Medical Cannabis in Children

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ABSTRACT

The use of medical cannabis in children is rapidly growing. While robust evidence currently exists only for pure cannabidiol (CBD) to treat specific types of refractory epilepsy, in most cases, artisanal strains of CBD-rich medical cannabis are being used to treat children with various types of refractory epilepsy or irritability associated with autism spectrum disorder (ASD). Other common pediatric disorders that are being considered for cannabis treatment are Tourette syndrome and spasticity. As recreational cannabis use during youth is associated with serious adverse events and medical cannabis use is believed to have a relatively high placebo effect, decisions to use medical cannabis during childhood and adolescence should be made with caution and based on evidence. This review summarizes the current evidence for safety, tolerability, and efficacy of medical cannabis in children with epilepsy and in children with ASD. The main risks associated with use of Δ9-tetrahydrocannabinol (THC) and CBD in the pediatric population are described, as well as the debate regarding the use of whole-plant extract to retain a possible “entourage effect” as opposed to pure cannabinoids that are more standardized and reproducible.

KEY WORDS: Autism, cannabis, CBD, children, epilepsy, THC

NEUROACTIVITY OF CANNABIS

The cannabis plant has a substantial effect on social behavior in humans. It enhances interpersonal communication and decreases hostile feelings. Similar to other plants, cannabis contains hundreds of compounds, including terpenes and flavonoids, many of which have a known or presumed neurological effect. Cannabis also contains over a hundred unique compounds called phytocannabinoids (plant-derived cannabinoids). The two main phytocannabinoids are cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC). These...
compounds were characterized in 1963 and 1964, respectively, by Professor Raphael Mechoulam and colleagues from Israel.\textsuperscript{5,6} Mechoulam found that THC is the plant’s main psychoactive component, responsible for the feeling of a “high.” This effect in the brain is mediated by an abundant G-protein-coupled receptor, which he named cannabinoid type 1 receptor (CB\textsubscript{1}R). A second receptor that is also directly activated by THC was isolated later from macrophages in the spleen and was named cannabinoid type-2 receptor (CB\textsubscript{2}R).\textsuperscript{7} Accordingly, the main effect mediated by CB\textsubscript{2}R is immunomodulation. This receptor is not significantly expressed in the brain under normal conditions but can be found on glial cells in various brain pathologies.

The two main endogenous ligands of the cannabinoid receptors (“endocannabinoids”) are N-arachidonylethanolamine (AEA or anandamide) and 2-arachidonoylglycerol (2-AG).

Figure 1 demonstrates the endocannabinoid system. Endocannabinoids are produced “on demand” in postsynaptic neurons and act as retrograde signaling messengers in overactive brain circuits. By activating CB\textsubscript{1}R in presynaptic neurons, they modulate the synaptic release of neurotransmitters into the synaptic cleft and attenuate the synaptic activity in that circuit.\textsuperscript{8} After reuptake of the endocannabi-
binoids to the presynaptic neuron by the endocannabinoid membrane transporter, they are immediately hydrolyzed.

While THC directly activates the endocannabinoid system through CB1R, CBD does not activate CB1R directly and is not psychoactive.9 Cannabidiol has a relatively high toxicity threshold and appears to have anxiolytic, antipsychotic, and neuroprotective properties that may be mediated through receptors such as serotonin 5-HT1A, glycine α3 and α1, TRPV1, GPR55, and PPARγ, and by inhibiting adenosine reuptake.10–13 Cannabidiol also inhibits the enzyme fatty acid amide hydrolase (FAAH) that degrades anandamide, the endogenous ligand of CB1R, and hence can indirectly activate the endocannabinoid system (Figure 1).

While 99% pure cannabinoids are more reproducible and standardized than whole-plant extract and thus preferred as a study drug, several studies suggest a synergistic effect for the numerous cannabidiols in the whole-plant extract.4,14–19 This so-called “entourage effect” remains controversial.20

Future studies should directly assess the effects of pure cannabinoids versus whole-plant extracts in various disorders among different target populations.

**MAIN RISKS OF CANNABIS IN CHILDREN**

The current knowledge on the long-term side-effects of cannabinoids is based mainly on longitudinal follow-up of recreational cannabis users.21–23 Several large studies have demonstrated that the main risks of decreased motivation,24–26 addiction,27 mild cognitive decline,28,29 and schizophrenia30–32 are directly related to the THC and CBD concentrations in the strain used,33 i.e. the higher the ratio of THC to CBD, the greater the risk. The risk is also elevated among those with younger onset of use (<18 years) and in the presence of other risk factors, such as a family history of schizophrenia and concomitant use of alcohol and tobacco.33,34 Notably, these studies contained very few participants under 10 years old and did not assess daily use of medical cannabis.

Longitudinal follow-up studies in children with epilepsy receiving pure CBD suggest high tolerability and safety,35–37 but these studies included very few participants younger than 5 years old.

