

Medical Cannabis for Autism Spectrum Disorder, is it an option?

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Abstract

Objective: A literature review was conducted to evaluate the validity of medical cannabis as an adjunctive treatment in the management of individuals with Autism Spectrum Disorders.

Background: Autism spectrum disorder (ASD) is a developmental disability that can cause significant social, communication and behavioral challenges. The learning, thinking, and problem-solving abilities of people with ASD can range from gifted to severely challenged.

Since there is no medical test to diagnose the disorders, the provider must listen to the parent/ caretaker and look at the child's behavior and development to make a diagnosis. Unfortunately, many children do not receive a final diagnosis until much older.

A deficiency in the endocannabinoid system in the body is considered as the reason for many disorders and recent researchers' state that it might help in the treatment of autism. The chronic neuroinflammation can be eased with the help of the antioxidants which are present in the cannabis plant.

The theory of Clinical Endocannabinoid Deficiency (CED) was based on the concept that many brain disorders are associated with neurotransmitter deficiencies, affecting acetylcholine in Alzheimer's disease, dopamine in Parkinsonian Syndromes, serotonin and norepinephrine in depression, and that a comparable deficiency in endocannabinoid levels might be manifest similarly in certain disorders that display predictable clinical features as sequelae of this deficiency.

Design/Methods: A literature review was conducted of the National Center for Biotechnology Information, U.S. National Library of Medicine PubMed from 2012-2018 specific to the topic of medical cannabis and autism spectrum disorder.

Conclusion: This literature review supports the feasibility of cannabis based medicine as a promising treatment option in children with ASD. Based on the promising results, it is recommended that large, double blind, placebo controlled cross-over trials be launched in jurisdictions where medical cannabis can be studied without limitations from the federal government.

Introduction

Autism spectrum disorder (ASD) is a developmental disability that can cause significant social, communication and behavioral challenges. The learning, thinking, and problem-solving abilities of people with ASD can range from gifted to severely challenged. A diagnosis of ASD now includes several conditions that used to be diagnosed separately: autistic disorder, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome. These conditions are now all called autism spectrum disorder [1].

Epidemiology

According to the Center for Disease Control, the United States is number one in the incidence of autism i.e., 168 in 10,000 American children have the disorder, which equates to 1 in 59 children! [2].

Diagnosis

Since there is no medical test to diagnose the disorders, the provider must listen to the parent/ caretaker and look at the child's behavior and development to make a diagnosis. The American Academy of Pediatrics (AAP) recommends that all children be screened for ASD at ages 18 and 24 months, along with regular developmental surveillance [3,4]. Unfortunately, many children do not receive a final diagnosis until much older.

Causes and Risk Factors

These include, but are not limited to the following:

- Genes (GRIN2B) are one of the risk factors that can make a person more likely to develop ASD [5].
- Children who have a sibling with ASD are at a higher risk of also having ASD [6-11]. ASD tends to occur more often in people

who have certain genetic or chromosomal conditions, such as fragile X syndrome or tuberous sclerosis [12-15].

- When taken during pregnancy, the prescription drugs valproic acid and thalidomide have been linked with a higher risk of ASD [16,17].
- Children born to older parents are at greater risk for having ASD [18].

A newer thought for the cause of autism includes the concept of too many synapses; an interesting feature of brain development is that the number of synapses actually decreases as children grow older. Toddlers and pre-schoolers have more synapses than teenagers, and those “extra” synapses are supposed to get “pruned” away as the years go. In autism, the number of synapses is normally high early in life, but fails to decrease in the usual way. As a result, teenagers with autism end up with more synapses than is typical. Patients with autism may carry a mutation that prevents one of their ubiquitin genes (RNF8) from working properly. To understand the role of ubiquitin genes in brain development, scientists removed the ubiquitin gene (RNF8) in neurons in the cerebellum of young mice [the cerebellum is one of the key brain regions affected by autism], the researchers found that neurons that lacked the RNF8 protein formed about 50 percent more synapses – the connections that allow neurons to send signals from one to another – than those with the gene. The researchers found that the strength of the signal was doubled in the mice that lacked the protein [19,20].

“Unconventional” thoughts for the cause of autism include Dr. Martha Herbert, author of “THE AUTISM REVOLUTION—whole body strategies for making life all it can be”, which offers a revolutionary new view of autism: “Autism is not hardwired into a child’s genes and destined to remain fixed forever, instead, autism is a collection of challenges, i.e., less than optimal nutrition, toxic exposures, a weak or depressed immune system and stress [21].”

