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Autism Spectrum Disorder and Medical Cannabis: Review and Clinical Experience

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Autism spectrum disorder (ASD) is a multifactorial, pervasive neurodevelopmental disorder defined by the core symptoms of significant impairment in social interaction and communication as well as restricted, repetitive patterns of behavior. In addition to these core behaviors, persons with ASD frequently have associated noncore behavioral disturbance (ie, self-injury, aggression), as well as several medical comorbidities. Currently, no effective treatment exists for the core symptoms of ASD. This review reports the available preclinical and clinical data regarding the use of cannabis and cannabidiol in the treatment of core symptoms, noncore symptoms and comorbidities associated with ASD. Additionally, we describe our clinical experience working with children and young adults with ASD who have used cannabis or cannabidiol. At present, preclinical and clinical data suggest a potential for therapeutic benefit among some persons with ASD and that it is overall well tolerated. Further research is required to better identify patients who may benefit from treatment without adverse effects.
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Introduction

Autism spectrum disorder (ASD) is a multifactorial, pervasive neurodevelopmental disorder affecting 1 in 54 children in the United States, based on surveillance data obtained from a cohort born in 2016.[1] Consistently, such studies have demonstrated clear gender predominance in the condition, with males 4 times more likely to be affected than females. Data obtained from the California Department of Developmental Services, widely considered one of the most reliable long-term records of ASD prevalence trends in the United States, has demonstrated an increase in prevalence by a factor of 25 from birth year 1970 to 2012 and by as much as a factor of 1000 from birth year 1931 to 2012.[2] In the United States, the total cost per year for children (birth to 17 years of age) with ASD has been estimated between $11.5 billion and $60.9 billion (US dollars in 2011) due to a variety of direct and in-direct costs, including but not limited to medical care, special education, intensive behavioral intervention, loss of parental productivity, and out-of-home placement.[3,4] Given the rising prevalence and significant economic and social costs associated with ASD, it is critical that continued efforts be made toward better understanding the underlying etiologies and finding improved therapies for the condition.

This review reports the available preclinical and clinical data regarding the use of cannabis and cannabidiol (CBD) in the treatment of core symptoms, noncore symptoms and comorbidities associated with ASD.

DSM-V: Core Symptoms of ASD

ASD is defined by a set of criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders. The most recent edition (DSM-V) identifies the core symptoms required for the diagnosis as significant impairment in social interaction and communication as well as restricted, repetitive patterns of behavior.[5] The DSM-V further divides ASD into 3 levels, based on the degree of impairment (level 1: requiring support; level 2: requiring substantial support; level 3: requiring very substantial support). Unfortunately, very little has been done to determine the distribution of severity among those

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on the autism spectrum or if there have been changes in the distribution associated with the increase in prevalence over the last several years.

Human communication is complex with disorders being multifactorial. The impairment in communication seen in children and adults with ASD is a key point of interest given the profound effects it has on the individual, the familial support system, and greater society. Human communication can be further divided into several subcategories, including verbal, written, visual, and nonverbal/social communications. As many as 30% of children with ASD remain minimally verbal despite years of behavioral and educational intervention.[6] Additionally, many children with ASD develop deviant speech in the form of echolalia, the immediate or delayed repetition of words or phrases that someone else has said with a similar intonation.[7]

In addition to communication impairments, a core symptom of ASD is restricted, repetitive patterns of behavior. Such behavior varies significantly from individual to individual but can include stereotyped motor movements frequently referred to as self-stimulating behaviors or "stimming" (ie, hand-flapping, finger twisting), behavior involving lining up or ordering items, or preoccupation with topics of interest. While such behaviors have the potential to be disruptive based on social definitions of normalcy, they do not appear to have negative effects on exploration and learning potential in developing children.[8] In fact, they may develop into special topics of interest in adulthood, which can in turn be used as a tool to connect with others and further integrate into society.

Noncore Symptoms and Comorbidities of ASD

Within the last decade, more attention has been directed toward the comorbidities frequently associated with ASD, their impact on daily life, and the potential role they may play in further identifying the underlying etiology of ASD.[9] These can affect multiple different systems.

Neurological and Psychiatric

Epilepsy and Electroencephalography (EEG) Abnormalities: The correlation between epilepsy and ASD has long been known; however, the exact prevalence of epilepsy among children with ASD and vice versa remains unclear. Reports have varied widely, but estimate that 20%-25% of children with ASD have epilepsy.[10] Within the general population, epilepsy occurs at a higher prevalence among people with concurrent intellectual disabilities (ID). It has been estimated that between 16% and 50% of persons with ID have epilepsy.[11] Similar findings have been observed among the ASD population, which may explain the variability in estimating the prevalence of concurrent epilepsy. In particular, a meta-analysis found the pooled prevalence of epilepsy for ASD patients with ID was 21.4% vs 8% in ASD patients without ID.[12] Furthermore, people with ID are significantly more likely to have increased seizure frequency as well as epilepsy refractory to treatment with antiepileptic drugs.[13,14]

Among children with ASD, a strong discrepancy has been observed with regards to the risk of epilepsy and gender. The pooled prevalence of epilepsy in females with ASD was 34.5% vs 18.5% in males.[12] This increase in prevalence of epilepsy in females may be related to the increase in prevalence of learning disabilities also observed in females.[15] Additionally, several single-gene disorders (ie, Fragile X, tuberous sclerosis, *MECP2*-related disorder, FOXG1-related disorder) and copy number variants (ie, 16p11 deletions, 15q11-13 duplications), have been associated with both ASD and epilepsy.[10] That being said, only 10%-20% of people with ASD have known genetic anomalies, and many individuals with these genetic anomalies do not have concurrent ASD.[16]

Approximately 20% of individuals with ASD have been found to have epileptiform discharges on resting state EEG studies in the absence of clinical seizures.[17] Additionally, individuals with ASD have been found to have nonepileptiform abnormalities in resting state EEG studies, including a U-shaped pattern of electrophysiological power alterations, overall local overconnectivity, long-range under-connectivity, and enhanced power in the left hemisphere of the brain.[18] While the significance of such findings is not well understood, it provides further insight into what may be a distinct subgroup of people with ASD.