Animal studies suggest that using pure CBD and its analogue cannabidivarin (CBDV) during early development is relatively safe38,39 while the use of THC, with or without CBD, during early development was found to impair brain structure and function.40–43

Short-term adverse events of pure CBD or CBD-rich whole-plant extracts include somnolence, weight loss, and increased liver transaminases.33,39,44–47

**MEDICAL CANNABIS FOR CHILDREN WITH EPILEPSY**

Epilepsy is a common neurological disorder, affecting 0.5%–1% of the world’s population.48 Despite the availability of many effective antiepileptic drugs, about one-third of epileptic patients will continue to have treatment-refractory seizures.49 If a patient continues to have seizures despite appropriate treatment trials with three medications, the probability of achieving seizure freedom with subsequent medications is less than 3.5%.49 In such cases, treatment options include epileptic surgery, vagal nerve stimulation, or ketogenic diet. However, for the numerous patients who are not eligible for surgery or do not respond to these treatments, medical cannabis may offer more hope for seizure reduction compared with other pharmacological interventions.

Cannabis treatment for seizures has a long history; it has been used as an anticonvulsant in the ancient Middle East and India for at least 4000 years.50 More recently, leading nineteenth-century neurologists Sir John Russell Reynolds and Sir William Richard Gowers sporadically used THC-rich cannabis to treat seizures. The use of cannabis for epilepsy gradually ceased following the introduction of phenobarbitone in 1912 and phenytoin in 1937. Small studies, mainly of THC-rich cannabis for children with epilepsy, re-emerged in the 1970s with mixed results. Following the discovery of the endocannabinoid system in the 1990s and its major role in neuromodulation, including the attenuation of overactive brain circuits, studies in animal models and anecdotes of successful treatment in refractory epilepsy cases began to accumulate. However, larger-scale clinical studies of cannabinoids in epilepsy were only conducted in recent years.50 These studies focus on the safer cannabidiol, CBD, which seems to have more of an antiepileptic effect than THC in preclinical studies.

A plant-derived pure CBD compound (brand name: Epidiolex) was approved by the US Food and Drug Administration (FDA) in 2018 for treating two severe forms of epilepsy—Dravet and Lennox–Gastaut syndromes51—following a series of successful safety and efficacy studies.36,32–54
A recent systematic review and meta-analysis of the efficacy and tolerability of pure CBD and CBD-rich medical cannabis revealed that CBD is more effective than placebo for treatment-resistant epilepsy, regardless of the etiology of the epileptic syndrome.\textsuperscript{37} Adverse events included somnolence, decreased appetite and weight, irritability, increased seizure frequency, and diarrhea (in some of the studies). Laboratory abnormalities included elevation of liver transaminases in patients who also received valproic acid. Short-term adverse events were found to be similar for pure CBD and CBD-rich medical cannabis. Adverse events were more frequent at treatment onset compared with long-term follow-up.\textsuperscript{37} Clinicians should also be aware of cross-reactivity between CBD or CBD-rich medical cannabis and antiepileptic medications that are also metabolized by the cytochrome P450 complex. Notably, active metabolites of benzodiazepines significantly increase with concomitant use of CBD and CBD-rich medical cannabis.

**MEDICAL CANNABIS FOR CHILDREN WITH AUTISM SPECTRUM DISORDER**

Autism spectrum disorder (ASD) affects up to 2.5% of children worldwide and is a major public health challenge.\textsuperscript{55} Individuals with ASD have social and communication difficulties, stereotyped or repetitive behaviors and interests, sensory problems, and, in many cases, cognitive impairment and disruptive behaviors. These deficits are present in early childhood and lead to significant disability.\textsuperscript{56} Approximately 50% of children and adolescents with ASD demonstrate behavioral difficulties, including tantrums, non-compliance, aggression, and self-injury.\textsuperscript{57–59} This rate is higher than in any other neurodevelopmental disorder.\textsuperscript{60–65} The behavioral difficulties of children with ASD increase their social isolation\textsuperscript{66,67} and often cause more distress to caregivers than the core autistic symptoms.\textsuperscript{68–70} Maladaptive behaviors also limit the child’s ability to benefit from intervention efforts, thereby impairing the long-term prognosis.\textsuperscript{71}

Standard treatment for these problems is based on behavioral interventions\textsuperscript{71–75} combined with medications,\textsuperscript{76,77} particularly atypical antipsychotics\textsuperscript{78–84} and mood stabilizers.\textsuperscript{85} However, both the efficacy and tolerability of pharmacotherapy in children with ASD are less favorable than among typically developing children with similar symptoms.\textsuperscript{86} As a result, despite extensive behavioral and medical treatment, 40% of the children and youth with ASD suffer from maladaptive behavior\textsuperscript{87} that severely impacts their quality of life and takes a heavy toll on their families.\textsuperscript{69,88} The frustration from current medical treatment leads to an exceptionally high percentage of parents seeking help from complementary and alternative medicine.\textsuperscript{89,90}

Epilepsy is one of the most common comorbid conditions in ASD, affecting 10%–30% of children and youth with ASD,\textsuperscript{91} and several pathophysiological processes are implicated in both disease processes.\textsuperscript{92} Hence, the positive effect of cannabinoids in refractory patients is relevant for individuals with ASD.