The Endocannabinoid System and Autism

The Endocannabinoid System (ECS) was discovered by Dr. Raphael Mechoulam, being a pioneer in this area in the mid-1960’s [22]. Endogenous cannabinoids are the chemicals our own bodies make to naturally stimulate the cannabinoid receptors, which are CB1, CB2 and non-CB1/CB2 aka GPR55 and the endogenous cannabinoids are, Anandamide, 2-Arachidonoylglycerol (2-AG), noladin ether, Virodhamine and N-arachidonoyl-dopamine (NADA) [23]. Physical, mental or emotional stressors support the endogenous production of cannabinoids.

How does the Endocannabinoid System (ECS) relate to autism?

- Plasma anandamide concentrations are lower in children with autism spectrum disorder [24].
- The ECS is affected in conditions often present in subsets of patients diagnosed with ASD, such as seizures, anxiety, intellectual disabilities, and sleep pattern disturbances [25].
- Neuroinflammation had been shown in postmortem brain specimens from ASD patients. The growing number of medical benefits of the ECS, such as their ability to regulate processes like neuroinflammation, neurogenesis and memory, raise the question of their potential role as a preventive treatment of ASD [26].
- Early studies in autism animal models have demonstrated alterations in the brain’s Endocannabinoid System. Autism is also characterized by immune system dysregulation. This

alteration includes differential monocyte and macrophage responses, and abnormal cytokine and T cell levels, as well as mRNA and protein for CB2 receptor and EC enzymes—further indicating the involvement of the EC system in autism-associated immunological disruptions. These new findings offer a novel perspective in autism research and indicate that the EC system could represent a novel target option for autism pharmacotherapy [27].

- Endocannabinoid signaling in specific circuits of the brain is context dependent and selectively recruited. Therefore, playing a key role in many human health and disease conditions of the central nervous system, thus opening the avenue to the therapeutic exploitation of eCB-oriented drugs for the treatment of psychiatric, neurodegenerative, and neuroinflammatory disorders. These insights open new vistas on the neural basis of social behavior and social impairment [28,29].

Treatment

There are many different types of treatments available [30,31].; the different types of treatments can generally be broken down into the following categories:

- Medication, i.e., antiepileptics, antidepressants, anxiolytics, antipsychotics, mood stabilizers and muscle relaxers.
- Behavior and Communication Approaches, i.e., Discrete Trial Training (DTT), Applied Behavior Analysis (ABA), Early Intensive Behavioral Intervention (EIBI), Pivotal Response Training (PRT), Verbal Behavior Intervention (VBI).
- Dietary Approaches--gluten free diet, vitamin therapy, anti-yeast therapy, anti-bacterial therapy, probiotics, detoxification.
- Complementary and Alternative Medicine, i.e., music therapy, occupational therapy, physical therapy, chiropractic manipulation, sensory integration.

Cannabis, Cannabinoids and Medical Cannabis

Cannabis plants produce a unique family of terpeno-phenolic compounds called cannabinoids, some of which produce the "high/euphoria" which may be experienced from consuming a subspecies of cannabis. There are 483 identifiable chemical constituents known to exist in the cannabis plant, and at least 85 different cannabinoids have been isolated from the plant [32,33]. The two cannabinoids usually produced in greatest abundance are cannabidiol (CBD) and/or Δ^9 -tetrahydrocannabinol (THC), but only THC is psychoactive [34].

Since the early 1970s, Cannabis plants have been categorized by their chemical phenotype or "chemotype", based on the overall amount of THC produced, and on the ratio of THC to CBD [35]. Although overall cannabinoid production is influenced by environmental factors, the THC/CBD ratio is genetically determined and remains fixed throughout the life of a plant [36].

Non-drug plants produce relatively low levels of THC and high levels of CBD, while drug plants produce high levels of THC and low levels of CBD. When plants of these two chemotypes cross-pollinate, the plants in the first filial (F1) generation have an intermediate chemotype and produce intermediate amounts of CBD and THC. Female plants of this chemotype may produce enough THC to be utilized for drug production [37].

Medical cannabis, is cannabis and cannabinoids that are recommended by physicians for their patients [38]. The use of cannabis as medicine

has not been rigorously tested due to production restrictions and other governmental regulations [39]. Limited evidence suggests that cannabis can reduce nausea and vomiting during chemotherapy, improve appetite in people with HIV/AIDS, and reduce chronic pain and muscle spasms [40-42]. The Cannabis plant has a history of medicinal use dating back thousands of years in many cultures [43].

