The role of cannabinoids in neurodevelopmental disorders of children and adolescents

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Introduction. Neurodevelopmental disorders have a multifactorial etiology that results from the interaction between biological and environmental factors. The biological basis of many of these disorders is only partially understood, which makes therapeutic interventions, especially pharmacological ones, particularly difficult. The impact of medical cannabis on neurological and psychiatric disorders has been studied for a long time. This study aimed to review the currently available clinical and pre-clinical studies regarding the use of cannabinoids in pediatric neurodevelopmental disorders and to draw attention to the potential therapeutic role of cannabidiol in this field.

Development. Cannabidiol is an endocannabinoid system modulator and exerts its effects on both developing and mature brains through numerous mechanisms. Cannabidiol holds a relatively high toxicity limit and current literature suggests that it may have anxiolytic, antipsychotic, and neuroprotective properties. Clinical evidence suggests that early treatment with cannabidiol might be a promising therapy for neurodevelopmental disorders, including intellectual disability, autism spectrum disorders, tics, and attention/deficit hyperactivity disorder.

Conclusions. This review hopefully draws attention to an emerging body of evidence concerning cannabidiol's significant potential to safely improve many of the common symptoms affecting children and adolescents with neurodevelopmental disorders, especially autism spectrum disorder.

Key words. Autism spectrum disorder. Cannabidiol. Cannabinoids. Endocannabinoid system. Neurodevelopment. Neurodevelopmental disorders.

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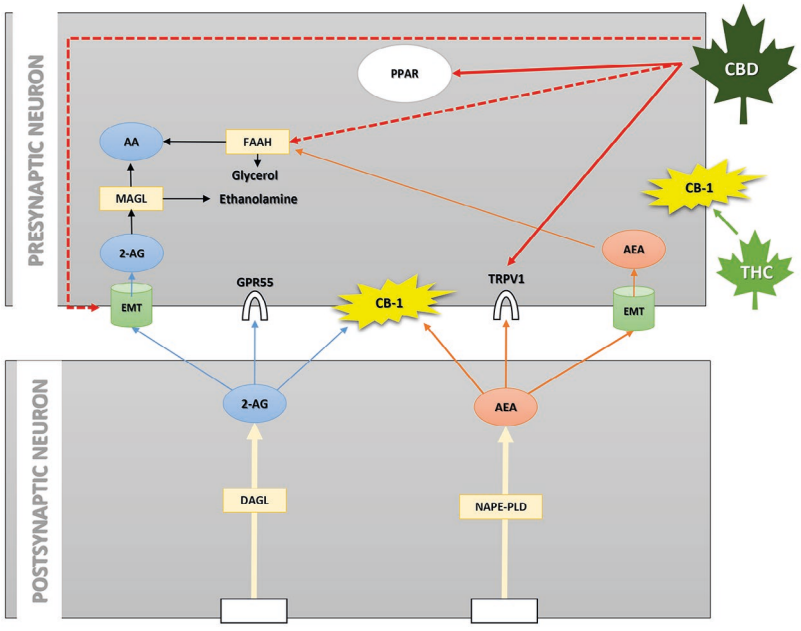
Introduction

Brain development is a crucial period of development when numerous neurophysiological changes occur, such as neurogenesis, neuronal migration, axonal growth, dendritic maturation, development of nerve cell networks and new synapses, myelination, and proliferation of glial cells [1]. Therefore, any events or experiences during this period will impact the individual's long-term behavioral phenotype and neurological development [1]. Neurodevelopmental disorders have a multifactorial etiology that results from the interaction between biological and environmental factors. The impact of perinatal exposures on the developing brain is paramount.