The CB1 receptor is highly expressed in the frontal cortex and subcortical areas associated with social functioning.\textsuperscript{93,94} The CB1 receptors and their endogenous ligands anandamide and 2-AG regulate social play and social anxiety in animal models\textsuperscript{95–100} and in humans.\textsuperscript{101–103}

Activation of the endocannabinoid system in the nucleus accumbens (anandamide mobilization and consequent activation of CB1 receptors) driven by oxytocin, a neuropeptide that reinforces social bonding, was demonstrated to be necessary and sufficient to express the rewarding properties of social interaction.\textsuperscript{104} Reduced endocannabinoid activity was demonstrated in several animal models of ASD,\textsuperscript{105} including monogenic (fragile-X,\textsuperscript{106} neuroligin 3\textsuperscript{107}), polygenic (BTBR\textsuperscript{108}), and environmental (rat valproic acid\textsuperscript{109}) models. Activation of the endocannabinoid system\textsuperscript{105–108} and administration of CBD\textsuperscript{105} have been shown to restore social deficits in some models. A single oral administration of 600 mg CBD to 34 men (17 neurotypicals and 17 with ASD) increased prefrontal gamma-aminobutyric acid (GABA) activity in neurotypicals and decreased GABA activity in those with ASD.\textsuperscript{109} Additionally, children with ASD have been found to have lower peripheral endocannabinoid levels.\textsuperscript{110,111}

Therefore, dysregulation of the endocannabinoid system may play an important role in ASD pathophysiology and may represent a target for pharmacological intervention.\textsuperscript{112}

Four uncontrolled case-series, including 60,\textsuperscript{113,114} 53, and 18 children with ASD and severe behavioral problems, reported high tolerability and efficacy of artisanal CBD-rich cannabis strains.\textsuperscript{44–47} In the largest cohort, data collection was partial, and there was also an unknown overlap between the first three
cohorts. Most participants were followed for at least 6 months, and the retention rate was about 80%.

The treatment was reported to substantially decrease the irritability and anxiety in most of the participants and to improve the social deficits in about half of the subjects, but these results should be interpreted cautiously.

Cannabinoid treatment is associated with a relatively high placebo effect, compared with other pharmacological treatments. Placebo effect is expected to be even higher in ASD studies which use subjective behavioral assessments. Hence, placebo-controlled studies are required even for a preliminary assessment of efficacy. To date, only one controlled study was completed (NCT02956226) and another is ongoing (NCT03202303).

NCT02956226 was a phase 2, proof-of-concept trial, conducted in a single referral center, Shaare Zedek Medical Center, Jerusalem, Israel. In this double-blind, placebo-controlled trial, 150 children (age 5–21 years) with ASD and behavioral problems (Clinical Global Impression of Severity ≥4), were randomized (in a 1:1:1 ratio) to receive either placebo or one of two cannabinoid solutions for 12 weeks. The cannabinoid solutions were: (1) whole-plant cannabis extract containing cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) in a 20:1 ratio; and (2) purified CBD and THC in the same ratio and dose, without other components of the cannabis plant such as minor cannabinoids, terpenes, and flavonoids which may also contribute to the therapeutic effect in an entourage effect. The rationale for THC use was previous experience with similar cannabis strains in open-label studies and the known effects of THC on social behavior. The taste, smell, and texture of the three study interventions were carefully adjusted for similarity, which was approved by a professional taster. Participants received either placebo or cannabinoids for 12 weeks to test efficacy, followed by a 4-week washout, and crossed-over to receive another treatment for 12 weeks to further assess tolerability. The treatments were given orally as an add-on to any pre-existing treatment, with an average CBD dose of 5.5 mg/kg/day, divided into three daily doses. There were no serious treatment-related adverse events. The most prevalent adverse events were somnolence and loss of appetite. In some of the measures, cannabinoids reduced the irritability and even the core symptoms of autism significantly more than placebo, with no advantage of the whole-plant extract over the pure cannabinoids.

MEDICAL CANNABIS FOR CHILDREN WITH SPASTICITY AND OTHER INDICATIONS

An open-label study of 25 children (age 1–17 years) with a complex motor disorder demonstrated improvement in spasticity and dystonia, sleep difficulties, pain severity, and quality of life. The participants received one of two artisanal strains of CBD-rich cannabis for 5 months: either a 20:1 CBD:THC ratio or a 6:1 ratio. No significant differences were found between the two strains. Two case series, one with 12 children with treatment-refractory spasticity related to developmental disorders and one with 7 children with pantothenate kinase-associated neurodegeneration (PKAN), reported improvement in the spasticity and dystonia in some of the children after treatment with dronabinol, a synthetic form of THC (spasticity) or various cannabis strains (PKAN). Case reports of children who received cannabis for other indications included cases of: neuropathic pain and comorbid major depressive disorder (dronabinol, n=2), anxiety and sleep in PTSD (CBD, n=1), and Tourette syndrome (THC, n=1). Larger open-label studies and randomized studies are required prior to clinical use of cannabis for these indications.