Medical Cannabis and Autism in the United States of America

Which are the medical cannabis friendly states for autism? [44].

- Delaware—In Nov. of 2015, it was the first state to make autism a qualifying condition.
- Georgia—for adults over 18, or if younger than 18, for severe autism only.
- Louisiana—across the spectrum and no age requirement/limitation
- Michigan—it was added to their existing comprehensive medical cannabis law in 2018.
- Minnesota—it was added by petition in 2017.
- Pennsylvania—it was included in the original bill that created their comprehensive medical cannabis program in 2016.

How can a child be “qualified” for medical cannabis in jurisdictions where medical cannabis is legal, but not included in the qualifying conditions? In many other “legal” states, doctors can qualify and recommend cannabis because autism is a debilitating condition. For example, Florida's law allows any condition diagnosed as "debilitating" by a certifying physician as long as it can be “linked” to one of the named qualifying conditions. Conditions that are “comorbid” and can “be linked” with autism are:

- Epilepsy
- Neurological Conditions, i.e., MS or ALS
- Crohn's disease
- Post-Traumatic Stress Disorder

Endocannabinoid Deficiency

The theory of Clinical Endocannabinoid Deficiency (CED) was presented in 2001 in two publications, but more thoroughly explored in 2004 in an article that has subsequently been cited frequently in the literature with the greatest evidence for CED being for migraine, fibromyalgia, and irritable bowel syndrome (IBS) [45].

The theory of CED was based on the concept that many brain disorders are associated with neurotransmitter deficiencies, affecting acetylcholine in Alzheimer's disease, dopamine in Parkinsonian Syndromes, serotonin and norepinephrine in depression, and that a comparable deficiency in endocannabinoid levels might be manifest similarly in certain disorders that display predictable clinical features as sequelae of this deficiency [46].

All humans possess an underlying endocannabinoid tone that reflects of levels of anandamide (AEA) and 2-arachidonoylglycerol (2-AG), the centrally acting endocannabinoids, their synthesis, catabolism, and the relative density of cannabinoid receptors in the brain. If endocannabinoid function were decreased, it follows that a lowered pain threshold would be operative, along with derangements of digestion, mood, and sleep among the almost universal physiological systems subserved by the endocannabinoid system (ECS) [47].

A deficiency in the endocannabinoid system in the body is considered as the reason for many disorders and recent researchers' state that it might help in the treatment of autism [24,25,28,29]. The chronic

neuroinflammation can be eased with the help of the antioxidants which are present in the cannabis plant [26,27]. Cannabis helps with mood and behavior of the patients in terms of emotions & aggressive outbursts [28]. Cannabinoids are believed to remove the damaged brain cells and to improve the efficiency of mitochondria [48]. With the help of CBD, children can be protected from the neurodegenerative diseases [49]. Cannabinoids help the brain to achieve breakthroughs in learning, which also helps in gaining consciousness and better understanding [50]. For the sleep issues, this can be addressed by bringing the endocannabinoid system into balance, ensuring proper health [51].

Clinical Studies

In a retrospective study performed by Dr. Aran, in Israel, assessed the safety, tolerability and efficacy of cannabidiol (CBD) based medical cannabis, as an adjuvant therapy, for refractory behavioral problems in children with ASD. Sixty children with ASD (mean age was 11.8±3.5, range 5.0–17.5; 77% low functioning; 83% boys) were treated with oral CBD and tetrahydrocannabinol (THC) at a ratio of 20:1. The dose was up-titrated to effect (maximal CBD dose – 10mg/kg/d). Tolerability and efficacy were assessed using a modified Liverpool Adverse Events Profile, the Caregiver Global Impression of Change (CGIC) scale, the Home Situations Questionnaire–Autism Spectrum Disorder (HSQ-ASD) and the Autism Parenting Stress Index (APSI). Results revealed that following the cannabis treatment, behavioral outbreaks were much improved or very much improved (on the CGIC scale) in 61% of patients. The anxiety and communication problems were much or very much improved in 39% and 47% respectively. Disruptive behaviors were improved by 29% from 4.74±1.82 as recorded at baseline on the HSQ-ASD to 3.36±1.56 following the treatment.

