THC 10 % product resulted in the most AEs, and more AEs were reported following all cannabis products relative to placebo, and more AEs following THC 10 % relative to other products. Reported AEs following THC 10 % product administration included: sedation, psychomotor effects, dizziness, cough, throat burning, dry mouth, feeling cold, and feeling high. All three cannabis products resulted in reports of throat burning and dry mouth while sedation, psychomotor effects, and dizziness were more common in the THC 10 % product. A 5 s syncopal episode and seizure following THC/CBD 9 %/9 % product administration was experienced by one participant who subsequently made full recovery.

3.4.2. CBD; effects in spasticity associated with neurodevelopmental conditions

Fairhurst et al. (2020) conducted an RCT to explore the efficacy, safety, and tolerability of a specific cannabis extract (Nabiximols: THC: CBD ratio of 1:1) in seventy-two children presenting with spasticity secondary to cerebral palsy or traumatic central nervous system injury (Fairhurst et al., 2020). Enrolled children had reported inadequate efficacy or (unspecified) unacceptable side effects to their existing treatment regime. The researchers acquired subjective (self-reported and caregiver-reported) and objective (observer-rated) primary outcomes, using a 0 to 10 Numerical Rating Scale probing change from baseline in level of spasticity. Secondary endpoint outcomes enquired regarding changes in sleep quality, pain, health-related quality of life, comfort, depression, and safety (Fairhurst et al., 2020). After the 12-week treatment duration, no significant difference in the spasticity NRS between Nabiximols and placebo groups were reported, and likewise for secondary outcomes.

Safety was monitored by AE reporting throughout the trial. Reported serious adverse events (SAEs) were lower in the Nabiximols group than the placebo group, with four Nabiximols group participants experiencing SAEs. These included changes in two seizure profiles, food aversion and retching, and a viral upper respiratory tract infection. Two participants experienced AEs in the Nabiximols arm; retching for one participant and oropharyngeal pain, stomatitis, and lower respiratory tract infection for another. One participant, with no history of psychiatric disorder, experienced a mild and non-serious hallucination after 6 weeks of Nabiximols. 51 % of the group had an antecedent history of epilepsy. While this indication was not formally measured during the trial, rates of frequency and duration of seizure events reduced or disappeared altogether for several patients in the Nabiximols arm.

3.4.3. CBD; behavioral effects in attention-deficit hyperactivity disorder

Cooper et al. (2017) conducted a pilot RCT to explore behavioral effects of cannabinoids in ADHD. This trial of thirty participants using Sativex (THC:CBD, 1:1) reported no statistically significant reduction of ADHD symptoms. Cognitive performance and activity level (head movements) measured using the Quantitative Behavioral Test (QbTest (Iberstadt, 2012)) served as the primary outcome measure, while ADHD and emotional lability (EL) symptoms were monitored with secondary measures. Participants underwent random assignment to either the active treatment or the placebo group. Although the active group attained observably better scores than the placebo group, there was no significant difference in QbTest scores between groups. Sativex was associated with improvement in hyperactivity/impulsivity ($p = 0.03$) and response inhibition (computerised go/no-go task; $p = 0.05$), and a tendency towards improvement for inattention ($p = 0.10$) and EL ($p = 0.11$). However, no outcomes reached significance following adjustment for multiple comparisons. It is therefore yet to be elucidated whether, in a controlled manner, other combinations of cannabinoids, including CBD, are effective for alleviating ADHD-associated symptoms.

Safety monitoring took place at days 4, 8, 12, 14 and 28, whereby participants completed a standard side-effect rating scale and were given an opportunity to share any AEs they were experiencing. In the Sativex group, there was one SAE (muscular seizures/spasms) and three reports of mild AEs (light headedness and diarrhea). A SAE (a cardiovascular problem) also occurred for one participant in the placebo group.

3.4.4. CBD; behavioral effects in ASD

Aran et al. (2021) conducted a placebo-controlled, double-blind, cross-over design with two types of cannabinoid extracts in one hundred and fifty children and young adults with ASD (Aran et al., 2021). Fifty participants received a whole-plant cannabis extract of CBD + THC (BOL-DP-O-01-W), and fifty received purified CBD + THC (BOL-DP-O-01); both extracts with the same 20:1 ratio of CBD to THC. The remaining fifty participants received a placebo. Compounds were administered daily during two treatment periods of 12 weeks, separated by a 4-week washout period.