DISCUSSION

Public interest in cannabis-based treatment is rapidly growing, especially in disorders with substantial unmet needs such as pediatric ASD and refractory epilepsy. This review summarizes current knowledge on the neuroactivity of cannabinoids, potential risks, and evidence of efficacy and tolerability in epilepsy and ASD. While most patients receive a variety of artisanal strains, only pure CBD for epilepsy has been rigorously evaluated in controlled trials thus far, with modest but significant improvement in motor seizures and acceptable tolerability. Adverse events included somnolence and reduced appetite. Important interactions with antiepileptic drugs include an increased risk of hepatotoxicity with valproic acid and an increased level of active metabolites with benzodiazepines, contributing to somnolence and potentially to efficacy.

While some studies suggest that artisanal strains with a very high ratio of CBD:THC (e.g. 20:1) are as safe and potent as pure CBD, this issue should be evaluated in future studies. Notably, artisanal preparations, if used, should be obtained from government-controlled sources (preferably good manufacturing practices-approved) as several studies
demonstrated significant inconsistency between product labels and actual content in many cases.

In ASD, the gap between published evidence and public beliefs is much wider. Preclinical studies and case series, reporting successful treatment with artisanal CBD-rich cannabis strains in children with ASD and severe irritability, have triggered widespread use of various cannabis strains in children with ASD, despite a lack of published controlled studies. Moreover, parents often request medical cannabis to treat the core autistic symptoms—not the associated irritability—and this request often comes from parents of children younger than 5 years. Some parents prefer to try medical cannabis for irritability as a first-line treatment, as it is perceived as natural and hence safer, compared with the FDA-approved antipsychotics, risperidone and aripiprazole. Many families are interested in products with a relatively high content of THC, which carries a higher risk of severe neurobehavioral comorbidities in this vulnerable population compared with the general population.

In our opinion, the use of medical cannabis in ASD should be currently limited to clinical trials and highly selected cases of treatment-resistant severe irritability.