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Text Revision* (DSM-5-TR), recognizes six categories under the neurodevelopmental disorders chapter: intellectual disability, communication disorders, autism spectrum disorders (ASD), attention/deficit hyperactivity disorder (ADHD), specific learning disorders, and neurodevelopmental motor disorders. These may occur in the context of a recognized genetic syndrome, like fragile X syndrome, Prader-Willi syndrome, and 22q11.2 deletion syndrome. Current literature recognizes neurodevelopmental disorders as a leading cause of morbidity in children, causing great distress to them and their families and representing large costs for society [2]. The prevalence of neurodevelopmental disorders differs depending on the study. Recent meta-analysis calculated a pooled worldwide ADHD prevalence of 7.2% among children [3]. Intellectual disability prevalence ranges from 3.2% worldwide and 1.10% in the USA [4,5]. The co-existence of more than one neurodevelopmental disorder is frequent. Studies suggest that approximately 4% of affected children have at least two diagnoses and a two to four times increased risk of developing a psychiatric disorder compared to typically developing children [2,3].

Comorbidities lead to a greater compromise in children's performance in social, academic, and family domains causing reduced quality of life, and

Figure. Endocannabinoid (ECB) system. N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD) produces anandamide (AEA) from membrane phospholipids in the postsynaptic neuron. Diacylglycerol lipase (DAGL) produces 2-arachidonoylglycerol (2-AG) from membrane phospholipids in the postsynaptic neuron. It activates cannabinoid receptor type 1 (CB-1) and transient receptor potential vanilloid-1 (TRPV1) on the presynaptic neuron by crossing the synapse area retrogradely. The following reuptake to the presynaptic neuron by the AEA activates nuclear receptors —peroxisome proliferator-activated receptor γ (PPAR)— and degradation by fatty acid amide hydrolase (FAAH) occurs. THC directly activates CB-1; CBD inhibits fatty acid amide hydrolase and ECB membrane transporter (EMT) (increasing anandamide levels), the endogenous ligand of CB-1. Like anandamide, CBD activates PPAR and TRPV1. (Adapted from Aran A, Cayam-Rand D. Medical cannabis in children. Rambam Maimonides Med J. 2020; 11: e0003.)



poorer long-term prognosis, with implications in the choice of treatment.

The biological basis of many of these disorders is only partially understood, which makes therapeutic interventions, especially pharmacological ones, particularly difficult. Furthermore, many therapeutic options are based on studies conducted on neurotypical subjects, older children, and adults. New treatments with clearer associations between etiology and biological factors are required to support these individuals lifelong. The impact of medical cannabis on neurological and psychiatric disorders has been studied for a long time. Although there are some studies reporting promising results, anecdotal evidence of possible therapeutic effects on neurodevelopmental disorders has also emerged [3]. The increase in the acceptance of cannabis' medical benefits has shifted government policies in favor of cannabis decriminalization/legalization in jurisdictions such as Canada, Israel, Uruguay, most USA states, and Australia.

The two main cannabinoids are cannabidiol (CBD) and Δ^9-tetrahydrocannabinol (THC). While THC is psychoactive, by directly activating the endocannabinoid (ECB) system, CBD is not psychoactive. In children, the only strong scientific evidence of the effectiveness of CBD as a therapeutic option are two specific epileptic syndromes: Dravet syndrome and Lennox-Gastaut syndrome [4,6].

Objectives

This study aimed to review the currently available clinical and pre-clinical studies regarding the use of cannabinoids in pediatric neurodevelopmental disorders and to draw attention to the potential therapeutic role of CBD in this field.

Development

Endocannabinoid system and cannabinoids

The ECB system is widely expressed in the central nervous system (CNS), playing a role in synaptic plasticity regulation through retrograde signaling. This system is composed of the cannabinoid receptors type 1 (CB-1, mainly in the nervous system) and type 2 (CB-2, mainly expressed in immune cells), their ECB signaling molecules (anandamide and 2-arachidonoylglycerol), and their metabolic enzymes (N-acyl phosphatidylethanolamine-specific phospholipase D, diacylglycerol lipase, fatty acid amide hydrolase, and monoacylglycerol lipase) [1,4].