Outcome measures included the Home Situation Questionnaire-ASD, the Clinical Global Impression-Improvement scale (CGI—I), the Social Responsiveness Scale (SRS-2), and Autism Parenting Stress Index. No effects were observed following the purified treatment, while disruptive behaviors, indicated by the CGI-I scale, were significantly reduced in participants who received the whole-plant extract CBD compared with placebo ($p = 0.005$). SRS-2 scores indicated significant improvement in the core ASD symptom domain of social functioning following whole-plant extract CBD treatment compared with placebo ($p = 0.009$). This investigation contained a sample group with a broad range of cognitive abilities, however, resulting in inapplicable questionnaire items for some participants (Aran et al., 2021).

Caregivers completed a structured questionnaire regarding AEs every 4 weeks. They rated new AEs as mild, moderate, or severe. There were no treatment-related severe AEs or SAEs. Reported AEs that were more common during cannabinoid treatment included somnolence, decreased appetite, weight loss, tiredness, euphoria, and anxiety. Mild AEs were not significantly more frequent during cannabinoid treatment relative to placebo, while moderate AEs were reported for forty-four whole-plant extract participants, forty-five pure cannabinoids participants, and for twenty-sex placebo participants.

Efron et al. (2021) conducted a randomised, double-blind, placebo-controlled, two-armed, parallel-design trial of CBD in children with intellectual disability (ID) alongside severe behavioral problems (SBP) (Efron et al., 2021). Participants were randomised to receive either 98 % CBD in oil (Tilray, Canada) or a placebo oil orally for 8 weeks. The dose was up-titrated over 9 days to 20 mg/kg/day in 2 divided doses per day. A total of eight children participated, with four receiving active treatment, all of whom had received a diagnosis of ASD. Results from three participants in the CBD group were obtained. Inferential statistics indicated a significant reduction in the primary outcome measure, the Aberrant Behavior Checklist – Irritability subscale (ABC-I) score, at the end of treatment compared to baseline (mean reduction of 12 points).

Safety outcomes were collected pre-treatment and at day 66 from parents using the Monitoring of Side Effects Scale (MOSES). There were no reported SAEs during or following the trial. For the CBD group, there was one report of each of the following treatment emergent symptoms: rolled up eyes, tics/grimace, ear ringing, drooling/pooling, abdominal pain, decreased appetite, increased appetite, constipation, decreased weight, increased weight, restlessness/pacing/can't sit still, jitter/jumpiness/nervousness, acne, urination, incontinence/nocturnal enuresis, crying/feelings of sadness, drowsiness/lethargy/sedation, excessive sleep, and insomnia. For the placebo group, there were three reports of increased weight and one report of each of the following: increased appetite, headache, and nose congestion/running nose.

3.4.5. CBD; neurophysiological effects in the autistic brain

CBD is postulated to influence E/I signaling pathways by regulating glutamate and GABA transmission (Pretzsch et al., 2019a). This action has potential implications for aberrant E/I circuits in neurodevelopmental conditions like ASD. As part of a large investigation into the role of phyto-cannabinoids in ASD, Pretzsch et al. (2021, 2019a, 2019c, 2019b) provided four separate reports of the acute effects of CBD and CBDV (a homolog of CBD) in adult males with and without ASD using fMRI and Proton Magnetic Resonance Spectroscopy (^{1}H-MRS). Two studies investigated the acute effects of 600 mg CBD (Pretzsch et al., 2019a; Pretzsch et al., 2019b) and the other two of 600 mg CBDV (Pretzsch et al., 2021; Pretzsch et al., 2019c) in thirty-four males, seventeen of which had ASD.

Pretzsch et al. (2019b) first published the RCT that used fMRI to investigate how the acute administration of a 600 mg dose of pure CBD influences fractional amplitude of low-frequency fluctuations (fALFF) in participants with and without ASD (Pretzsch et al., 2019b). Reflecting a different aspect of the BOLD signal, fALFF is a method used to quantify

brain activity differences across regions during resting state (Zou et al., 2008). In the ASD group, CBD significantly increased regional fALFF and FC within and between the cerebellar vermis and the right fusiform gyrus, which are regions implicated in ASD pathophysiology (Pretzsch et al., 2019b).