REFERENCES

1. Tart CT. Marijuana intoxication common experiences. Nature 1970;226:701–4. CrossRef
2. Salzman C, Kochansky GE, Van Der Kolk BA, Shader RI. The effect of marijuana on small group process. Am J Drug Alcohol Abuse 1977;4:251–5. CrossRef
3. Salzman C, Van Der Kolk BA, Shader RI. Marijuana and hostility in a small-group setting. Am J Psychiatry 1976;133:1029–33. CrossRef
4. Russo EB. The case for the entourage effect and conventional breeding of clinical cannabis: no “strain,” no gain. Front Plant Sci 2018;9:1969. CrossRef
5. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964;86:1646–7. CrossRef
6. Mechoulam R, Shvo Y. Hashish–I: The structure of cannabidiol. Tetrahedron 1963;12:2073–8. CrossRef
7. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature 1993;365:61–5. CrossRef
8. Guerrero-Alba R, Barragán-Iglesias P, González-Hernández A, et al. Some prospective alternatives for treating pain: the endocannabinoid system and its putative receptors GPR18 and GPR55. Front Pharmacol 2018;9:1496. CrossRef
9. Szkudlarek HJ, Desai SJ, Renard J, et al. Δ9-Tetrahydrocannabinol and cannabidiol produce dissociable effects on prefrontal cortical executive function and regulation of affective behaviors. Neuropsychopharmacology 2019;44:817–25. CrossRef
10. Campos AC, Fogaça MV, Scarante FF, et al. Plastic and neuroprotective mechanisms involved in the therapeutic effects of cannabinoids in psychiatric disorders. Front Pharmacol 2017;8:269. CrossRef
11. McGuire P, Robson P, Cubala WJ, et al. Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: a multicenter randomized controlled trial. Am J Psychiatry 2018;175:225–31. CrossRef
12. Devinsky O, Cilio MR, Cross H, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55:791–802. CrossRef
13. Iannotti FA, Hill CL, Leo A, et al. Nonpsychotropic plant cannabinoids, cannabidiavarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. ACS Chem Neurosci 2014;5:1131–41. CrossRef
14. Ben-Shabat S, FridE E, Sheskin T, et al. An entourage effect: inactive endogenous fatty acid glycerol esters enhance 2-arachidonoyl-glycerol cannabinoid activity. Eur J Pharmacol 1998;353:23–31. CrossRef
15. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 2011;163:1344–64. CrossRef
16. Sanchez-Ramos J. The entourage effect of the phyto-cannabinoids. Ann Neurol 2015;77:1083. CrossRef
17. Blasco-Benito S, Seijo-Vila M, Caro-Villalobos M, et al. Appraising the “entourage effect”: Antitumor action of a pure cannabinoid versus a botanical drug preparation in preclinical models of breast cancer. Biochem Pharmacol 2018;157:285–93. CrossRef
18. Ferber SG, Namdar D, Hen-Shoval D, et al. The “entourage effect”: Terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders. Curr Neuropsychopharmacol 2020;18(2). CrossRef
19. Namdar D, Voet H, Ajjampura V, et al. Terpenoids and phytocannabinoids co-produced in Cannabis sativa strains show specific interaction for cell cytotoxic activity. Molecules 2019;24:pii:E3031. CrossRef
20. Santiago M, Sachdev S, Arnold JC, McGregor IS, Connor M. Absence of entourage: terpenoids commonly found in Cannabis sativa do not modulate the functional activity of Δ9-THC at human CB1 and CB2 receptors. Cannabis Cannabinoid Res 2019;4:165–76. CrossRef
21. Schrot RJ, Hubbard JR. Cannabinoids: medical implications. Ann Med 2016;48:128–41. CrossRef
22. Levine A, Clemenza K, Rynn M, Lieberman J. Evidence for the risks and consequences of adolescent cannabis exposure. J Am Acad Child Adolesc Psychiatry 2017;56:214–25. CrossRef
23. Krebs MO, Kebir O, Jay TM. Exposure to cannabinoids can lead to persistent cognitive and psychiatric disorders. Eur J Pain 2019;23:1225–33. CrossRef
24. Morgan CJ, Freeman TP, Schafer GL, Curran HV. Cannabidiol attenuates the appetitive effects of delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis. Neuropsychopharmacology 2010;35:1879–85. CrossRef
25. Morgan CJ, Gardener C, Schafer G, et al. Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being. Psychol Med 2012;42:391–400. CrossRef
26. Zlebnik NE, Cheer JF. Beyond the CB1 receptor: is cannabidiol the answer for disorders of motivation? Annu Rev Neurosci 2016;39:1–17. CrossRef
27. Hurd YL, Yoon M, Manini AF, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. Neurotherapeutics 2015;12:807–15. CrossRef
28. Morgan CJ, Schafer G, Freeman TP, Curran HV. Impact of cannabidiol on the acute memory and psychomimetic effects of smoked cannabis: naturalistic study. Br J Psychiatry 2010;197:285–90. CrossRef
29. Lorenzetti V, Solowij N, Yücel M. The role of cannabinoids in neuroanatomic alterations in cannabis users. Biol Psychiatry 2016;79:e17–31. CrossRef
30. Iseger TA, Bossong MG. A systematic review of the antipsychotic properties of cannabidiol in humans. Schizophr Res 2015;162:153–61. CrossRef
31. Silva TB, Balbino CQ, Weiber AF. The relationship between cannabidiol and psychosis: a review. Ann Clin Psychiatry 2015;27:134–41.
32. Ortiz-Medina MB, Perea M, Torales J, et al. Cannabis consumption and psychosis or schizophrenia development. Int J Soc Psychiatry 2018;64:690–704. CrossRef
33. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med 2014;370:2219–27. CrossRef
34. French L, Gray C, Leonard G, et al. Early cannabis use, polygenic risk score for schizophrenia and brain maturation in adolescence. JAMA Psychiatry 2015;72:1002–11. CrossRef
35. Laux LC, Bebin EM, Checketts D, et al. Long-term safety and efficacy of cannabidiol in children and adults with treatment resistant Lennox-Gastaut syndrome or Dravet syndrome: expanded access program results. Epilepsy Res 2019;154:13–20. CrossRef
36. Szafarski JP, Bebin EM, Comi AM, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: expanded access program results. Epilepsia 2018;59:1540–8. CrossRef
37. de Carvalho Reis R, Almeida KJ, da Silva Lopes L, de Melo Mendes CM, Bor-Seng-Shu E. Efficacy and adverse event profile of cannabidiol and medicinal cannabis for treatment-resistant epilepsy: systematic review and meta-analysis. Epilepsy Behav 2019;102:106635. CrossRef
38. Huizenga MN, Sepulveda-Rodriguez A, Forcelli PA. Preclinical safety and efficacy of cannabidiol in early life seizures. Neuropharmacology 2019;148:189–98. CrossRef
39. Cepría N, Vargas C, Garcia-Toscano L, et al. Cannabidiol administration prevents hypoxia-ischemia-induced hypomyelination in newborn rats. Front Pharmacol 2019;10:1131. CrossRef
40. Schey AF, Borsó M, Wager-Miller J, et al. Cannabidiol exposure via lactation in rats disrupts perinatal programming of the gamma-aminobutyric acid trajectory and select early-life behaviors. Biol Psychiatry 2019;in press. CrossRef
41. Schey AF, Melis M, Trezza V, Manzoni OJJ. Consequences of perinatal cannabis exposure. Trends Neurosci 2019;42:871–84. CrossRef
42. Thorpe HHA, Hamidullah S, Jenkins BW, Khokhar JY. Adolescent neurodevelopment and substance use: receptor expression and behavioral consequences. Pharmacol Ther 2019;197:98. CrossRef
43. Schonhofen P, Bristot LJ, Crippa JA, et al. Cannabinoid-based therapies and brain development: potential harmful effect of early modulation of the endocannabinoid system. CNS Drugs 2018;32:697–712. CrossRef
44. Aran A, Cassuto H, Lubotzky A, Wattad N, Hazan E. Brief report: Cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems-a retrospective feasibility study. J Autism Dev Disord 2019;49:1284–8. CrossRef
45. Barchel D, Stolar O, De-Haan T, et al. Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. Front Pharmacol 2019;9:1521. CrossRef
46. Bar-Lev Schleider L, Mechoulam R, Saban N, Meiri G, Novack V. Real life experience of medical cannabis treatment in autism: analysis of safety and efficacy. Sci Rep 2019;9:200. CrossRef
47. Fleury-Teixeira P, Caixeta FV, Ramires da Silva LC, Brasil-Neto JP, Malcher-Lopes R. Effects of CBD-enriched Cannabis sativa extract on autism spectrum disorder symptoms: an observational study of 18 participants undergoing compassionate use. Front Neurol 2019;10:1145. CrossRef

48. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 2010;51:883–90. CrossRef

49. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. JAMA Neurol 2018;75:279–86. CrossRef

50. Russo EB. Cannabis and epilepsy: an ancient treatment returns to the fore. Epilepsy Behav 2017;70:292–7. CrossRef

51. U.S. Food and Drug Administration. FDA news release: FDA approves first drug comprised of an active ingredient derived from marijuana to treat rare, severe forms of epilepsy. Available at: www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm61046.htm (accessed January 9, 2020).

52. Devinsky O, Marsh E, Friedman D, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15:270–8. CrossRef

53. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376:2011–20. CrossRef

54. Devinsky O, Patel AD, Cross JH, et al. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378:1888–97. CrossRef

55. Xu G, Strathearn L, Liu B, et al. Prevalence and treatment patterns of autism spectrum disorder in the United States, 2016. JAMA Pediatr 2019;173:153–9. CrossRef

56. American Psychiatric Association. Autism Spectrum Disorder, 299.00 (F84.0). In: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. Arlington, Virginia: American Psychiatric Publishing; 2013:50–5. CrossRef

57. Hartley SL, Sikora DM, McCoy R. Prevalence and risk factors of maladaptive behaviour in young children with autistic disorder. J Intell Disabil Res 2008;52:819–29. CrossRef

58. Mukaddes NM, Fatch R. High rates of psychiatric comorbidity in individuals with Asperger’s disorder. World J Biol Psychiatry 2010;11:486–92. CrossRef

59. Kanne SM, Mazurek MO. Aggression in children and adolescents with ASD: prevalence and risk factors. J Autism Dev Disord 2011;41:926–37. CrossRef

60. Green J, Gilchrist A, Burton D, Cox A. Social and psychiatric functioning in adolescents with Asperger syndrome compared with conduct disorder. J Autism Dev Disord 2009;39:279–93. CrossRef

61. Bradley EA, Summers JA, Wood HL, Bryson SE. Comparing rates of psychiatric and behavior disorders in adolescents and young adults with severe intellectual disability with and without autism. J Autism Dev Disord 2004;34:151–61. CrossRef

62. Gadow KD, DeVincent CJ, Pomeroy J, Azizian A. Psychiatric symptoms in preschool children with PDD and clinic and comparison samples. J Autism Dev Disord 2004;34:379–93. CrossRef

63. Eisenhower AS, Baker BL, Blacher J. Preschool children with intellectual disability: syndrome specificity, behaviour problems, and maternal well-being. J Intell Disabil Res 2005;49:657–71. CrossRef

64. Brereton AV, Tonge BJ, Einfeld SL. Psychopathology in children and adolescents with autism compared to young people with intellectual disability. J Autism Dev Disord 2006;36:863–70. CrossRef

65. Hill J, Furniss F. Patterns of emotional and behavioural disturbance associated with autistic traits in young people with severe intellectual disabilities and challenging behaviours. Res Dev Disabil 2006;27:517–28. CrossRef

66. Scahill L, McDougle CJ, Aman MG, et al. Effects of risperidone and parent training on adaptive functioning in children with pervasive developmental disorders and serious behavioral problems. J Am Acad Child Adolesc Psychiatry 2012;51:136–46. CrossRef

67. Maskey M, Warnell F, Parr JR, Le Couteur A, McConachie H. Emotional and behavioural problems in children with autism spectrum disorder. J Autism Dev Disord 2013;43:851–9. CrossRef

68. Hastings RP, Kovshoff H, Ward NJ, degli Espinosa F, Brown T, Remington B. Systems analysis of stress and positive perceptions in mothers and fathers of pre-school children with autism. J Autism Dev Disord 2005;35:635–44. CrossRef

69. Lecavalier L, Leone S, Wiltz J. The impact of behaviour problems on caregiver stress in young people with autism spectrum disorders. J Autism Dev Disord 2013;43:204–16. CrossRef

70. Hayes SA, Watson SL. The impact of parenting stress: a meta-analysis of studies comparing the experience of parenting stress in parents of children with and without autism spectrum disorder. J Autism Dev Disord 2013;43:629–42. CrossRef