Endocannabinoids are produced 'on-demand' in postsynaptic neurons and act as retrograde signaling messengers in overexcited brain cascades. Through the activation of CB-1 located in presynaptic neurons, they modulate the synaptic release of neurotransmitters into the synaptic cleft decreasing the synaptic activity. After the reuptake of the presynaptic neuron by the ECB membrane transporter (EMT), endocannabinoids are immediately hydrolyzed.

CBD is an ECB system modulator and exerts its effects on both developing and mature brains through numerous mechanisms (Figure). CBD can modulate the ECB system directly via CB-1 and indirectly by regulating endocannabinoid levels as an agonist of the transient receptor potential vanil-

loid-1, facilitating serotoninergic transmission through 5-HT1A receptors, and interacting with the peroxisome proliferator-activated receptor γ through the G-protein-coupled receptor (such as GPR55, GPR3, GPR6, and GPR12).

Unlike THC which directly activates the ECB system through CB-1, CBD inhibits fatty acid amide hydrolase and EMT, increasing anandamide levels, the endogenous ligand of CB-1, and hence indirectly activating the ECB system. Like anandamide, CBD activates peroxisome proliferator and agonist of the transient receptor potential vanilloid-1 [4].

CBD holds a relatively high toxicity limit and current literature suggests that it may have anxiolytic, antipsychotic, and neuroprotective properties [1,4]. Unlike CBD, THC is strongly psychoactive and its effects on the developing brain include short-term changes in mood, appetite, behavior, and cognition [4]. The uncertainty of THC's safety and long-term effects has shifted medical community attention to CBD, emerging as a potential therapeutic option due to its relative abundance in the plant (40%), lack of psychoactive effects, safety profile, and supposed advantages. Several studies suggest a synergetic effect of the majority of cannabis compounds in the whole-plant extract –the 'entourage effect'– although this remains controversial [4]. Additionally, recent studies suggest a favorable two-way interface between THC and CBD, because THC may reinforce CBD's beneficial properties while CBD diminishes THC's psychotropic effects.

Nevertheless, it is crucial to bear in mind that THC's psychoactive properties and strong neural interactions can be harmful after long-term chronic exposure, especially during brain development in children.

Despite this data, the precise mechanisms of CBD's beneficial effects are still not entirely understood [3]. Concerning potential adverse effects of CBD, somnolence, diarrhea, and loss of appetite are the most reported in children [5,6]. Several large studies have shown that the main risks of addiction, minor cognitive deterioration, and schizophrenia are directly related to the THC and CBD concentrations; a lower ratio of CBD:THC and early onset of treatment imply a higher risk of detrimental neurodevelopmental consequences [5].

Autism spectrum disorder

ASD is a relatively common neurodevelopmental disorder characterized by social communication difficulties and restricted and repetitive interests [7,8]. Worldwide, the estimated ASD prevalence ranges from 0.08 to 9.3%, and in European countries from 0.42 to 3.13% [9]. ASD management is quite demanding and challenging as it is commonly associated with behavioral and psychiatric comorbidities. Aggression is observed in approximately 70% of ASD children and adolescents, including self-injurious behaviors in more than 25% [5]. In Europe, there are two approved therapeutic options for behavioral impairment associated with ASD: aripiprazole and risperidone. However, for many patients with ASD these pharmacotherapies, whether used alone or in combination, may have suboptimal efficacy and tolerability. This highlights the necessity for innovative therapeutic approaches. Because the clinical anomalies in these patients have been partially linked to dysregulation of the ECB system, CBD therapy has been used in recent ASD clinical trials (Table).

In 2018, Barchel et al [10] performed a prospective study with 53 participants (4-22 years) treated with CBD oil over 30 to 588 days. During the follow-up interviews, parents/caregivers' reported a self-injury and aggression improvement in 67.6% and worsening in 8.8%; hyperactivity symptoms improved in 68.4%, did not change in 28.9% and worsened in 2.6%; sleep problems improved in 71.4% and worsened in 4.7% and anxiety improved in 47.1% and worsened in 23.5% of the patients. Adverse effects were mild, predominantly somnolence and loss of appetite.