Using ^{1}H-MRS, Pretzsch and colleagues conducted two RCTs investigating Glx and GABA concentrations in the basal ganglia (BG) and dorsomedial pre-frontal cortex (DMPFC), one following acute administration of 600 mg CBD (Pretzsch et al., 2019a) and the other 600 mg CBDV (Pretzsch et al., 2019c). They observed the impacts of the two phyto-cannabinoids on Glx (a composite of glutamate + glutamine) and GABA concentrations in the basal ganglia (BG) and dorsomedial pre-frontal cortex (DMPFC). These regions have been associated with ASD symptoms and are thought to be strongly modulated by CBD due to the presence of 5-HT1A and GPR55 receptors, which are activated by CBD (Bilge and Ekici, 2021; Castillo et al., 2012). Findings demonstrated that the acute dose of CBD significantly increased levels of Glx in the BG, and decreased Glx in the DMPFC for both groups. Following CBD, GABA levels were increased in the neurotypical group, but decreased GABA levels in the ASD group, with this effect being most pronounced in the DMPFC (Pretzsch et al., 2019a). In contrast, the CBDV trial revealed significantly increased levels of Glx in the BG but not in the DMPFC for both participant groups. The shift in Glx levels in the BG was negatively correlated with baseline Glx concentrations for the ASD group, however this effect was not observed in the neurotypical group. CBDV did not impact GABA levels in either region in either group (Pretzsch et al., 2019c).

The second CBDV study utilised fMRI to measure change in striatal functional connectivity (FC) following CBDV administration (Pretzsch et al., 2021). At baseline, the right inferior ventral striatum and the left putamen were hyperconnected in ASD participants compared with neurotypical controls. The single dose of CBDV significantly reduced strong striatal FC for the ASD group but had no significant effects for the control group. FC between the right ventral rostral striatum and the right posterior superior temporal gyrus was also increased in ASD participants at baseline and was significantly reduced following CBDV administration. CBDV also increased FC between these regions for the neurotypical group.

Safety aspects within each of the above studies were monitored via the same method: three brief health checks at time of dosage administration, following dosage, and following the scans. Across the studies, no participants experienced any subjective or objective ill-effects/harm following administration of the study drugs.

4. Discussion

The purpose of this systematic review was to summarise and evaluate the published RCTs that administered CBD to participants with neurodevelopmental disorders. We examined the characteristics and outcomes of nine published RCTs. Despite implementing strict inclusion criteria, this small selection of literature was found to be highly varied in terms of both participant characteristics and study design. Across all included RCTs, ages ranged widely (children to adult participants) and cognitive profiles were widespread, with one study focusing specifically on participants with ID (Efron et al., 2021). Further, four studies did not exclude participants taking concomitant medications known to interact with GABAergic systems (Abi-Jaoude et al., 2022; Aran et al., 2021; Efron et al., 2021; Fairhurst et al., 2020). Treatment characteristics (i.e., dose, administration route/method, and phyto-cannabinoid ratios) were highly variable across the included trials.

The material disparity in treatment characteristics across the included RCTs is problematic. It is well-recognised that the pharmacology of both THC and CBD is multifarious - both phyto-cannabinoids exert effects via multiple pathways (Almeida and Devi, 2020; Samarut et al., 2019). The inclusion of studies that have used a combination of THC and CBD impedes the designation of outcomes to CBD-related effects alone, as identified effects in these studies could instead be driven by THC or a combination of both compounds. Furthermore, THC and CBD have been postulated to have synergistic (Samarut et al., 2019) and antagonistic effects on one another (Ishak et al., 2018).

Dosage regimens also varied considerably across trials. While individually allocated (i.e., weight-based) CBD dosage is accepted, it poses challenges in reaching comparable clinical outcomes across participants and population groups. The anxiolytic effects of CBD can draw a bell-shaped dose-response curve, suggesting that dosage, as well as administration method/route are a complex yet critical factors for clinical trials involving this compound (Blessing et al., 2015; Linares et al., 2019). The selected primary and secondary outcome measures were also inconsistent across the nine trials, as were reporting standards, with some reporting subscale outcomes as opposed to total scores (Efron et al., 2021). This inconsistency prevents comparison of identical outcome measures across trials.

Broad age ranges (Abi-Jaoude et al., 2022; Cooper et al., 2017; Pretzsch et al., 2021; Pretzsch et al., 2019a; Pretzsch et al., 2019c; Pretzsch et al., 2019b) and functional levels within participant groups was also evident in the majority of evaluated trials. Examining chronic CBD administration in ASD children without concomitant ID may assist in isolating subgroups that share responses to the treatment. Further, five of the included studies did not involve neurotypical control groups. Neurotypical population comparisons may valuably highlight divergences in etiopathology between diagnostic categories. Only one published RCT has responded to recent clinical interest in CBD for pain and spasticity reduction in patients with demyelinating diseases, such as multiple sclerosis. Given the limited extant research, uncertainty regarding the efficacy of CBD in alleviating dystonia or spasticity in CMDs remains.