Pain and Headaches: Pain can be defined as "a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components."[19] Pain has long been a concern for families and caretakers of persons with ASD, particularly with regards to identifying its signs. This proves to be exceptionally challenging given limitations in communication and differences in sensory integration often seen in ASD. In particular, persons with ASD frequently have hyposensitivities and/or hypersensitivities, depending on the situation and involved sensory modalities.[20]

Headaches are very common with epidemiologic studies estimating that 54.4% of all children and adolescents experience headaches and 9.1% experience migraines.[21] They are diagnosed primarily by history. The majority of people suffering from headaches have no imaging or biologic markers to indicate the presence of the condition. Given the overall high prevalence and challenges in diagnosis, headaches are a frequent concern for caretakers of persons with ASD, especially for those patients with limited communication. Additionally, migraine headaches have been associated with sensory hyperreactivity and anxiety in the general population and are postulated to have similar associations and thus an overall higher frequency in persons with ASD.[22] As discussed above, pain is a known trigger for noncore behaviors of ASD, including aggression and self-injurious behavior, making the identification and appropriate treatment of pain essential in the treatment of persons with ASD.

Irritability, Aggression, and Self-injurious Behaviors: These are common, noncore symptoms associated with ASD.[23] A recent study found that of a sample of 1380 children with ASD of varying levels of severity, 56% were currently

engaged in aggressive behavior toward caregivers and 68% had demonstrated some form of aggression at some point to a caregiver. There was no association identified between the presence of aggressive behaviors and the severity of ASD symptoms, level of intellect, language or communication skills, gender, level of parental education, or parental marital status. However, previous studies have identified an association between severe core symptoms of ASD and a disruptive behaviors, including but not limited to self-injury, aggression, unusual play with objects, playing with bodily secretions, eye-poking, clothing removal, inappropriate sexual behavior, and elopement.[24]

While aggressive behaviors can be difficult to characterize, it is important to note that there are many explanations as to why they may occur, including both physiologic and social causes.[25] A single individual can demonstrate one or many forms of behavioral disturbance, with variable frequency, intensity, duration and causation. In some instances, it is possible to identify the underlying cause of the behavioral disturbance to better apply an appropriate intervention. However, this is often not the case as lack of communication and rigidity, among many other barriers, make identifying and addressing the source of the behavioral disturbance a challenge. Currently, only 2 medications, risperidone (Risperdal) and aripiprazole (Abilify), have been approved by the Food and Drug Administration (FDA) for ASD-associated behavioral disturbances in children. Many other medications, including various antidepressants, stimulants, antipsychotics, and anticonvulsants/antiepileptics, have been prescribed off-label in an attempt to better control such behaviors.[26]

Depression: Common features of depression include dysphoric mood, anhedonia, and sad affect, which can be difficult to identify in persons with ASD, especially those with limited communication. The challenges in identification may be responsible for the perceived increased prevalence of psychiatric comorbidity among persons with ASD with higher functional status when compared to those more severely affected.[27] Depression may present as increased agitation, self-injurious behaviors, and outbursts in persons with ASD.[28] As previously mentioned, there are several reasons for such behavioral disturbances, including but not limited to depression, making the diagnosis of depression in ASD challenging. Debate exists as to whether psychiatric conditions like depression should be considered a feature of ASD vs an independent symptom given the high prevalence of such conditions in persons with ASD.[29]

Nevertheless, several studies have attempted to identify and further characterized psychiatric comorbidities in ASD. In one such study, 10% of children with ASD had experienced at least one episode meeting criteria of major depression and nearly 13% of children with ASD had experienced symptoms consistent with subsyndromal symptomatic depression.[28] Other studies have supported increased frequency of comorbid psychopathology, but has varied significantly in their prevalence estimates for each condition separately.[29]

Anxiety and Obsessive Compulsive Disorder (OCD): Much like depression, anxiety can be difficult to identify in persons with ASD. Anxiety may instead present as sleep problems, self-injurious behavior, outbursts, insistence on sameness, as well as sensory hypo- or hyperresponsiveness.[30] It is estimated that approximately 40% of persons with ASD are diagnosed with at least one anxiety disorder, including social phobia (17%-30%), specific phobias (30%-44%), generalized anxiety disorder (15%-35%), separation anxiety disorder (9%-38%) and OCD (17%-37%).[31] OCD proves to be particularly challenging to identify in persons with ASD since cardinal features of ASD include the presence of restricted, repetitive patterns of behavior.

Tics and Tourette Syndrome: Tourette syndrome is a neurological disorder characterized by involuntary, repetitive, and stereotyped movements and vocalizations referred to as tics. In Tourette syndrome, tics often fluctuate in intensity, frequency, and characteristics over time. However, to meet diagnostic criteria for Tourette syndrome, patients must demonstrate multiple motor tics and at least one vocal tic for at least 1 year.[5] Similarly to ASD, onset typically occurs before the age of 7 with boys 3-5 times more likely to develop the condition.[32] Approximately 35% of children with Tourette syndrome additionally meet criteria for diagnosis with ASD. Previous studies conducted in the late 1990s have suggested an increased frequency of Tourette syndrome in children with ASD, between 6.5%-8.1%, when compared to children without ASD.[33,34] The same study found that between 24.4% and 34% of children with ASD demonstrated motor or verbal tics though not meeting their criteria for Tourette syndrome. Unfortunately, no recent studies have been conducted to further evaluate the frequency of Tourette syndrome in children with ASD, particularly as the prevalence of ASD has risen significantly over the last 20 years.

