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Safety and Efficacy of Medical Cannabis in Autism Spectrum Disorder Compared with Commonly Used Medications

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Abstract

Objective: The objective of this study was to evaluate the safety and efficacy of medications commonly used in autism spectrum disorder (ASD) and compare this to what current research has shown regarding medical cannabis use in this population.

Methods: Searches were performed to collect information surrounding currently used medications and their safety and efficacy profiles, biologic plausibility of cannabis use for symptoms of ASD, and studies detailing cannabis' safety and efficacy profile for use in the ASD population. Results were used to compare medications to cannabis as a proposed treatment.

Results: The heterogeneity of ASD produces great difficulties in finding appropriate treatment, leading to many medication changes or treatment trials throughout a patient's life. Commonly prescribed medications display varying levels of efficacy, safety, and tolerability between patients and symptoms targeted. Some of the most common side effects cited are also considered the most troubling symptoms associated with ASD; aggression, anxiety, irritability, and a negative effect on cognition, leading many patients to discontinue use as the side effects outweigh benefits. Recent case reports and retrospective studies have displayed the potential efficacy, safety, and tolerability of cannabidiol (CBD)-rich medical cannabis use for treating both core symptoms of ASD and many comorbid symptoms such as irritability and sleep problems. Studies have also identified circulating endocannabinoids as a possible biomarker for ASD, providing another possible method of diagnosis.

Conclusions: Currently, there are no approved medications for the core symptoms of ASD and only two medications Food and Drug Administration approved for associated irritability. Prescribed medications for symptoms associated with ASD display varying levels of efficacy, safety, and tolerability among the heterogeneous ASD population. At the time of this study there are no published placebo-controlled trials of medical cannabis for ASD and the observational studies have limitations. CBD-rich medical cannabis seems to be an effective, tolerable, and relatively safe option for many symptoms associated with ASD, however, the long-term safety is unknown at this time.

Keywords: cannabinol; medical marijuana; pharmaceuticals; tetrahydrocannabinol; psychopharmacology; autism spectrum disorder

Introduction

Autism spectrum disorder (ASD), as defined by the Centers for Disease Control and Prevention (CDC), is a developmental disability that can cause significant social, communication, and behavioral challenges. Diagnostic criteria for ASD from *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-V) are as follows[1]:

- Persistent deficits in social communication and social interaction across multiple contexts, manifested by deficits in social/emotional reciprocity, nonverbal communicative behaviors, or in developing, maintaining, and understanding relationships.
- Restricted, repetitive patterns of behavior, interests, or activities, manifested by stereotyped or

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repetitive motor movements, insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior, highly restricted, fixated interests that are abnormal in intensity or focus, or hyper- or hyporeactivity to sensory input.
- Symptoms must be present in early developmental period.
- Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning.
- Disturbances are not better explained by intellectual disability or global developmental delay.

While not in the diagnostic criteria, irritability, and aggression are some of the most common and challenging symptoms. In addition to these diagnostic criteria, symptoms vary greatly between patients, ranging from minimal to profound challenges that impact daily living.[2] In addition to the symptoms listed above, most patients with ASD also suffer from comorbidities, such as attention-deficit/hyperactivity disorder (ADHD), intellectual disability, epilepsy, sleep disorders, anxiety, and many other psychiatric or medical comorbidities.[1,2] These comorbidities and the heterogeneity of ASD symptoms make it difficult to appropriately treat the disorder, leading to many medication changes or treatment trials throughout the patient's life.[3]

Current interventions focus on behavioral and educational therapies, with pharmacotherapy playing a minor role.[4] Pharmacotherapy is primarily used to address symptoms, such as irritability, aggression, hyperactivity, tantrums, rapidly changing mood, and deliberate self-injury, which lead to greater difficulties in social communication and interaction.[5]

Risperidone and aripiprazole are approved by the U.S. Food and Drug Administration (FDA) to address irritability associated with ASD.[6] Currently, no other drugs are FDA approved for use with ASD. However, many medications, such as selective serotonin reuptake inhibitors (SSRIs) and stimulants, are used off-label to address the troubling symptoms of ASD.[7] A study by Madden et al.[8] found that close to half of insured children with ASD are receiving pharmacologic interventions with stimulants, antipsychotics, and antidepressants.

In addition, many parents are seeking help through alternative methods, such as natural remedies, supplements, and chelating agents.[9] Similarly, ASD support groups and parents are looking at cannabis as a potential treatment for symptoms associated with ASD.[10] In 2019, the state of Colorado passed House Bill 19-1028, which added ASD to the list of qualifying conditions for medical cannabis and encouraged further research exploring medical cannabis as treatment of pediatric conditions, including ASD.[11]

Due in part by the rising evidence of biologic plausibility for cannabis as a possible treatment for ASD patients and the ever-increasing number of states legalizing medical cannabis use, parents and providers alike are looking at cannabis as a possible solution to the current gap in treatment options for ASD.[12,13] This review aims to evaluate the safety and efficacy of cannabis as a potential treatment for ASD and comparatively evaluate commonly used medications based on their safety and efficacy profiles in this population.