The multipart investigation by Pretzsch and colleagues has contributed important preliminary data regarding the effects of acute administration of CBD and CBDV on levels of GABA and Glx. This research identified differences in CBD responsivity between individuals with and without ASD. Their outcomes suggest that CBD may exert differential neurobiological effects in ASD compared to neurotypical individuals (Pretzsch et al., 2019b). Given reduced GABA concentrations have been identified in several cortical areas of the ASD brain (Gaetz et al., 2014; Harada et al., 2011; Puts et al., 2017; Rojas et al., 2014), this finding prompts the need for further inquiry into CBD's effects in ASD. However, these studies did not explore extended CBD administration on brain function or behavior, and therefore, it is unknown whether acute brain changes predict longer-term neurophysiological responses. Further, the investigation employed very small sample sizes. Such underpowered investigations are unlikely to adequately account for the high degree of heterogeneity known to be present in ASD (Masi et al., 2017). Other investigations probing long-term effects of CBD in ASD have not incorporated functional neuroimaging techniques to comprehensively examine brain-behavior relationships (Aran et al., 2021; Bar-Lev Schleider et al., 2019). Future work combining imaging and/or neuroanalytic methods with clinical and behavioral measures is likely to be critical for gaining a deeper understanding of the effects of CBD in neurodevelopmental disorders.

This review has highlighted that the benefit of whole-plant extracts compared to isolates of cannabis remains uncertain. Aran et al. (2021) explored two phyto-cannabinoids, a whole-plant cannabis extract with a 20:1 CBD:THC ratio and a purified treatment with the same CBD:THC ratio, but lacking the additional terpenes, flavonoids, and minor cannabinoids. Terpenes have been postulated to contribute to the overall effect of cannabinoids (Ferber et al., 2020). Aran et al. (2021) acknowledged that while whole-plant cannabis extracts, but not pure cannabinoids, were able to decrease ASD-related disruptive behaviors (CGI-I) and autism symptom severity (SRS-2), relative to placebo, their findings were not sufficient to affirm an optimal 'entourage' effect across cannabis strains with the same CBD:THC ratio.

4.1. Observational studies

Observational and retrospective reports have also attempted to elucidate the efficacy and safety profile of CBD in neurodevelopmental disorders. They may serve to inform more reliable research methods like RCT assessments. Not meeting inclusion criteria for this review, Libzon et al. (2018) conducted a pilot study in children with complex motor disorders. They administered an CBD-enriched 5 % oil formulation (CBD:THC of 6:1 and 20:1), measuring severity of dystonia and spasticity, motor function ability, and quality of life. All participants demonstrated mood and appetite improvement, and participants receiving their 20:1 product demonstrated improved constipation, whereas subjects treated with their THC:CBD (6:1) product demonstrated sleep improvement (Libzon et al., 2018).

Anecdotal reports suggest that individuals with ADHD experience fewer cognitive impairments following cannabis use than other subgroups, alongside symptom reduction (Cooper et al., 2017; D'Souza et al., 2008; Harty et al., 2015). These reports are unsubstantiated and complex due to the likely variability in cannabinoid ratios (including THC and CBD) by self-reporting participants (Harty et al., 2015). While findings from the pilot RCT conducted by Cooper et al. (2017) support the potential benefits of cannabis self-medication in ADHD (Stueber and Cuttler, 2022), their findings highlight the pressing demand for further CBD and ECS research for this population. In contrast to the results from the RCT by Cooper et al. (2017), Strohbeck-Kuehner et al. (2008) provide an uncontrolled collection of clinical reports from 30 treatment-resistant ADHD patients reporting that medicinal cannabis is an effective and well-tolerated treatment (Strohbeck-Kuehner et al., 2008).