A recent study comparing children with a dual diagnosis of Tourette syndrome and ASD to children with ASD alone identified several differences, including age of diagnosis, IQ score, and pattern of behavior.[35] Interestingly, children diagnosed with both Tourette syndrome and ASD were on average 21 months older at the time of diagnosis, had an IQ score 6 points higher on average, and had more restricted and repetitive behaviors when compared to children with ASD without Tourette syndrome. Recent research has focused on identifying genetic abnormalities in children with a dual diagnosis of Tourette syndrome and ASD in the hopes of further understanding the etiologies of these 2 conditions.

Allergies and Autoimmune Conditions

Patient families and caregivers have long reported a perceived increase in the frequency of food and environmental allergies in persons with ASD. The Interactive Autism Network, a national online registry established in 2006, was created to accelerate research in the ASD field. Early survey data from the Interactive Autism Network found that more than 16% of responding families were utilizing special diets in the care of their child with ASD, with the gluten-free/casein-free diet being the most popular.[36] Other surveys have found that up to 38% of children with ASD have specific dietary interventions in place.[37]

A recent population-based, cross-sectional study found that children with ASD were significantly more likely to have food, respiratory and skin allergies (11.25%, 18.73%, and 16.81%, respectively) when compared to children without ASD (4.25%, 12.08%, and 9.84%, respectively), supporting early observations made by families and caregivers.[38] The increased frequency of allergies observed in children with ASD remained statistically significant even when adjusting for demographic and socioeconomic variables as well as other allergic conditions. Other forms of atopic disease in early childhood, including asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis, have been found to be associated with the development of ASD, with an estimated hazard ratio of 3.4.[39] Greater numbers of atopic comorbidities increase the risk of developing ASD in a dose-dependent manner. Similar findings have been observed in attention deficit hyperactivity disorder, though to a lesser extent when compared to ASD.

Gastrointestinal Symptoms

Another frequent concern of families and caregivers has been the increased frequency of comorbid gastrointestinal disorders. Survey data found that parents have identified a significant increase in prevalence of gastrointestinal symptoms, particularly constipation and diarrhea, in their children with ASD (42%) when compared to their unaffected siblings (12%).[40] Furthermore, there appears to be a correlation between the severity of core symptoms of ASD and the presence of gastrointestinal symptoms. A separate report found an increased frequency of abnormal stooling patterns, including increased number of bowel movements, increased frequency of loose stool, and bulky stools, in children with ASD and history of language regression (42%) when compared to children with ASD without history of language regression (12%).[41]

A cross-sectional study comparing children with ASD, children other developmental disabilities, and children developing typically found a significantly higher lifetime prevalence of gastrointestinal symptoms in children with ASD, supporting the findings of previous parental surveys. Approximately 70% of children with ASD had a positive history of GI symptoms, including abnormal stool pattern, frequent constipation, frequent vomiting, and frequent abdominal pain, compared to 42% in children with other developmental disorders and 28% in typically developing children. The most common gastrointestinal symptom reported was constipation, often accompanied by fecal encopresis. A recent meta-analysis again identified an increased frequency of gastrointestinal symptoms in children with ASD when compared to control groups (Odds Ratio (OR) 4.42), with constipation (OR 3.86), diarrhea (OR 3.63), and abdominal pain (OR 2.45) being the most common complaints.[42]

In multiple population-based studies, children with ASD have consistently been found to have an increased frequency of comorbid inflammatory bowel disease (IBD).[43,44] In one such study, Lee et al. identified children with ASD to be 1.67 times more likely to have IBD. Furthermore, of the patients with IBD, children with ASD were found to have higher prescription rates for second-tier biologic therapeutic agents, including adalimumab and certolizumab, suggesting children with ASD have more severe or refractory IBD when compared to children with IBD without ASD.

Gastroesophageal reflux disease (GERD) is a highly prevalent condition characterized by feelings of heartburn and frequent regurgitation, affecting between 10%-20% of people in the United States.[45] Severe forms of the condition can be very painful and can significantly affect quality of life.[46] Given the high prevalence of GERD among the general population, it is reasonable that at least similar rates of GERD exist among those with ASD. However, the nature of the symptoms can make it difficult to identify the presence of GERD in persons with ASD due to differences in sensory perception and/or limited verbal communication.

In recent years, researchers have started to investigate the role of the human microbiome in both health and disease, including neurologic and psychiatric conditions as well as immune dysregulation.[47,48] For these reasons, recent efforts have focused on better characterizing and identifying differences in the gastrointestinal microflora between persons with ASD and neurotypical controls. Findings have included a higher abundance of *Clostridium, Lactobacillus*, and *Desulfovibrio* species as well as a decreased *Bacteroidetes/Firmicutes* ratio and decreased abundance of *Prevotella, Coprococcus*, and *Veilonellaceae* species in persons with ASD.[49,50] Furthermore, the severity of core ASD symptoms as well as the presence of behavioral disturbances has been correlated in some instances to the changes observed in the gastrointestinal microflora.

Cannabis Overview

Cannabis sativa has been used for its medicinal properties for millennia, with the earliest accounts dating back to 5000 B.C.[51] It was not until 1925 that cannabis became regulated as an illicit substance when it was included in an international treaty originally intended to control the opium trade by the League of Nations.[52] In 1961, cannabis was restricted further during the United Nations Single Convention on Narcotic Drugs. A decade later, cannabis was labeled during the United Nations Convention on Psychotropic Substances as a schedule I controlled substance, reserved for drugs believed to have no accepted medical use, thus hindering research efforts. Studies over the last few decades have identified several biologically active compounds in *Cannabis sativa,* including cannabinoids, terpenoids, flavonoids, and alkaloids among others. More than 80 different cannabinoids have been isolated (Figure 1), with CBD and Δ^9-tetrahydrocannabinol (THC) being thought to have the most bioactivity and thus studied the most. In the United States, cannabis remains a federal schedule I substance, although several states have legalized cannabis for medicinal and/or recreational purposes.