In 2019, Aran et al [7] published a brief report relating to a retrospective study that evaluated the tolerability and efficacy of cannabidiol-rich cannabis in 60 participants (5-18 years) with ASD and severe behavioral problems, treated with CBD-oil for 13 months. Patients were assessed using specific questionnaires. The authors described a high retention rate (73%), improvement of aggressive behavior (61%), anxiety (39%), and communication (47%). Adverse events included sleep disturbances (14%), irritability (9%), and loss of appetite (9%). One girl who ingested higher THC doses had a transitory serious psychotic event that required an antipsychotic. In the same year, Fleury-Teixeira et al [11] reported that based on data collected from a standardized form answered by patient's parents/caregivers, among the 15 patients (6-17 years) who ingested CBD oil over 30-588 days (10 non-epileptic and 5 epileptic patients) only one patient revealed no improvement in ASD symptoms. Although the clearest improvements were observed in sleep and behavioral disorders, improvements were also noted in motor development, communication, social

Table. Summarized clinical results of cannabidiol (CBD) administration during neurodevelopment evaluations in patients with autism spectrum disorders (ASD), attention-deficit/hyperactivity disorder (ADHD), Gilles de La Tourette syndrome (GTS), intellectual disability (ID) and fragile X syndrome (FXS).

	Disorder	Experimental/clinical model	Drug dose and route	Major findings
Barchel et al (2018) [10]	ASD	Prospective study; a cohort of 53 patients (4-22 years); 30-588 days	CBD:THC ratio of 20:1 once a day; maximal daily dose: 16 mg/kg, oral	Overall improvement was reported in 74.5%
Aran et al (2019) [7]	ASD	Retrospective study; a cohort of 60 patients (5-18 years); 7-13 months	CBD:THC ratio of 20:1, 2-3 times a day with doses up-titrated over 2-4 weeks (starting CBD 1 mg/kg/day), oral	Considerable improvement in behavior problems, anxiety, and communication problems
Fleury-Teixeira et al (2019) [11]	ASD	Observational study; a cohort of 18 patients (6-17 years); 30-588 days	CBD:THC ratio of 75:1 twice a day (average CBD 4.6 mg/kg/day and average THC 0.06 mg/kg/day), oral	Significant improvement in ADHD, motor deficits, communication and social interaction deficits, behavioral disorders, sleep disorders, and seizures. The seizure reduction rate was of 50% in three cases and 100% in the other two cases
Bar-lev Shcleider et al (2019) [12]	ASD	Prospective study; a cohort of 188 patients (5-18 years); 6 months	CBD:THC ratio of 20:1. The dosage ranged from 1 drop (0.05 ml) three times a day to 20 drops three times a day, for 6 months, oral	Overall, more than 80% of the parents reported a significant or moderate improvement
Aran et al (2021) [13]	ASD	Placebo-controlled double-blind comparison of two oral cannabinoid solutions; a cohort of 150 patients (5-21 years); 3 months	1) Whole-plant cannabis extract containing CBD and THC at a 20:1 ratio; and 2) purified CBD and THC at a 20:1 ratio	Both cannabinoid solutions were administrated for 3 months and were well tolerated. Evidence for the efficacy of these interventions is mixed and insufficient
Cooper et al (2017) [15]	ADHD	Double-blind, randomized placebo-controlled experimental trial; a cohort of 30 adults (18-55 years); 6 weeks	CBD:THC ratio of 1:1; oral	Overall improvement was reported
Efron et al (2021) [16]	ID	Randomized, placebo-controlled pilot study of 8 patients (8-16 years); 8 weeks	98% CBD in oil; up-titrated over 9 days to 20 mg/kg/day in two divided doses (maximum dose of 500 mg twice daily)	Preliminary evidence favours CBD over the placebo, with all three participants with outcome data in the CBD group reporting a clinically significant behavior improvement
Müller-Vahl et al (2003) [17]	GTS	Randomized, double-blind, placebo-controlled study of 24 patients (18-68 years); 6-weeks	THC-gelatine capsules; up-titrated every 4 days to 10 mg/day	Global and detailed examiner ratings, self- rating scale, and a videotape-based rating scale demonstrated a significant or a trend toward a significant reduction in tics during 6 weeks of treatment with THC
Müller-Vahl et al (2002) [19]	GTS	Double-blind, placebo-controlled, crossover trial of 12 patients (18-66 years); single-dose followed by 4-weeks washout phase	THC-gelatine capsules; 5.0, 7.5 or 10 mg/day according to their body weight, sex, age and prior use of marijuana	Self-rating scale demonstrated significant reduction of motor and vocal tics and obsessive-compulsive behavior. Examiner's rating demonstrated a significant improvement in complex motor tics and a trend towards significant improvement in motor and vocal tics
Anis et al (2022) [20]	GTS	Open-label prospective study of 18 patients (20-50 years); 12-weeks	10% THC and 2% CBD; 1 drop or puff a day and increase by 1 drop or puff as needed	Significant 38% average reduction (p = 0.002) of tic severity and a 20% reduction (p = 0.043) of Premonitory Urge for Tic Scale
Tartaglia et al (2019) [21]	FXS	Case report of three patients with FXS (3-26 years); 15-30 months	Oral forms of botanically derived CBD+ solutions (43-50 mg CBD)	Noticeable reductions in social avoidance and anxiety. Improvements in sleep, feeding, motor coordination, language skills, anxiety, and sensory processing
Heussler et al (2019) [22]	FXS	Phase 1/2, open-label assessment; cohort of 20 patients (75% M) / (6-17 years); 12 weeks	Transdermal CBD gel; daily 50 mg dose, twice daily 50 mg dose, or twice daily 125 mg dose	Significant reductions in anxiety and behavioral symptoms