Heussler et al. (2022) conducted a notable open-label assessment of transdermal CBD gel (ZYN002) in 20 children and adolescents with a diagnosis of Fragile X Syndrome. The gel was administered twice daily and titrated from 50 mg to 250 mg across the 12-week duration of the trial. The Anxiety, Depression, and Mood Scale (ADAMS) served as the primary outcome measure and was administered at initial screening and again at week 12. The Aberrant Behavior Checklist - Community for FXS (ABC-C FXS), Pediatric Anxiety Rating Scale (PARS-R), Pediatric Quality of Life Inventory (PedsQLTM), three Visual Analogue Scales (VAS), and the Clinical Global Impression Scale - Severity (CGI—S) and Improvement (CGI—I) served as secondary outcomes. At week 12, a statistically significant reduction was recorded in all ADAMS subscales except depressed mood, all ABC-C FXS subscale scores, PARS-R total severity score, and PedsQL total score (Heussler et al., 2022).

4.2. Current randomised controlled trials

Thirteen RCTs involving chronic administration of CBD in participants with diagnosed neurodevelopmental disorders are currently underway (ANZCTR.org.au, ClinicalTrials.gov). They are summarised in Table 3. While study designs do differ, with treatment durations ranging from 6 to 34 weeks, uniformity is becoming more apparent, with the implementation of similar psychometric measures, particularly observed within TS and ASD studies.

4.3. Considerations for future trials

At present, this literature review indicates that we clearly lack a rigorous evidence base to support the clinical use of CBD in neurodevelopmental disorders. Research into CBD for neurodevelopmental disorders will benefit from large multi-site clinical RCTs with analogous experimental design, methodology, and treatment characteristics. Establishing targeted pharmaceutical interventions for specific domains of functioning and disorders is challenging, however, as symptomatology arises from varied etiological pathways. Heterogeneity across symptom profiles also complicates the process of establishing reliable biological markers that directly reflect behavioral improvements, and unanimous outcome measures used across clinical trials are yet to be established (Brugha et al., 2015). Future trials should endeavour to standardise aspects related to the treatment drug. For instance, establishing consistent administration duration (i.e., acute or chronic), dosage regimens, route of administration (e.g., oral capsule, oil, vapour inhalation), and trial duration will be important. Further to this, consensus regarding CBD:THC ratio, and whether to administer whole-plant extract or an isolate will also assist in reducing the tremendous variability across trials.

Long-term effects of prolonged medical cannabinoid usage on the developing brain remains uncertain. Exposure to THC during adolescence can detrimentally impact neural connectivity and functions related to alertness, self-awareness, learning, memory, and executive function (Śmiarowska et al., 2022; Volkow et al., 2014). Daily THC use has been linked to an increased risk of psychotic disorders (Di Forti et al., 2019; Marconi et al., 2016) and nonpsychotic bipolar disorder (Jefsen et al., 2023). However, attributing risk of these disorders to cannabis use is challenging as establishing direct causality in such studies is not possible (Volkow et al., 2014). CBD is generally well-tolerated and does not engender the same risk profile as THC (Devinsky et al., 2016; Iffland and Grotenhermen, 2017). Adverse effects associated with CBD including sleepiness, fatigue, diarrhea, and liver harm are uncommon (Bergamaschi et al., 2011a). Considering their divergent safety profiles, it is necessary to differentiate between CBD and THC when studying their potential long-term effects including psychosis risk.

Neurobiological theories that explain phenotypic subdomains associated with neurodevelopmental disorders are receiving increasing attention, such as the E/I hypothesis (Sohal and Rubenstein, 2019) and ECS dysregulation (Aran et al., 2019b; Schultz and Siniscalco, 2019). The E/I imbalance theory of ASD suggests hyper-glutamatergic or hypo-GABAergic signaling occurs across brain regions and networks that are involved in language, social interaction, and multisensory perception (Harada et al., 2011; Rubenstein, 2010). Thus, a symptom-specific approach may be of particular benefit to neurodevelopmental disorder subgroups. Given the shared prevalence of certain phenotypic profiles across neurodevelopmental disorders, it may allow related findings (i.e., comparable symptom-specific measures) to be linked across diagnostic categories. This approach may be more sensitive in informing targeted treatment options for specific behavioral challenges, rather than for general diagnostic constructs.

A symptom-specific approach can also be employed to probe neurobiological effects following CBD treatment. Phenotypic subdomains like social processing difficulties, common to both ASD and ADHD profiles, have been hypothesised to arise from similar neural circuitry irrespective of diagnosis (Di Martino et al., 2013; Gellner et al., 2021). Associations between altered E/I circuitry in the posterior superior temporal sulcus (pSTS), temporoparietal junction (TPJ), amygdala, and prefrontal cortex (PFC) (Cochran et al., 2015; Ford et al., 2017; Tebartz van Elst et al., 2014) and social difficulties (Ford et al., 2017; Guo et al., 2019) suggest that CBD may alter GABAergic signaling in these brain regions, while also ameliorating social difficulties (Bergamaschi et al., 2011b; Kaplan et al., 2017). Employing concurrent measures of brain function and behavior may improve the current understanding of neurobiological mechanisms underlying key symptoms associated with neurodevelopmental disorders.