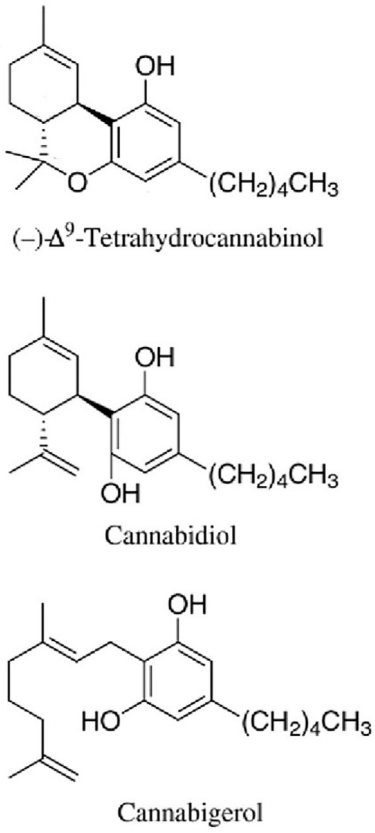

Figure 1 Chemical structures of main phytocannabinoids isolated from *Cannabis sativa:* Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabigerol (CBG).

Cannabidiol

The very first compound isolated in pure form from *Cannabis sativa* was cannabinol in 1899 by Thomas Hill Easterfield, a chemist and professor at the University at Cambridge.[53] Initially, it was wrongly assumed to be the main bioactive compound of the plant. It was not until over 40 years later that a second compound, CBD was isolated and nearly 65 years later that CBD was characterized structurally.[54,55] CBD is the second major component of *Cannabis sativa* and the most prevalent component in hemp, a nondrug variant of the plant species grown specifically for the industrial uses of its fiber. Given the lack of psychoactivity and potential for pharmacological effects, CBD has been the focus of much attention in the treatment of many conditions, including inflammatory and neurodegenerative diseases.[56]

Δ^9-Tetrahydrocannabinol

In 1964, THC was first isolated and characterized structurally.[57] It was later identified as the main component of *Cannabis sativa* as well as the most psychoactive of the cannabinoids, producing the altered sensory and time perception (the "high") sought out in recreational use of cannabis. Given its psychoactive qualities, THC has been the most difficult of the cannabinoids to investigate clinically due to regulatory and supply barriers. That being said, pharmacologic benefits of THC exist.[58] Dronabinol, a synthetic form of THC, was first approved in 1985 by the FDA for nausea and vomiting associated with cancer chemotherapy.

Cannabigerol

Cannabigerol (CBG) was first isolated and characterized structurally during the same research efforts that resulted in the identification of THC. CBG was later identified as the direct precursor of both CBD and THC.[59,60] Similarly to CBD, CBG does not have psychoactive properties.

Endogenous Cannabinoid System

The discovery of exogenous cannabinoids led to the subsequent discovery of the endocannabinoid system, responsible for modulation of many organ systems including the central and peripheral nervous systems, endocrine system, cardiovascular system, immune system, gastrointestinal tract, and reproductive system. Within the endocannabinoid system, there exist 2 primary types of cannabinoid receptors, cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2), each with unique tissue distribution and function (Table 1). Both CB1 and CB2 receptors belong to the superfamily of G-protein-coupled receptors and are bound by endocannabinoids, phytocannabinoids, or synthetic cannabinoids.[61] Endocannabinoids, like *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol, are lipid mediators derived from arachidonic acid that play an essential role in the regulation of many the physiological systems of the body. In the nervous system, endocannabinoids are synthesized on-demand and released from postsynaptic neurons, thus producing a reduction in the release of neurotransmitters.

Table 1 CBD Receptor Actions

Receptor	Action of CBD	Potential Physiological Effects
CB1	Indirect antagonist	Attenuation of psychoactive effects of THC
CB2	Indirect antagonist	Anti-inflammatory
TRP channels	Agonist, rapid desensitization	Analgesic, anti-inflammatory
5-HT1A	Agonist	Anxiolytic, analgesic
GPR55	Antagonist	Anticancer
PPARγ	Agonist	Anticancer

Adapted from White, 2019.[109]

Cannabinoid Type 1 Receptors

CB1 receptors are primarily expressed in the central nervous system, particularly in the basal ganglia, cerebellum, hippocampus, and cerebral cortex.[61] As such, activation of the CB1 receptor type has been implicated in the modulation of neurotransmitter release. CB1 receptors have also been found in peripheral tissue though at much lower concentrations.

The majority of CB1 receptors are coupled to G_i protein, which when activated result in the inhibition of adenylate cyclase thus decreasing intracellular cyclic adenosine monophosphate concentration, a second messenger, and increasing mitogen-activated protein kinase concentration.[62] CB1 receptors are also frequently coupled to G_o protein, which is the most abundant G protein within the central nervous system and regulates several cellular effectors including ion channels and enzymes allowing for cellular interpretation and response to extracellular signals.[63] In rare cases, CB1 receptors have been found coupled to G_s proteins, which alternatively stimulate adenylate cyclase.[62]

CBD has been found to have low binding affinity to the CB1 receptor. Instead, CBD has demonstrated a more significant role in allosteric modulation of the CB1 receptor, acting as an indirect antagonist, thus preventing activation of the receptor by other ligands.[64] Similarly, CBG has been found to have low affinity as a CB1 receptor antagonist.[65] On the contrary, THC acts as a potent partial agonist of the CB1 receptor, resulting in receptor activation and downstream modulation of neurotransmitter release. The effects of THC on the CB1 receptor are likely responsible for its psychoactivity.[66]