TDH: Δ^9-tetrahidrocannabinol.

interaction, and cognitive performance. The retention rate was high (83%) and adverse effects were mainly mild and/or transient and included somnolence, irritability, diarrhea, increased appetite, conjunctival hyperemia, and hyperthermia. Three patients suspended the treatment in the first month due to insomnia, irritability, increased heart rate, and exacerbation of the psychotic crisis. In 2019, Bar-lev Schleider et al [12], based on patient's parents/caregivers' follow-up interviews reported a retention rate of 82.4% after six months of treatment with medical cannabis. From this subgroup, 60.0% have been assessed, 30.1% reported a significant improvement, and 8.6% reported no change. After one month, 4.2% of patients interrupted the treatment and after six months it increased to 8.3%. At least one adverse effect was noted in 25.2% of the patients: restlessness (6.6%), somnolence (3.2%), psychoactive effects (3.2%), increased appetite (3.2%), digestive disorders (3.2%), dry mouth (2.2%) and lack of appetite (2.2%). In 2021, Aran et al [13] published a placebo-controlled double-blind comparison of two oral cannabinoid solutions, and data collected from caregiver questionnaires described a considerable difference between the groups in non-compliant behavior and parenting stress measures. Frequent adverse events included somnolence, decreased appetite, weight loss, asthenia, euphoria, and anxiety.