While lacking in scientific control and reproducibility compared with RCTs, naturalistic observational studies may also be a suitable avenue for exploring CBD in neurodevelopmental disorders. Their flexibility and external validity may be of particular value when exploring under-researched pharmaceuticals that are increasingly prescribed. Consistent selection of standardised psychometric measures, alongside similar reporting styles, will also greatly support broad evaluation of CBD efficacy. There is also scope for research involving chronic CBD administration to clarify whether neurophysiological, neuroimaging, or neuroanalytic methods can detect neurochemical responses to longer-term intervention (Sagar et al., 2021). Finally, long-term tolerability of CBD in children lacks sufficient inquiry (Aran et al., 2021).

Table 3
Current trials.

Trial ID	Recruitment status	Trial location	Enrollment / estimated enrollment	Clinical indication	Age range (years)	Treatment/s	Treatment duration	Study phase and design	Primary outcome
NCT05219370	Recruiting	Be'er Ya'aqov, Israel	244	Attention-deficit hyperactivity disorder	>18	- CBD rich oil - CBG rich oil - CBD and CBG rich oil	1 month	Phase 2, randomised, parallel assignment	Test of Variables of Attention (TOVA)
NCT03087201	Completed	- Aachen, Germany - Cologne, Germany - Freiburg, Germany - Hannover, Germany - Luebeck, Germany - Munich, Germany	98	Tourette Syndrome	>18	Sativex, THC: CBD, 1:1 ('Nabiximols')	13 weeks	Phase 3, randomised, parallel assignment	Yale Global Tic Severity Scale (YGTSS)
ACTRN12618000545268	Completed	Queensland, Australia	22	Tourette Syndrome	18–70	Oral THC: CBD, 1:1	6 weeks	Phase 2, randomised, crossover assignment	YGTSS
NCT05184478	Recruiting	Victoria, Australia	10	Tourette Syndrome	12–18	Oral THC:CBD 10:15	10 weeks	Phase 1/2, randomised, crossover assignment	- Study medication tolerance - Parental questionnaires - Self-report questionnaires
NCT05212493	Active, not recruiting	Zerifin, Israel	128	Autism Spectrum Disorder	5–25	- Seach CBD: THC 10:1 oil - Candoc CBD:THC 20:1 oil	6 months	Phase 3, randomised, parallel assignment	- Metabolite blood levels - Conners Questionnaire
NCT04520685	Recruiting	Colorado, United States	70	Autism Spectrum Disorder	5–17	Oral CBD (100 mg/ml)	27 weeks	Phase 2, randomised, crossover assignment	Aberrant Behavior Checklist – 2nd Edition (ABC-2)
NCT05015439	Not yet recruiting	Maryland, United States	40	Autism Spectrum Disorder	>18	Oral CBD	14 weeks	Phase 1, randomised, parallel assignment	ABC-2
NCT04745026	Recruiting	- London, United Kingdom - Glasgow, United Kingdom - Sabadell, Spain - Barcelona, Spain - Ontario, Canada - Ontario, Canada - Brisbane, Australia - Washington, United States - Texas, United States - Ohio, United States - New York, United States - Massachusetts, United States - Florida, United States - California, United States - Arizona, United States	160	Autism Spectrum Disorder	6–17	CBD oil (Epidiolex)	12 weeks	Phase 2, randomised, parallel assignment	- ABC-2 - Vineland Adaptive Behavior Scales-3 (VABS-3) Scores - Clinical Global Impression Improvement (CGI—I) Scores - Clinical Global Impression Severity (CGI—S) Scores

(*continued on next page*)

Table 3 (*continued*)