Cannabinoid Type 2 Receptors

CB2 receptors are primarily expressed in tissue involved in the immune system including spleen, tonsils, thymus, and lymphoid tissues as well as on the surface of leukocytes.[61] CB2 receptors have also been found in the pancreas, bone marrow, uterus, lung, and central nervous system at much lower concentrations. Of note, CB2 receptors are not as well understood as CB1 receptors. Given the high expression of CB2 receptors on immune-related tissues, it is thought that CB2 receptors are involved in the regulation of immune cells. Furthermore, CB2 receptor activation is thought to play an essential role in inducing immune cell apoptosis, suppressing proliferation of immune cells, suppressing production of proinflammatory cytokines, increasing production of anti-inflammatory cytokines, inducing development of regulatory T cells and promoting migration of immune cells.[67,68]

Like CB1 receptors, the majority of CB2 receptors are coupled to G_i protein.[62] In contrast to CB1 receptors, CB2 receptors have not demonstrated the ability to transduce signals through G_s proteins.[69] Activation of CB2 receptors thus primarily results in the suppression of adenylyl cyclase and subsequently downregulates the downstream signaling responses mediated by cyclic adenosine monophosphate. Additionally, activation of the CB2 receptor generally has no effect on ion channels.

Similar to its effect on CB1 receptors, CBD has been found to have low binding affinity to CB2 receptor as well as a potential role as a negative allosteric modulator.[70] THC acts as a potent partial agonist of the CB2 receptor, resulting in receptor activation and downstream modulation of the immune system.[61] CBG acts as a competitive partial agonist to CB2 receptors, inhibiting activation of the receptor by other ligands including THC.[71]

Transient Receptor Potential Channels

Transient receptor potential (TRP) channels are a superfamily of trans-membrane cation channels involved in the sensation of many chemical and physical stimuli including pain, temperature, different kinds of taste, pressure, vision, and itch.[72] As such, TRP channels are essential to many physiological and pathological processes. Within the brain, many subfamilies of TRP channels are highly expressed including TRP canonical, TRP melastatin, and TRP vanilloid (TRPV).[73] TRP channels have been found to regulate a broad array of neuronal and glial functions including developmental and homeostatic functions of the brain. Dysregulation of the TRP channel functions have been implicated in many neurologic and psychiatric disorders. In particular, TRP channel overexpression and overactivation resulting in neuronal hyperexcitability has been a topic of much research interest toward better understanding the pathophysiology and treatment of epilepsy.

TRP channels are additionally essential to the physiology and pathology of the immune system.[74] TRP channels are expressed on the surface of many immune cells, especially macrophages and T cells. Activation of such TRP channels results in modulation of immune functions including migration, phagocytic activity, as well as cytokine expression and release. Within the central nervous system, TRP channels act as sensors of immune efforts by responding to the local release of reactive oxygen and nitrogen species produced by the activation of nearby macrophages and neutrophils.

Interestingly, some TRP channels, especially TRPV1, have demonstrated rapid desensitization, rendering the channel refractory to further stimulation after it has been activated.[72] It is for this reason that topical application of capsaicin, a potent TRPV1 agonist, produces an analgesic effect.[75] Similarly, CBD and CBG have been found to activate and rapidly desensitize the TRPV1 channel.[72] On the contrary, THC has not been found to modulate the TRPV1 channel.

TRPV2 channels are also involved deeply in the inflammatory process and perception of pain.[72] Like TRPV1, the TRPV2 channels are quickly desensitized after activation. Whereas TRPV1 channels can be activated by endogenous, phytogenic, or synthetic cannabinoids, TRPV2 channels are primarily activated by phytocannabinoids, including CBD, CBG, and THC. Both CBD and CBG have been found to activate several other TRP channels including TRPV3, TRPV4, TRPA1, and TRP melastatin 8. On the contrary, THC has not been found to activate other TRP channels as of yet.

Given the significant neurologic and immunologic dysregulation seen in many persons with ASD and the clear role

TRP channels play within those systems, it is possible that a TRP channelopathy may be to blame in some persons. The presence of such TRP channelopathies has been documented in a few individuals with ASD, though its phenotypic effects are not fully understood.[76] The ability of CBD and CBG to activate and desensitize several TRP channels suggests a therapeutic potential against neuronal hyperexcitability, inflammation and chronic pain seen in many conditions, including ASD.

Other Physiological Effects of CBD

Despite recent discoveries in better understanding the endocannabinoid system, much remains unclear. Recently, CBD has been found to modulate the endocannabinoid system through other mechanisms including inhibition of the reuptake and degradation of anandamide, an endogenous cannabinoid with similar qualities to THC.[77] CBD has been found to be a partial agonist of 5-HT1A receptors, especially within areas of the brain felt to play an important role in anxiety disorders including the basal ganglia, bed nucleus of the stria terminalis, prelimbic prefrontal cortex, and dorsal raphe nucleus.[78,79]

CBD blocks an orphan G-protein-coupled receptor 55, which is present in many different forms of cancer and correlates with the aggressiveness of the malignancy.[80] CBD is thought to activate the peroxisome proliferator-activated receptor γ, important in regulation of cellular growth and differentiation and thus the development of malignancy when dysregulated.[81]

CBD acts directly and indirectly on spinal glycine receptors, particularly the $\alpha 1$ and $\alpha 3$ subunits, providing analgesia for inflammatory pain.[82,83] CBD decreases the production and release of proinflammatory cytokines, including interleukin-1β, interleukin-6, and interferon-β, from Lipopolysacchride (LPS)-activated microglial cells.[84] CBD has been found to induce functional regulatory T cells (Tregs), resulting in further immune suppressive action.[85]

In summary, CBD has exhibited anticonvulsant, anxiolytic, antitumorigenic, anti-inflammatory, and immune-regulatory actions. This in combination with the absence of psychoactive effects has made CBD the main target of many research efforts toward identifying potential therapeutic benefits.

Medical Marijuana in the United States

Legalization of Medical Marijuana

In 1996, California became the first state to approve legalization of marijuana for medical purposes through Proposition 215.[86] As of March 2019, a total of 34 states, District of Columbia, Guam, Puerto Rico, and the US Virgin Islands have approved comprehensive and publicly available medical marijuana programs.[87] Twelve additional states allow the use of "low THC, high CBD" products for medical reasons, though no standard definition exists. Additionally, 10 states and the District of Columbia allow the use of marijuana recreationally.