Methods

A review of current literature on the treatment of ASD symptoms with both pharmaceuticals and cannabis was conducted through Google Scholar and Medline. Any articles that included research regarding medications for ASD, the biologic plausibility surrounding cannabis and ASD, and information on the safety and efficacy of cannabis use in this population were considered. A symptom-specific approach was used in this review.

An initial search was performed to determine the amount of research currently available regarding therapeutics and cannabis for ASD. Phrases used for this search included; "Autism Spectrum Disorder," "autism," "medication," "cannabis," "marijuana," "cannabinoids," "marihuana," "hash oil," "hashish," and medical subject heading (MeSH) terms for "autistic disorder," "cannabis," "cannabinoids," "therapeutics," "marijuana smoking," and "marijuana abuse." Relevant studies cited in other articles were also included in reviews.

Subsequent searches regarding medications used for ASD were narrowed to include specific drug names for the most commonly used pharmaceuticals. Preference was given to recent randomized controlled trials (RCTs) testing the safety and efficacy of the medication for use in the ASD population, specifically children and adolescents with ASD.

Due to the paucity of research regarding cannabis use as a potential treatment for ASD, narrowing of search criteria was not necessary for this section. Animal studies and opinion articles were excluded to maintain an unbiased and relevant up-to-date review of cannabis safety and efficacy for use in the human ASD population.

Research providing insight into the biologic plausibility of cannabis use for ASD was found by searching "autism spectrum disorder" and "cannabinoids" or "cannabis" and by scanning the references of included articles about cannabis safety and efficacy for use in the ASD population. Many of these articles are based on information found through animal studies investigating the endocannabinoid system, and thus were included based on applicability of information presented.

All publications were reviewed in detail to assess the population included in the study, exposures and outcomes measured, any potential biases or limitations, and the quality of evidence provided. Quality of evidence was determined based on GRADE principles.[14] Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was referenced while conducting this review to provide a basis in constructing this report.[15]

Medications Commonly Used for ASD

Due to the diverse nature of ASD, various medications have been investigated for their effectiveness in treating ASD symptoms. Currently used medications typically target specific troubling symptoms, with irritability receiving the most coverage.[6]

As part of a national survey on treatment effectiveness for autism by Coleman et al.,[7] 505 participants rated the benefits and adverse events on 26 commonly prescribed medications. This study provides valuable information about which symptoms of ASD experience benefit from different medications and the side effect profile of those medications, allowing determination of overall effectiveness.

Due to the heterogeneity of ASD, many patients try several different medications before finding one that provides the desired relief. The survey by Coleman et al.,[7] found that 11% of children (0–12 years) with ASD had tried four or more medications and 18% of teens (13–18) had tried six or more medications. In addition, many patients experience symptom severity that cannot be managed by one medication alone and as a result are prescribed multiple medications.[3] The most commonly prescribed medications were stimulants, followed closely by antipsychotics, anticonvulsants, and SSRIs.[7] Because these medications are prescribed to target specific symptoms, this review will discuss the safety and efficacy of medications grouped by symptom.

Social interaction/communication

Deficits in social interaction and social communication are symptoms necessary to make a diagnosis of ASD according to the DSM-5. Despite this, there are currently no FDA-approved medications for addressing these symptoms. However, treatments are emerging that show some promise.

Memantine, an N-methyl-D-aspartate receptor antagonist, showed significant improvements in social interactions, reductions in stereotyped behaviors, and overall improvement on the Gilliam Autism Rating Scale in an RCT of 60 children with ASD.[16] This study tested Memantine as adjunct treatment in children 14 years of age or younger compared with a control group of ASD patients, but did not evaluate for treatment-emergent side effects. Another RCT of Memantine showed no significant side effects in the treatment group compared with placebo. However, symptom improvement was no different than placebo.[17] These trials indicate that Memantine may be a well-tolerated and safe medication to use in the ASD population, but its viability in improving symptoms remains undetermined.

Another medication with potential to improve social functioning for ASD patients is Oxytocin. Growing evidence shows that reduced oxytocinergic function may contribute to reduced social interaction and communication in ASD patients.[18] As a result of these findings, synthetic oxytocin has emerged as a possible treatment for the social deficits associated with ASD.[19] Results from RCTs show conflicting evidence for the efficacy of oxytocin to improve social challenges in these patients. A study conducted by Dadds et al.[20] found no improvement in emotion recognition, repetitive behaviors, eye contact, or quality of social interactions in a double-blind, placebo-controlled study of 38 children with ASD. Anagnostou et al.[21] found some evidence for improvements in emotion recognition and a broad measure of quality of life in adults with ASD after receiving treatment with oxytocin.