Trial ID	Recruitment status	Trial location	Enrollment / estimated enrollment	Clinical indication	Age range (years)	Treatment/s	Treatment duration	Study phase and design	Primary outcome
ACTRN12622000437763	Recruiting	Victoria, Australia	34	Autism Spectrum Disorder	5–12	Oral CBD:THC 20:1 (Medigrowth CBD100)	12 weeks	Phase 2, randomised, crossover assignment	Social Responsiveness Scale – 2
NCT04821856	Recruiting	- Victoria, Australia - New South Wales, Australia	140	Intellectual Disability and Severe Behavioral Problems	6–18	Oral CBD	10 weeks	Phase 2, randomised, parallel assignment	ABC-2
NCT04977986	Recruiting	- California, United States - Florida, United States - Georgia, United States - Illinois, United States - Maryland, United States - Massachusetts, United States - Minnesota, United States - Mississippi, United States - New Jersey, United States - New York, United States - North Carolina, United States - Ohio, United States - Oklahoma, United States - Pennsylvania, United States - South Carolina, United States - Texas, United States - Utah, United States - Washington, United States - New South Wales, Straliaia - Queensland, Australia - Victoria, Australia - Dublin, Ireland - Leicester, United Kingdom - London, United Kingdom - Manchester, United Kingdom	204	Fragile X Syndrome	3–17	Transdermal CBD gel (ZYN002)	18 weeks	Phase 3, randomised, parallel assignment	Aberrant Behavior Checklist-Community Fragile X Factor Structure (ABC-C FXS)
NCT03614663	Completed	- Arizona, United States - California, United States - Colorado, United States - Georgia, United States - Illinois, United States - Maryland, United States - Massachusetts, United States	202	Fragile X Syndrome	3–17	Transdermal CBD gel (ZYN002)	12 weeks	Phase 3, randomised, parallel assignment	ABC-C FXS

(*continued on next page*)

Table 3 (*continued*)

Trial ID	Recruitment status	Trial location	Enrollment / estimated enrollment	Clinical indication	Age range (years)	Treatment/s	Treatment duration	Study phase and design	Primary outcome
		- New Jersey, United States - New York, United States - North Carolina, United States - Ohio, United States - Oklahoma, United States - Pennsylvania, United States - South Carolina, United States - Washington, United States - New South Wales, Straliaia - Queensland, Australia - Victoria, Australia - Wellington, New Zealand							
NCT05098509	Active, not recruiting	- California, United States - Colorado, United States - Georgia, United States - Iowa, United States - Kansas, United States - Maryland, United States - Massachusetts, United States - New York, United States - Ohio, United States - Pennsylvania, United States - Tennessee, United States - Texas, United States - Utah, United States - Washington, United States	220	Prader-Willi Syndrome	8–65	Oral CBD (RAD011)	34 weeks	Phase 2/3, randomised, parallel assignment	Hyperplagia (HQ-CT) Questionnaire

5. Conclusion

This systematic review provides a timely critical examination of the published RCTs investigating CBD as a therapeutic intervention for neurodevelopmental disorder subgroups. We have highlighted encouraging, preliminary evidence for the compound's potential in improving specific difficulties associated with these populations, although individual outcomes were not comparable across the small and varied collection of published trials. We identify that the lack of rigorous testing (i.e., comprehensive RCTs) leaves some uncertainty regarding the reality of CBD as a viable therapeutic option for neurodevelopmental disorders. While the extant literature highlights several promising findings, the suitability of CBD in ameliorating core symptom domains across neurodevelopmental disorders is far from resolute, with scope for improvement in establishing more consistent research methodology and larger sample sizes. Participant profiles, study designs, outcome measures, and active treatment properties differ substantially across the trials explicated in this review. It is a distinctly critical moment for researchers investigating CBD as a viable pharmacological intervention for symptoms associated with neurodevelopmental disorders. To fully understand the therapeutic potential of CBD there will need to be considerable movement on the current state of evidence. The urgent need for large multi-site RCTs is uncontroversial. This approach would allow for specific symptom domains to be rigorously probed. To improve options for individuals facing complex neurodevelopmental challenges, the existing anecdotal and observational evidence must be empirically validated by RCTs with standardised treatment characteristics and methodology.

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Declaration of competing interest

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Data availability

Data will be made available on request.

Appendix A

Search syntax for meta-analysis (Medline, PsycInfo, CINAHL complete)