It is important to note that of the states that allow medicinal use but not recreational use of marijuana, there exists significant variability in the conditions and circumstances that qualify for medicinal use. Some states explicitly list ASD as a condition qualifying for medical marijuana; whereas several others are considered "autism friendly" in that their laws allow a physician to make recommendations at his or her discretion for "debilitating" conditions.

At the federal level, cannabis remains classified as a Schedule I substance under the Controlled Substances Act. In September 2018, the Drug Enforcement Administration categorized CBD separately from cannabis and other derivatives as a Schedule V substance, the least restrictive schedule of the Controlled Substances Act. The new classification of CBD as a Schedule V substance was in large part due to the FDA approval of Epidiolex, an ultrapurified CBD solution. Epidiolex was approved in June 2018 for the treatment of seizures in patients 2 years and older with Dravet or Lennox-Gastaut syndrome, 2 severe forms of epilepsy.

Parental Groups and Nonprofits

Even before legalization of medicinal marijuana, many family members and caregivers of children with ASD and other chronic medical illness expressed interest in the potential therapeutic effects of cannabis and CBD. This prompted the development of many informal groups, especially online, for family members to discuss their own experiences and share information. From here, multiple formal organizations were developed with the goal of disseminating information and advocating for policy change.

Founded in 2014, Mothers Advocating Medical Marijuana for Autism is a 501(c)(3) nonprofit organization created with the mission to "educate and empower families and caregivers to advocate for the legal use of medical cannabis for autism."[88] Also founded in 2014, CannaMoms is a 501(c)(3) nonprofit organization founded by Moriah Barnhart following her daughter's experience with cannabis while undergoing chemotherapy, "dedicated to raising awareness of and access to alternative and supplemental healthcare options for critically or chronically ill, medically complex, and special needs children."[89] Founded in 2016, Whole Plant Access 4 Autism is another organization created with the mission to "educate, and operate for, promote and support the education of, the public with respect to alternatives to traditional medicine for the treatment and management of autism."[90] The aforementioned organizations are examples of common sources of information sought out by many parents and caregivers to children with ASD considering the use of cannabis or CBD. Of note, many of these websites and organizations vary greatly in the quality and transparency of the information provided. Nonetheless, advocacy from many of these parent groups have been critical to policy changes resulting in legalization of cannabis for medicinal purposes.

CBD for Noncore Symptoms and Comorbidities of ASD

Neurological and Psychiatric

Epilepsy: Cannabis has been used as a treatment for epilepsy for millennia, but only recently have adequately powered placebo-controlled, randomized trials been conducted to fully understand the role of CBD in the treatment of seizures. Approximately 30% of patients with epilepsy have treatment resistance, associated with severe morbidity and increased mortality.[91] While any form of epilepsy can be treatment resistant, seizures associated with Dravet Syndrome, Lennox-Gastaut Syndrome, Febrile Infection-Related Epilepsy Syndrome, and Tuberous Sclerosis Complex are most frequently refractory to treatment. Several studies have found reduction in the number of seizures with treatment of CBD, so much so that GW Pharmaceuticals began development of Epidiolex, an ultrapurified CBD, mentioned above. In the phase 3 clinical trials for Epidiolex, the medication was associated with a median reduction in convulsive seizure frequency of 39% in patients with Dravet syndrome and a median reduction in drop seizure frequency of 44% in patient with Lenox Gastaut syndrome.[92,93] The medication was generally well tolerated with the most common adverse effects being somnolence, diarrhea, decreased appetite, fatigue, pyrexia, and vomiting. The approval of Epidiolex by the FDA for treatment of epilepsy has prompted continued interest in the potential therapeutic role of CBD in other conditions.

Pain: As mentioned previously, pain perception is extremely complex in both neurotypical persons and persons with ASD. Historically, medical marijuana has been used for the treatment of pain in patients with terminal illness. More recently, medical marijuana and CBD have been proposed as alternatives for the management of chronic pain. A recent systematic review and meta-analysis examining 28 randomized trials totaling 2454 patients with chronic pain found that when compared to placebo, cannabinoids were associated with a greater reduction in pain (37% vs 31%; OR 1.41, 95%; Confidence Interval (CI) 0.99-2.00).[94] Many studies have found that neuropathic and visceral pain types, classically very difficult to treat, may be more responsive to the treatment with cannabinoids.[95-97] As such, there are several ongoing efforts toward further optimization and integration of such therapies into the standards of care.[98]

Depression and Anxiety: Animals models of CBD demonstrate antianxiety and antidepressive effects.[99] In mice, CBD exerts rapid and sustained antidepressant effects, which are accompanied by significantly enhanced serotonin and glutamate levels.[100] The mechanisms of the antidepressive effects of CBD are both molecular and structural and include increased Brain Derived Neurotrophic Factor levels as well as synaptogenesis in the medial prefrontal cortex and increased neurogenesis in the hippocampus.[101] Clinical trials have not yet been conducted to confirm these findings in humans. In fact, concern exists that the opposite results may occur in humans. Recreational use of cannabis is associated with increased risk of depression and suicidal ideation.[102.] Anxiety, on the other hand, does not show statistically significant differences in cannabis users. It is worth noting, however, that these longitudinal evaluations of recreational users may not translate to CBD since recreational cannabis is very high in THC content. Furthermore, recreational users may be using cannabis to treat anxiety or depression, making this population less generalizable to patients with ASD.