Despite mixed evidence for oxytocin's efficacy in treating social deficits of ASD, neither study found significant side effects or issues tolerating oxytocin, as compared with placebo, in adults or children.[20,21] As with Memantine, these trials indicate that oxytocin may be a well-tolerated and safe medication for ASD, but efficacy remains undetermined.

At the date this review was written, two medications, Balovaptan[22] and Bumetanide,[23] are undergoing phase 3 trials for use in patients with ASD to address core symptoms, specifically social interaction and communication. The phase 2 clinical trial of balovaptan demonstrated no significant improvement in social responsiveness when compared with placebo after

12 weeks; however, measures of communication, socialization, and daily living skills showed improvement when compared with placebo, and this relationship strengthened with higher doses.[24]

Similar results were demonstrated in the phase 2 trial for bumetanide; no significant improvement in social responsiveness when compared with placebo, however improvement was seen in the secondary measure of repetitive behaviors.[25] Balovaptan was found to have no serious side effects and was well tolerated by the study participants; however, bumetanide was found to have some adverse effects related to the diuretic effects of the medication, orthostatic hypotension, and hypokalemia, but neither affected treatment outcomes[24,25]

Repetitive behavior/interests/activities

Repetitive behaviors have been the target of most pharmacologic treatments as they are often considered to be one of the most problematic symptoms.[26] SSRIs are often prescribed for this purpose in the ASD population and numerous studies have been published. These studies present mixed results for the safety and efficacy of any SSRI to treat these symptoms.

A national survey by Coleman et al.[7] found fluoxetine and sertraline as the most commonly prescribed SSRIs, both showing a positive self-reported benefit to risk score. However, the most commonly mentioned adverse events included aggression, anxiety, irritability, and depression, which are among the most troubling ASD symptoms.

Fluoxetine was found to reduce repetitive behaviors compared with placebo in children, but had no significant effect in reducing global autism severity.[27] This study also reported no significant differences between overall frequencies of side effects experienced in the fluoxetine treatment group versus placebo. However, the treatment group did report more sedation (17.9% vs. 11.1%), agitation (46.2% vs. 44.4%), and anorexia (15.4% vs. 11.1%) than those in the placebo group. A study testing fluoxetine use in adult ASD patients found it to be effective in reducing compulsions and improving the global autism score when compared with placebo.[28] Similar to the study with fluoxetine use in children, there was no significant difference in side effects between treatment and placebo groups, although one patient receiving fluoxetine did report suicidal ideation versus none in the placebo group.[28]

A large RCT investigating the effectiveness of the SSRI citalopram in children with high levels of repetitive behavior found no difference between treatment and placebo groups for repetitive behaviors or global autism improvements.[29] Additionally, citalopram use was associated with more frequent adverse events, with 97.3% reporting at least one treatment-emergent adverse event versus 86.8% of the placebo group ($p = 0.03$).

The most common adverse events in the citalopram group were increased energy level (38.4% vs. 19.7% in placebo group), stereotypy (11.0% vs. 1.3%), impulsiveness (19.2% vs. 6.6%), decreased attention (12.3% vs. 2.6%), hyperactivity (12.3% vs. 2.6%), difficulty falling asleep (23.3% vs. 9.2%), and dry skin (12.3% vs. 1.3%).[29] Two children in the citalopram group also experienced seizures. One child required hospitalization due to prolonged seizure with loss of consciousness and continued frequent seizures despite discontinuation of treatment. The other had a history of seizures and was able to continue the trial after addition of an anticonvulsant medication.[29]

In general, SSRIs have mixed efficacy in the ASD population. Fluoxetine appears to be generally safe and effective, although many still reported adverse effects.[27] Sertraline is the other most commonly prescribed SSRI, but there are no studies available evaluating its efficacy in reducing stereotypy or improving global autism scores. Citalopram, another SSRI, appears to be no more effective than placebo and is not prescribed as often as fluoxetine or sertraline.[7]

Irritability, aggression, and agitation

Two antipsychotics, risperidone and aripiprazole, have been FDA approved to manage irritability associated with ASD.[6] While both medications have shown efficacy in this population, they also cause frequent side effects.[30–32]

Risperidone has shown significant improvements for irritability and hyperactivity in children and adolescents when compared with placebo.[33] Treatment-related adverse effects were consistent with the known risperidone profile, including increased appetite, sedation, somnolence, and increased weight.[34] Adverse events that led to discontinuation included one case of aggression in the placebo group and one case of sedation in the risperidone group.[33]