The study population in the clinical trials described were ASD patients in distinct developmental stages, the majority were males. In all five studies, CBD was delivered as CBD-enriched cannabis extract oil containing both CBD and THC administered orally. In four of them, the CBD:THC ratio was 20:1 [9-12], while in one study, it was 75:1 [11]. The treatments with CBD:THC oil presented elevated retention rates. Nevertheless, evidence regarding elevated adherence and retention rates for low doses of CBD in ASD patients is meaningful. Some patients described adverse effects throughout treatment with CBD, however, improvements in ASD and comorbidity-related symptoms were noted in all four studies, such as a decrease in anxiety, sleep problems, hyperactivity, aggressive behavior, and self-injury. Additionally, improvement in patients' autonomy, motor, and cognitive performances, and communication and social interaction were also illustrated. The clinical evidence summarized in table suggests that early treatment with CBD might be a promising therapy for ASD. However, it is neccesary to highlight the methodological limitation in all five studies since they were based on questionnaires to parents, which contributes to the subjective nature of the conclusions reached. It is vital that CBD's efficacy in treating ASD symptoms may be confirmed through randomized, double-blind placebo-controlled multicenter trials. Some clinical studies are currently being carried out (NCT03900923, NCT03849456, NCT03202303, NCT04520685, NCT04745026 and NCT04517799). However, additional studies must be conducted to clarify if CBD treatment benefits are due to CBD isolated effects or the 'entourage effect' previously mentioned.

Attention deficit hyperactivity disorder

ADHD is the most common neurobehavioral disorder of childhood, affecting around 3-5% of children, and the second most frequent chronic disorder in this population [13,14]. It severely affects academic achievement, well-being and social skills. There are recognized effective treatments such as psychostimulants (methylphenidate, amphetamines) and non-psychostimulants (atomoxetine, guanfacine), however, there are non-responders and partial responders, and these medications are not always well tolerated which requires novel therapeutic approaches. The mechanism for potential therapeutic effects of CBD in ADHD is unknown and there have been no publications regarding pediatric patients until this moment. In 2017, Cooper et al [15] published a double-blind, randomized placebo-controlled experimental trial that enrolled 30 adult participants (18-55 years) and reported significant improvement in hyperactivity/impulsivity (p = 0.03), inattention (p = 0.10) and emotional lability symptoms (p = 0.11) (Table). Two serious adverse effects were described during this study: sudden onset of muscular spasms and a participant who was taking a placebo experienced tachycardia and dyspnea. To our knowledge, CBD clinical trials are not being conducted in children with ADHD at the time this article was written.

Intellectual disabilities

50% of the individuals with intellectual disability have sever comorbid behavioral disorders. These disruptive behaviors can be a risk to individuals and their families. Therapeutic options used to treat severe behavioral problems in intellectual disability are associated with a high risk of undesirable effects and have suboptimal efficacy. In 2021, Efron et al [16] published preliminary evidence from a pilot study with 8 participants favoring active treatment with CBD compared to placebo. All 3 partici-

pants of the CBD group reported a clinically significant change in neurobehavior (Table). Although the sample was extremely small, these data are consistent with previous open-label observational studies supporting the requirement for properly randomized controlled trials to assess the efficacy of CBD in the pediatric population [7-9]. Currently, a large, randomized placebo-controlled study involving 140 children aged 6-18 years with intellectual disability aiming to compare oral purified CBD 8-week effects in severe behavioral problems with placebo is being conducted (NCT04821856).