Motor Tics and Tourette Syndrome: In 1988, 3 patients with Tourette Syndrome were reported to have an improvement in tics while smoking marijuana.[103] A survey of patients with Tourette Syndrome revealed a reduction or complete remission of tics in 82% of patients.[104] A single-dose prospective trial of 12 patients demonstrated an improvement in complex motor tics on self-reporting patient questionnaires and by an independent examiner.[105] A follow-up prospective study of 24 patients using 10 mg of THC over 6 weeks revealed a significant improvement in self and observer-rated scores with no decline in neuropsychological measures.[106] These improvements in motor and vocal tics may relate to a direct effect on motor function since endocannibinoid receptors exist within the striatum or may be secondary to a reduction in anxiety, which indirectly reduces tics.[107]

CBD and Gastrointestinal Symptoms

Both use of whole-plant cannabis and CBD have been anecdotally used with high frequency in patients with gastrointestinal symptoms and underlying gastrointestinal disorders, including GERD, dysmotility, emesis, abdominal pain, irritable bowel syndrome, and IBD.[108]

As mentioned previously, cannabinoids have long been used for the treatment of nausea and vomiting in chemotherapy patients with the use of Dronabinol, a synthetic form of THC. In addition to their antiemetic function, cannabinoids have been found to play an important role in gastric motility and colonic emptying.[109] In particular, cannabinoid agonists targeting the CB1 receptor have been found to delay gastric emptying especially in females and inhibit colonic motility, providing its observed therapeutic effect in patients with chronic diarrhea.[110]

GERD is the result of transient lower esophageal sphincter (LES) relaxations typically postprandially to relieve gastric pressure on the LES from gastric distension. A placebo-controlled study looking at 18 healthy volunteers found that administration of THC significantly inhibited LES relaxations postprandially on manometry.[111] These findings suggest that endocannabinoid receptors may play a role in the pathophysiology GERD and that modulation of those receptors may be therapeutic. Interestingly, a separate study found that CB1 receptor antagonists also decreased the frequency of transient LES relaxations in healthy subjects.[112]

IBD, consisting of Crohn's disease and ulcerative colitis, are chronic inflammatory conditions of the gastrointestinal tract thought to be the result of a hyperreactive immune system toward the gut microbiota and their associated products. Given the known immune modulating effects of CBD, it has been hypothesized that treatment with CBD may alleviate some of the underlying disease in these patients. Patient surveys have found that a significant number of patients with

IBD currently or have previously used marijuana for treatment of disease-related symptoms including abdominal pain, nausea, and diarrhea.[113] Interestingly, one such patient survey found that the use of cannabis for more than 6 months at any period of time for patients with Crohn's disease was a strong predictor of that patient requiring surgery (OR 5.03, 95% CI 1.45-17.46) even after correcting for demographic factors, tobacco smoking status, time since IBD diagnosis, and use of biologic therapeutic agents.[114] It is difficult to know if prolonged use of cannabis was causally associated with the increased surgical rates or if prolonged use was simply the result of patients suffering with more significant disease.

CBD and Core Symptoms of ASD

Given the anticonvulsant, anxiolytic, and anti-inflammatory properties of CBD and the observed benefits for persons with such conditions, it is reasonable to question if CBD provides benefits to persons with ASD. In the first of its kind, a study out of Israel followed 188 patients with ASD who were treated with medical cannabis between 2015 and 2017 to assess the efficacy and safety of therapy.[115] Of the 188 children, the mean age was 12.9 years, with 14 (7.4%) patients being younger than the age of 5. Mirroring the gender bias of ASD, 154 (81.9%) of patients were male. Twenty seven (14.4%) of the children had the additional diagnosis of epilepsy. Other comorbidities included attention deficit hyperactivity disorder, Tourette syndrome, Celiac disease, and anxiety disorders. Prior to initiation of treatment with cannabis, the most common symptoms were restlessness (90.4%), rage attacks (79.8%), agitation (78.7%), sleep problems (60.1%), and speech impairment (60.1%). The majority of patients received cannabis oil containing 30% CBD and 1.5% THC, applied under the tongue 3 times a day with each dose consisting of 79.5 ± 61.5 mg CBD and 4.0 ± 3.0 mg THC. Questionnaires measuring patient symptoms and global assessment were used after 6 months at which point 155 (82.4%) of patients were in active treatment. Of the 93 (60%) patients assessed after 6 months of treatment, 28 patients (30.1%) reported a significant improvement, 50 (53.7%) moderate, 6 (6.4%) slight and 8 (8.6%) had no change in their symptoms. Twenty-three patients (25.2%) experienced at least one adverse effect with the most common being restlessness (6.6%). The authors concluded that cannabis appeared to be a well-tolerated, safe and effective option to relieve symptoms, especially noncore behaviors, associated with ASD.

The research group at Shaare Zedek Medical Center followed their retrospective analysis with a prospective trial of 150 persons with ASD, ages ranging from 5 to 21 years. The trial was a double blinded, randomized, placebo-controlled trial with crossover to assess the potential therapeutic effects of cannabinoids on behavioral problems.[115] To be included, participants had moderate or greater behavioral problems as measured by a rating of greater than 4 on the Clinical Global Impression-Severity. Study arms included placebo (olive oil), whole cannabis plant extract (CBD:THC ratio of 20:1) in a 160/8.0 mg/mL olive oil-based solution, and lastly a solution of 99% pure CBD and 99% pure THC mixed at a 20:1 ratio in a 160/8.0 mg/mL olive oil-based solution. The primary endpoint of this study was the change from baseline Home Situations Questionnaire-Autism Spectrum Disorder score following treatment with whole cannabis plant extract or purified extract vs placebo. Patients were randomized to receive 1 out of 3 treatments for 12 weeks followed by crossover to another treatment for a second 12-week period. The study was completed in December 2018 with publication of the results pending.

Our Clinical Experiences

Much like other institutions, the Neurology Division at Tufts Medical Center's Floating Hospital for Children in Boston, MA has seen a growing population of patients with ASD. Parents have increasingly sought out alternative treatment options for core and noncore symptoms of ASD, including cannabis. As such, we performed a retrospective analysis within our patients with ASD who have used cannabis for either core or noncore symptoms and summarized those experiences (see Tables 2 and 3).