TI "Neurodevelopmental disorder" OR TI "Neurodevelopment*" OR TI "autism*" OR TI "autism spectrum disorder*" OR TI "autism spectrum condition*" OR TI "autistic disorder" OR TI "Asperg*" OR TI "ASD" OR TI "attention deficit hyperactivity disorder" OR TI "attention-deficit/hyperactivity disorder" OR TI "attention deficit disorder with hyperactivity" OR TI "attention deficit hyperactivity" OR TI "ADHD" OR TI "Attention Deficit Disorder with Hyperactivity" OR TI "ADDH" OR TI "ADD" OR TI "ADHS" OR TI "Hyperkinesis" OR TI "hyperactivity" OR TI "inattention" OR TI "Tourette's syndrome" OR TI "Tourette syndrome" OR TI "Tourette*" OR TI "Tic disorder" OR TI "Tic*" OR TI "TS" OR TI "complex motor disorders" OR TI "dyspraxia" OR TI "learning disorders" OR TI "learning disability" OR TI "intellectual disability" OR TI "Developmental Language Disorder" OR TI "DLD" OR TI "Specific Language Impairment" OR TI "SLI" OR TI "Dyslexia" OR TI "Dyscalculia" OR TI "Developmental coordination disorder" OR TI "Developmental co-ordination disorder" OR TI "DCD" OR TI "Stereotypic movement disorders" OR TI "Apraxia of speech" OR TI "Dyspraxia of speech" OR TI "Fragile-X syndrome" OR TI "Down syndrome" OR TI "DS" OR TI "Rett syndrome" OR TI "Down*" OR TI "Rett*" OR TI "Hypogonadotropic hypogonadism" OR TI "Cerebral palsy" OR TI "CP" OR TI "Fetal alcohol syndrome" OR TI "FAS" OR TI "Minamata disease" OR TI "Conduct disorder"

AND

TI "cannabidiol" OR TI "CBD" OR TI "cannabidivarin" OR TI "CBDV" OR TI "medical marijuana" OR TI "medicinal marijuana" OR TI "medical cannabis" OR TI "medicinal cannabis" OR TI "cannabinoid" OR TI "exocannabinoid*" OR TI "phytocannabinoid*" OR TI "phyto-cannabinoid*".

Appendix B

Search syntax used for EMBASE

"Neurodevelopmental disorder":ti,ab OR "Neurodevelopment*":ti,ab OR "autism*":ti,ab OR "autism spectrum disorder*":ti,ab OR "autism spectrum condition*":ti,ab OR"autistic disorder":ti,ab OR "Asperg*":ti,ab OR "autism":ti,ab OR "attention deficit hyperactivity disorder":ti,ab OR "attention-deficit/hyperactivity disorder":ti,ab OR "attention deficit disorder with hyperactivity":ti,ab OR "attention deficit hyperactivity":ti,ab OR "ADHD":ti,ab OR "Attention Deficit Disorder with Hyperactivity":ti,ab OR "ADDH":ti,ab OR "ADD":ti,ab OR "ADHS":ti,ab OR "Hyperkinesis":ti,ab OR "hyperactivity":ti,ab OR "inattention":ti,ab OR "Tourettes syndrome":ti,ab OR "Tourette syndrome":ti,ab OR "Tourette*":ti,ab OR "Tic disorder":ti,ab OR "Tic*":ti,ab OR "TS":ti,ab OR "complex motor disorders":ti,ab OR "dyspraxia":ti,ab OR "learning disorders":ti,ab OR "learning disability":ti,ab OR "intellectual disability":ti,ab OR "Developmental Language Disorder":ti,ab OR "DLD":ti,ab OR "Specific Language Impairment":ti,ab OR "SLI":ti,ab OR "Dyslexia":ti,ab OR "Dyscalculia":ti,ab OR "Developmental coordination disorder":ti,ab OR "Developmental co-ordination disorder":ti,ab OR "DCD":ti,ab OR "Stereotypic movement disorders":ti,ab OR "Apraxia of speech":ti,ab OR "Dyspraxia of speech":ti,ab OR "Fragile-X syndrome":ti,ab OR "Down syndrome":ti,ab OR "DS":ti,ab OR "Rett syndrome":ti,ab OR "Down*":ti,ab OR "Rett*":ti,ab OR "Hypogonadotropic hypogonadism":ti,ab OR "Cerebral palsy":ti,ab OR "CP":ti,ab OR "Fetal alcohol syndrome":ti,ab OR "FAS":ti,ab OR "Minamata disease":ti,ab OR "Conduct disorder":ti,ab

AND

"Cannabidiol":ti,ab OR "CBD":ti,ab OR "cannabidivarin":ti,ab OR "CBDV":ti,ab OR "medical marijuana":ti,ab OR "medicinal marijuana":ti,ab OR "medical cannabis":ti,ab OR "medicinal cannabis":ti,ab OR "cannabinoid":ti,ab OR "exocannabinoid*":ti,ab OR "phytocannabinoid*":ti,ab OR "phyto-cannabinoid*":ti,ab.

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