71. Horner RH, Carr EG, Strain PS, Todd AW, Reed HK. Problem behavior interventions for young children with autism: a research synthesis. J Autism Dev Disord 2002;32:423–46. CrossRef
72. Dretzke J, Davenport C, Frew E, et al. The clinical effectiveness of different parenting programmes for children with attention deficit hyperactivity problems: a systematic review of randomised controlled trials. Child Adolesc Psychiatry Ment Health 2009;3:7. CrossRef

73. Reichow B, Barton EE, Boyd BA, Hume K. Early intensive behavioral intervention (EIBI) for young children with autism spectrum disorders (ASD). Cochrane Database Syst Rev 2012;10:CD009260. CrossRef

74. Oono IP, Honey EJ, McConachie H. Parent-mediated early intervention for young children with autism spectrum disorders (ASD). Cochrane Database Syst Rev 2013;4:CD009774. CrossRef

75. Bearss K, Johnson C, Smith T, et al. Effect of parent training vs parent education on behavioral problems in children with autism spectrum disorder: a randomized clinical trial. JAMA 2015;313:1524–33. CrossRef

76. Aman MG, McDougle CJ, Scabill L, et al. Medication and parent training in children with pervasive developmental disorders and serious behavior problems: results from a randomized clinical trial. J Am Acad Child Adolesc Psychiatry 2009;48:1143–54. CrossRef

77. Bearss K, Lecavalier L, Minshawi N, et al. Toward an exportable parent training program for disruptive behaviors in autism spectrum disorders. Neuropsychiatry (London) 2013;3:169–80. CrossRef

78. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. N Engl J Med 2002;347:314–21. CrossRef

79. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics 2004;114:e634–41. CrossRef

80. Research Units on Pediatric Psychopharmacology Autism Network. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. Am J Psychiatry 2005;162:1361–9. CrossRef

81. Williams SK, Scabill L, Vitiello B, et al. Risperidone and adaptive behavior in children with autism. J Am Acad Child Adolesc Psychiatry 2006;45:431–9. CrossRef

82. Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. Cochrane Database Syst Rev 2017;(8):CD008559. CrossRef

83. Accordino RE, Kidd C, Politte LC, Henry CA, McDougle CJ. Psychopharmacological interventions in autism spectrum disorder. Expert Opin Pharmacother 2016;17:937–52. CrossRef

84. Levine SZ, Kodesh A, Goldberg Y, et al. Initial severity and efficacy of risperidone in autism: results from the RUPP trial. Eur Psychiatry 2016;32:16–20. CrossRef

85. Canitano R. Mood stabilizers in children and adolescents with autism spectrum disorders. Clin Neuropharmacol 2015;38:177–82. CrossRef

86. Ji N, Findling RL. An update on pharmacotherapy for autism spectrum disorder in children and adolescents. Curr Opin Psychiatry 2015;28:91–101. CrossRef

87. Adler BA, Wink LK, Early M, et al. Drug-refractory aggression, self-injurious behavior, and severe tantrums in autism spectrum disorders: a chart review study. Autism 2015;19:102–6. CrossRef

88. Rivard M, Terroux A, Parent-Boursier C, Mercier C. Determinants of stress in parents of children with autism spectrum disorders. J Autism Dev Disord 2014;44:1609–20. CrossRef

89. Salomone E, Charman T, McConachie H, Warreyn P; Working Group 4, COST Action 'Enhancing the Scientific Study of Early Autism'. Prevalence and correlates of use of complementary and alternative medicine in children with autism spectrum disorder in Europe. Eur J Pediatr 2015;174:1277–85. CrossRef

90. Owen-Smith AA, Bent S, Lynch FL, et al. Prevalence and predictors of complementary and alternative medicine use in a large insured sample of children with autism spectrum disorders. Res Autism Spectr Disord 2015;17:40–51. CrossRef

91. Ballaban-Gil K, Tuchman R. Epilepsy and epileptiform EEG: association with autism and language disorders. Ment Retard Dev Disabil Res Rev 2000;6:300–8. CrossRef

92. Keller R, Basta R, Salerno L, Elia M. Autism, epilepsy, and synaptopathies: a not rare association. Neurosci Lett 2017;638:1353–61. CrossRef

93. Seeley WW, Zhou J, Kim EJ. Frontotemporal dementia: what can the behavioral variant teach us about human brain organization? Neuroscientist 2012;18:373–85. CrossRef

94. Glass M, Dragunow M, Faull RL. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. Neuroscience 1997;77:299–318. CrossRef

95. Moreira FA, Kaiser N, Monory K, Lutz B. Reduced anxiety-like behaviour induced by genetic and pharmacological inhibition of the endocannabinoid-degrading enzyme fatty acid amid hydrolase (FAAH) is mediated by CB1 receptors. Neuropsychopharmacology 2008;33:141–50. CrossRef
96. Cassano T, Gaetani S, Macheda T, et al. Evaluation of the emotional phenotype and serotonergic neurotransmission of fatty acid amide hydrolase-deficient mice. Psychopharmacology 2011;214:465–76. CrossRef