Gilles de la Tourette syndrome

Gilles de la Tourette syndrome is a relatively common childhood-onset neuropsychiatric disorder with a prevalence of 0.3-0.8% in school-age children and is strongly associated with many neurodevelopmental and psychiatric comorbidities, including ADHD, obsessive-compulsive behavior, depression, anxiety, sleep disorders, and rage attacks [17]. Current available therapeutic options are not sufficiently effective and do not change long-term prognosis [18]. Furthermore, they may cause severe side effects, such as parkinsonism, metabolic syndrome, and hyperprolactinemia, compromising the compliance. Two small, controlled trials have investigated the effect of oral THC in adult Gilles de la Tourette syndrome patients [17,19,20]. In 2002, Mueller-Vahl et al [19] published a double-blind, placebo-controlled, crossover trial of 12 patients (18-66 years) suggesting that a single-dose treatment with THC was effective and safe in the therapy of tics and obsessive-compulsive behavior in Gilles de la Tourette syndrome (Table). In 2003, the same authors [17] published a randomized controlled trial involving 24 patients favoring daily THC treatment compared to placebo with significant reduction in tics (Table). While these trials have shown promising results, the effect sizes were not as large and consistent as those reported by patients with regards to inhaled cannabis (smoked or vaporized) [20]. In 2022, Anis et al [20] published an open-label clinical trial demonstrating good efficacy and tolerability of medical cannabis in adult Gilles de la Tourette syndrome patients (Table). This study revealed predilection for smoked cannabis (80%) over oil drops. Common side effects included dry mouth (66.7%), fatigue (53.3%), and dizziness (46.7%). Six patients (40%) reported adverse cognitive side effects concerning time and visuospatial skills, processing speed and attention span. Less commonly (16,6%), worsening of obsessive-compulsive symptoms, panic attacks and anxiety were reported [20]. Despite the existence of a strong biological rational for the use of cannabinoid-based treatments in the Gilles de la Tourette syndrome population, further trials are needed to examine the overall efficacy and safety of cannabis-derived medications in this disorder, particularly in pediatric age. Some clinical studies are currently being carried out in adult Gilles de la Tourette syndrome patients (NCT03247244, NCT03087201 and NCT05115318).

Fragile X syndrome

Among individuals with the full mutation, symptoms of fragile X syndrome vary with age and gender and include anxiety (80%), social avoidance (80%), stereotyped behaviors (80%), ADHD (70%), ASD (60%), intellectual disability (~100% of males and up to 25% of females), aggression (40%), disrupted sleep (40%), and epilepsy (16%) [1]. Conventional therapeutic approaches include drugs to address sleep disorders (melatonin), anxiety (selective serotonin reuptake inhibitors and benzodiazepines), hyperactivity, deficits in attention (psychostimulants), and seizures (anticonvulsant drugs). The ongoing pharmacotherapies used, whether alone or in combination, may have potential adverse effects and are not well-tolerated in all fragile X syndrome children.

Many symptoms in fragile X syndrome might be associated with ECB system dysregulation, with a reduction of endogenous stimulation of endocannabinoid receptors. Tartaglia et al [21] suggested that CBD may have a therapeutic role in this fragile X syndrome-compromised ECB system. This study reported three cases of fragile X syndrome patients (one child and two adults) who received oral formulations of botanically derived CBD+ solutions with clinical symptom improvement. However, as previously noted, only placebo-controlled trials will be able to elucidate the true therapeutic effects of CBD/ CBD+ treatment on fragile X syndrome symptomatology. In 2019, Heussler et al [22] published a phase 1/2, open-label assessment of the safety, tolerability, and efficacy of transdermal CBD (ZYN002), a transdermal CBD gel, in a pediatric population with fragile X syndrome, and concluded CBD was well tolerated and produced significant clinical reductions in anxiety and behavioral symptoms. A larger randomized, double-blind, placebo-controlled, multiple-center study, with 212 pediatric participants is currently being conducted to assess the efficacy and safety of

ZYN002 for the treatment of fragile X syndrome (NCT03614663). The clinical evidence summarized in table suggests that early treatment with CBD might be a promising therapy for fragile X syndrome.

22q11.2 deletion syndrome

22q11.2 deletion syndrome is a multisystemic genetic disorder with an estimated prevalence of about 1 in 2,000 live births. The phenotypic expression is highly unpredictable and ranges from severe life-threatening conditions to slight clinical manifestations. 22q11.2 deletion syndrome patients have an increased risk for neurodevelopmental, cognitive, behavioral, and socioemotional impairments [23]. Common features in 22q11.2 deletion syndrome include poor cognition and intellectual disability, attention and executive functioning difficulties, learning disorders, emotional dysregulation, and social deficits [23]. Unlike ASD and fragile X syndrome, there have been no reports on the efficacy of CBD treatment on 22q11.2 deletion syndrome. Nevertheless, an open-label study to assess the safety, tolerability, and efficacy of CBD administered as a transdermal gel (ZYN002), in the treatment of pediatric patients with 22q11.2 deletion syndrome, is now taking place (NCT05149898). The goal would be to reduce behavioral symptoms to improve the quality of life of 22q11.2 deletion syndrome patients and their caregivers.