Our experience consists of 32 patients with a diagnosis of autism, who used cannabis-based products largely for treatment of aggression (including self-injurious behaviors) and comorbid epilepsy. All patients used either medical marijuana or hemp-based products, which were ingested orally. Within our patient group, 8 (25%) used cannabis primarily for epilepsy, 9 (26%) primarily for aggression, and 15 (44%) for a combination of both epilepsy and aggression. Among the epilepsy patients, 13 (62%) had evidence of a primary generalized epilepsy on EEG. Most of our patients had a history for developmental regression (63%), with an average age of regression of 22 months. Among the 20 patients with a history for developmental regression, 11 (55%) developed epilepsy and 18 (90%) later developed aggressive and self-injurious behaviors. The average age for the development of epilepsy was 5 years, whereas self-injury and aggression developed at 10 $^{1}/_{2}$ years of age on average. Among the 12 patients who did not have a history for developmental regression, only 2 (17%) later developed aggressive and self-injurious behaviors. This striking difference suggests that developmental regression is a risk factor for the later development of aggressive behaviors. This effectively causes a second regression with the initial regression as a toddler and the subsequent regression in preadolescence.

Overall, 20 out of 22 patients with epilepsy (91%) reported some improvement in seizure control. 12 out of 20 patients treated for aggression (60%) reported improvement. There were 4 patients who developed side-effects. These included increases in obsessive compulsive and repetitive behaviors, insomnia, and mania. No patients reported sedation; rather, the reported side-effects included only activating symptoms. Among those patients with side-effects, 3 were using a hemp-based product and 1 used a medical marijuana based oil.

Table 2 Patient Demographics

Number of Patients	32	Percentage
Male/female	22/10	69% male
Age at diagnosis of autism (months)	39 months (range 15 to 144)	
History of regression	20/32	63%
Average age of regression (months)	22 (range 12-48)	
History of epilepsy	22/32	69%
Average age of epilepsy onset (months)	62 (3 to 168)	
EEG generalized spike-wave discharges	13/21	62%
EEG focal spike-wave discharges	6/21	33%
EEG normal	2/21	10%
History of aggression/self-injurious behavior	20/32	63%
Average age of aggression/self-injurious behavior (years)	10.5 (range 4 to 16)	
CBD use primarily for epilepsy	8	25%
CBD use primarily for aggression	9	26%
CBD use for both epilepsy and aggression	15	44%
Patients with regression who later developed epilepsy	11/20	55%
Patients with regression who later developed aggression/self-injury	18/20	90%

Table 3 Response to Cannabis-Based Treatments

Patients reporting improvement in epilepsy on cannabis	20/22	91%
Patients with generalized epilepsy reporting improvement	11/13	85%
Patients with focal epilepsy reporting improvement	6/6	100%
Patients reporting improvement for aggression/self-injury	12/20	60%
Rate of adverse effects	4/32	Increases in OCD, repetitive behaviors, insomnia, mania (3 on Hemp oil, 1 on medical marijuana)

Based on our experience, cannabis-based products appear to hold promise for use in patients with ASD. The primary reasons for use in our patient population was treatment of aggressive (including self-injurious behaviors) and epilepsy. Patients were not using these products for core symptoms of ASD such as language and social development, so the response to therapy for core symptoms was not assessed in our patient population.

This preliminary, retrospective analysis demonstrated potential benefit for both epilepsy and aggression. The rates of epilepsy improvement in our cohort were higher than for current data on cannabis use in epilepsy.[92,93] This might reflect recall bias since this was a retrospective assessment, but may also suggest that patients with ASD are particularly responsive to treatment for their epilepsy with cannabis-based products. Self-injury and aggression were less responsive to treatment, but still more than half of patients reported some benefit. These results are similar to previous reports.[114]

One point of interest was the type of side-effects reported in the ASD population from cannabis-based products. The side-effects included increases in anxiety, repetitive behaviors, and manic-like symptoms. This stands in contrast to the side-effect of sedation reported in epilepsy trials for CBD[92,93] and suggest that patients with ASD may be susceptible to a different side-effect profile than other patient populations. In particular, patients with ASD may see higher rates of activating symptoms. This mirrors the side-effect of "restlessness" reported by the group at Shaare Zedek Medical Center.[114]

Conclusion

Given the rising prevalence and significant impact ASD can have, it is easy to understand why so many parents, caregivers and providers are looking for alternative interventions to provide benefits toward core behavioral, noncore behavioral, and comorbid symptoms. One such intervention has been the use of medical cannabis and more recently purified CBD. The current preclinical and clinical data suggest that the intervention has potential for therapeutic benefit among some persons with ASD and is overall well tolerated. That being said, our own clinical experience has demonstrated that while CBD can be quite beneficial, it is challenging to identify which patients will experience that benefit and which patients in turn may develop intolerable side effects.

ASD is diagnosed through the subjective evaluation of behavioral symptoms. As mentioned previously, there is good evidence that there exist multiple phenotypes that can produce the symptoms characteristic of ASD, each with its own unique etiology and likely epidemiology. This poses a unique challenge with regards to better characterizing the condition, identifying biomarkers for diagnosis, and most significantly developing targeted pharmacotherapy to address core behaviors, noncore behaviors, and associated comorbidities. With the development of future research endeavors, investigators should strongly consider using their inclusion criteria to attempt to focus in on one presumed phenotype. Additionally,

investigators should be cautious when applying results from one presumed phenotype to another. While CBD or medical cannabis may be therapeutic in persons with one phenotype of ASD, it may have opposite effects in persons with other phenotypes. Additional studies are required to better identify persons who may experience benefit with medical cannabis as well as optimization of protocols for administration including but not limited to CBD:THC ratio, use of other cannabinoids, dosages, frequency, and route of administration.

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