97. Trezza V, Damsteegt R, Manduca A, et al. Endocannabinoids in amygdala and nucleus accumbens mediate social play reward in adolescent rats. J Neurosci 2012;32:14899–908. CrossRef

98. Trezza V, Baarendse PJ, Vanderschuren LJ. The pleasures of play: pharmacological insights into social reward mechanisms. Trends Pharmacol Sci 2010;31:463–9. CrossRef

99. Seillier A, Advani T, Cassano T, Hensler JG, Giuffrida A. Inhibition of fatty-acid amide hydrolase and CB1 receptor antagonism differentially affect behavioural responses in normal and PCP-treated rats. Ing J Neuropsychopharmacol 2010;13:373–86. CrossRef

100. Seillier A, Martinez AA, Giuffrida A. Phencyclidine-induced social withdrawal results from deficient stimulation of cannabinoid CB1 receptors: implications for schizophrenia. Neuropsychopharmacology 2013;38:1816–24. CrossRef

101. Bergamaschi MM, Queiroz RH, Chagas MH, et al. Rimonabant effects on anxiety induced by simulated public speaking in healthy humans: a preliminary report. Hum Psychopharmacol 2014;29:94–9. CrossRef

102. Gunduz-Cinar O, MacPherson KP, Cinar R, et al. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. Mol Psychiatry 2013;18:813–23. CrossRef

103. Phan KL, Angstadt M, Golden J, Onyewuenyi I, Popovska A, de Wit H. Cannabinoid modulation of amygdala reaction to social signals of threat in humans. J Neurosci 2008;28:2315–19. CrossRef

104. Wei D, Lee D, Cox CD, et al. Endocannabinoid signaling mediates oxytocin-driven social reward. Proc Natl Acad Sci USA 2015;112:14084–9. CrossRef

105. Zamberletti E, Gabaglio M, Parolaro D. The endocannabinoid system and autism spectrum disorders: insights from animal models. Int J Mol Sci 2017;18 pii: E1916. CrossRef

106. Wang W, Cox BM, Jia Y, et al. Treating a novel plasticity defect rescues episodic memory in Fragile X model mice. Mol Psychiatry 2018;23:1798–806. CrossRef

107. Hosie S, Malone DT, Liu S, et al. Altered amygdala excitation and CB1 receptor modulation of aggressive behavior in the neuroligin-3 mice model of autism. Front Cell Neurosci 2018;12:234. CrossRef

108. Melancia F, Schiavi S, Servadio M, et al. Sex-specific autistic endophenotypes induced by prenatal exposure to valproic acid involve anandamide signalling. Br J Pharmacol 2018;175:3699–712. CrossRef

109. Pretzsch CM, Freyberg J, Voinescu B, et al. Effects of cannabidiol on brain excitation and inhibition systems; a randomised placebo-controlled single dose trial during magnetic resonance spectroscopy in adults with and without autism spectrum disorder. Neuropsychopharmacology 2019;44:1398–405. CrossRef

110. Karshon DS, Krasinska KM, Dallaire JA, et al. Plasma anandamide concentrations are lower in children with autism spectrum disorder. Mol Autism 2018;9:18. CrossRef

111. Aran A, Eylon M, Harel M, et al. Lower circulating endocannabinoid levels in children with autism spectrum disorder. Mol Autism 2019;10:2. CrossRef

112. Krueger DD, Brose N. Evidence for a common endocannabinoid-related pathomechanism in autism spectrum disorders. Neuron 2013;78:408–10. CrossRef

113. Lattanzii S, Brigo F, Trinka E, et al. Efficacy and safety of cannabidiol in epilepsy: a systematic review and meta-analysis. Drugs 2018;78:1791–804. CrossRef

114. Jones RM, Carberry C, Hamo A, Lord C. Placebo-like response in absence of treatment in children with autism. Autism Res 2017;10:1567–72. CrossRef

115. Hindocha C, Freeman TP, Schafer G, et al. Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial emotion recognition: a randomised, double-blind, placebo-controlled study in cannabis users. Eur Neuropsychopharmacol 2015;25:325–34. CrossRef

116. Libzon S, Schleider LB, Saban N, et al. Medical cannabis for pediatric moderate to severe complex motor disorders. J Child Neurol 2018;33:565–71. CrossRef

117. Kuhlen M, Hoell JI, Gagnon G, et al. Effective treatment of spasticity using dronabinol in pediatric palliative care. Eur J Paediatr Neurol 2016;20:898–904. CrossRef

118. Wilson JL, Gregory A, Wakeman K, et al. Cannabis use in children with pantothenate kinase-associated neurodegeneration. J Child Neurol 2019;34:804–8. doi:10.1177/0883073819890516. [Epub ahead of print] CrossRef

119. Wong SS, Wilens TE. Medical cannabinoids in children and adolescents: a systematic review. Pediatrics 2017;140:pii:e20171818. CrossRef