Prader-Willi syndrome

Prader-Willi syndrome is a rare genetic neurodevelopmental disorder associated with a distinct behavioral phenotype that includes severe hyperphagia and a variety of other symptoms such as anxiety, temper outbursts, obsessive-compulsive behaviors, rigidity, and social communication deficits [24]. Similarly to 22q11.2 deletion syndrome, there is no published evidence on the efficacy of CBD treatment on Prader-Willi syndrome patients. Currently, a randomized, double-blind placebo-controlled trial is being conducted to assess the efficacy and safety of cannabidivarin, a naturally occurring homolog of the CBD, in children and young adults with Prader-Willi syndrome (NCT03848481). It aims to obtain valid therapeutic options to reduce behavioral symptoms, such as irritability, improving the quality of life of Prader-Willi syndrome patients and their families.

Conclusions

This review hopefully draws attention to an emerging body of evidence concerning CBD's significant potential to safely improve many of the common symptoms affecting children and adolescents with neurodevelopmental disorders, especially ASD. Upcoming research addressing the establishment of definite relationships between CBD intake and modifications to the ECB system is needed to determine clearer risk-benefit associations and to screen for individuals with predictable benefits from this innovative therapeutic approach. CBD is currently the most promising therapeutic cannabinoid for children and adolescents due to its safety profile, relatively high toxicity limit, and broad-spectrum action based on CBD's anxiolytic, antipsychotic, and neuroprotective properties. Nevertheless, further studies are clearly needed on its mechanisms of action in each of the neurodevelopmental disorders mentioned, as well as on the most beneficial dose and administration frequency.

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El papel de los cannabinoides en los trastornos del neurodesarrollo de niños y adolescentes

Introducción. Los trastornos del neurodesarrollo tienen una etiología multifactorial que resulta de la interacción entre factores biológicos y ambientales. La base biológica de muchos de estos trastornos se comprende sólo parcialmente, lo que hace que las intervenciones terapéuticas, especialmente las farmacológicas, sean particularmente difíciles. El impacto del cannabis medicinal en los trastornos neurológicos y psiquiátricos se ha estudiado durante mucho tiempo. Este estudio tuvo como objetivo revisar los estudios clínicos y preclínicos actualmente disponibles con respecto al uso de cannabinoides en trastornos del neurodesarrollo pediátrico y llamar la atención sobre el posible papel terapéutico del cannabidiol en este campo.

Desarrollo. El cannabidiol es un modulador del sistema endocannabinoide y ejerce sus efectos tanto en cerebros en desarrollo como en cerebros maduros a través de numerosos mecanismos. El cannabidiol tiene un límite de toxicidad relativamente alto, y la bibliografía actual sugiere que puede tener propiedades ansiolíticas, antipsicóticas y neuroprotectoras. La evidencia clínica sugiere que el tratamiento temprano con cannabidiol podría ser una terapia prometedora para los trastornos del desarrollo neurológico, incluida la discapacidad intelectual, los trastornos del espectro autista, los tics y el trastorno por déficit de atención/hiperactividad.

Conclusiones. Es de esperar que esta revisión llame la atención sobre un cuerpo emergente de evidencia sobre el potencial significativo del cannabidiol para mejorar de manera segura muchos de los síntomas comunes que afectan a niños y adolescentes con trastornos del neurodesarrollo, especialmente el trastorno del espectro autista.

Palabras clave. Cannabidiol. Cannabinoides. Neurodesarrollo. Sistema endocannabinoide. Trastorno del espectro autista. Trastornos del neurodesarrollo.