Parents reported less stress as reflected in the APSI scores, changing by 33%[46]. In another study done in Chile, South America, the researchers expanded on preclinical studies' suggestion of a dysfunctional endocannabinoid system implicated in Autism Spectrum Disorder (ASD). 20 children and one adult patient were selected. Mean age: 9 years, 10 months (range: 26 mo-22 yo), 15 males. 66.7% of patients had significant improvement according to CGI-I and APSI. Most cases improved at least one of the core symptoms of ASD, including social communication, language, or repetitive behaviors. Additionally, sensory difficulties, food acceptance, feeding and sleep disorders, and/or seizures were improved in most cases. 71.5% of patients received balanced CBD: THC (1:1) extracts; 19.0% high-CBD (20:1); and 9.5% high-THC (1:4) extracts. Oral cannabis extracts were well tolerated. Two patients had more agitation and one had more irritability, effects that were solved by changing the strain. In this small series of ASD patients, oral cannabis extracts were dramatically more effective than conventional medicines [52].

Notice that the way the Chilean study addressed the three adverse reactions was by changing the strains that the patients were taking, therefore, it is paramount that the provider be aware of the different ratios and strains available at the local dispensaries.

A pending U.S. clinical trial, that's scheduled to start in October of 2018 and finalize in September 2021 will study the efficacy and safety of cannabidivarin (CBDV) in 100 children with ASD [53].

Commonly Used Cannabis Chemovars in Patients With Autism

Cannabis chemovars, which are commonly referred to as “strains” that are typically used for the management of patients with autism are:

- Blue Dream--A sativa-dominant hybrid and one that’s widely used among patients with autism, as well as PTSD. Many users tout Blue Dream to be the cannabis form of aspirin, which means that it should basically be in everyone’s medicine cabinet. LOL This is an excellent strain for daytime medication and can effectively suppress pain, discomfort, and all the symptoms of autism. Low doses of Blue Dream are recommended for the treatment of autism; to get the right low dose many parents turn to administering their children with tinctures of this excellent therapeutic strain [54].
- Green Crack-- Has become a household name in the medical cannabis community because of its far-reaching therapeutic benefits especially in the treatment of autism. Green Crack does wonders for the mind, and despite being an energetic strain can help relax the muscles in a way that few other strains can. This strain is a well-loved medical choice because it does not lead to a mental crash once the effects fade away, so it’s gentle enough for those with autism, allowing them to gently ease in and out of the euphoria. Patients will also appreciate that Green Crack helps put them in a more focused mood, while feeling happy, euphoric, and uplifted [54].
- Charlotte’s Web--Is a legendary medicinal strain for numerous debilitating disorders, particularly epilepsy, anxiety, and autism. This sativa strain is a strong CBD, with just an average of 3% THC which means that patients won’t get a “high” with Charlotte’s Web but it will provide the patient with all the therapeutic benefits that they need. However, take note when medicating with Charlotte’s Web; while for many cases it’s proven as an effective cure-all, some find no relief; it is best recommended to experiment with this at low to moderate doses and observe. When it does work, Charlotte’s Web has done miracles for countless cases, so it is definitely worth a try for cases of autism [54].
- Hindu Kush--This is a pure indica hailing from the mountain ranges after which it’s named after. Many patients of autism find great relief from medicating with Hindu Kush; i.e., its ability to induce a sense of calmness and tranquility is therapeutic for patients. Aside from autism, Hindu Kush is also known to be effective in treating pain, anxiety, depression, stress, and of course insomnia. Autistic patients can relax with the mellow, deep, yet euphoria it delivers. Because it’s a pure indica, Hindu Kush is recommended for medication only at night, helping autistic patients have a restful and deep slumber while helping them feel more refreshed the next day [54].

Discussion

This literature review supports the feasibility of cannabis based medicine as a promising treatment option in individuals with ASD; with significant improvements in the area of behavioral outbreaks, both disruptive and repetitive behaviors, anxiety and communication problems, i.e., social communication and language. Additionally, sensory difficulties, food acceptance, feeding and sleep disorders, and/or seizures were improved in most cases. And as a result of these positive findings, parents reported less stress as reflected in the Autism Parenting Stress Index (APSI) scores.

Conclusion

Based on the evidence regarding the endocannabinoid system and autism, together with the promising results of the two clinical trials, it is recommended that large, double blind, placebo controlled cross-over trials be launched to establish efficacy and safety of medicinal cannabis in jurisdictions where medical cannabis can be studied without limitations from the federal government.

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