Dangerous metabolic adverse effects can occur with antipsychotics. Scahill et al.[35] examined the effects of risperidone on appetite, weight, body mass index (BMI), waist circumference, and indices associated with metabolic syndrome and insulin resistance over a 24-week period. Growth curve analysis showed an increased in BMI from pretreatment to study conclusion,

and this effect was greater for those with increased appetite in the first 8 weeks. Significant increases were also seen in glucose levels, hemoglobin A1c, insulin, homeostatic model assessment-insulin resistance, alanine aminotransferase, and leptin by week 16.[35]

Aripiprazole has shown significant improvements in caregiver-rated and clinician-rated irritability, when compared with placebo.[31] Similar to risperidone, side effects can be more common and severe than with other medications. In the Marcus et al.[31] study, 10.2% of subjects in the treatment groups discontinued aripiprazole due to adverse events, with the most common being sedation ($n=7$), drooling ($n=4$), and tremor ($n=4$). These effects were not reported in the placebo group.

A study investigating the safety and tolerability of aripiprazole in pediatric ASD patients by Robb et al.[5] found most adverse events to be mild to moderate in severity, occurring early in treatment, and generally, other than weight gain, resolving with time. The most common adverse events seen in the aripiprazole group versus placebo included sedation (20.8% vs. 4.0%), fatigue (16.5% vs. 2.0%), vomiting (13.7% vs. 6.9%), increased appetite (12.7% vs. 6.9%), tremor (9.9% vs. 0.0%), and weight gain (mean 1.6 kg vs. 0.4 kg).

Some anticonvulsant medications have been found to be effective in treating irritability in children with ASD. Based on caregiver and clinician-rated scales, valproic acid (Depakote) was found to improve irritability compared with placebo.[36] The study was not sufficiently powered to identify side effects of treatment versus placebo.

Oxcarbazepine is another anticonvulsant prescribed to ASD patients to treat irritability.[7] A retrospective study by Douglas et al.[37] found that 47% of participants experienced improvements according to a clinician-rated irritability scale. However, many adverse events were observed, with 23% of patients stopping treatment as a result. These ranged from worsened irritability in four cases to hyponatremia and seizures in one case. Many ASD patients have comorbid epilepsy, thus drugs such as Depakote or oxcarbazepine are used to treat both irritability and seizures.[3] This will be discussed in greater detail in Seizures section.

Hyperactivity, attention, and cognition

ADHD symptoms are prevalent in children and adolescents with ASD and contribute to significant functional challenges.[6] Stimulants are often prescribed as they have been found to be effective in treating hyperactivity and impaired attention and cognition in the general population. However, more side effects and lower efficacy are seen in the ASD population compared with neurotypical youth with ADHD.[6,7]

A meta-analysis of data from four studies evaluating high-dose methylphenidate (stimulant) use in the ASD population found significant reductions in hyperactivity and inattention.[38] An additional RCT of methylphenidate versus placebo similarly displayed improvement of hyperactivity with medium and high doses.[39] Reported side effects were minimal, with the only significant difference between treatment and placebo being reduced appetite and insomnia.[38] However, the results of a national survey report high rates of methylphenidate side effects, including aggression, irritability, reduced appetite, and sleep problems.[7]

Another medication often prescribed to ASD patients for hyperactivity and attention deficit is atomoxetine (selective norepinephrine reuptake inhibitor). In a study by Harfterkamp et al.[40] improvements in hyperactivity and inattention were shown to be significant ($p<0.001$), when compared with placebo, in children with ASD receiving treatment with atomoxetine. Adverse events seen more by the atomoxetine treatment group as compared with placebo were nausea (29.2% vs. 8.2%), decreased appetite (27.1% vs. 6.1%), and early morning awakening (10.4% vs. 0.0%). Additionally, one patient in the atomoxetine group discontinued treatment due to fatigue versus none in the placebo group. These results are similar to another study evaluating atomoxetine use in the ASD population, which specified benefits as improvement of hyperactivity and inattention and side effects as irritability, nausea, and fatigue.[41]

Guanfacine (alpha2A-adrenergic receptor agonist) was FDA approved in 2009 to treat ADHD in the general population for ages 6–17 and has been prescribed to ASD patients for hyperactivity and inattention as well.[42] Guanfacine has been shown to be superior to placebo for both caregiver-rated and clinician-rated hyperactivity ($p<0.001$).[43] However, guanfacine was found to cause more frequent adverse events when compared with placebo: drowsiness (86.7% vs. 9.4%), fatigue (63.3% vs. 9.4%), decreased appetite (43.3% vs. 6.3%), irritability (36.7% vs. 9.4%), anxiety (30% vs. 3.1%), and mid-sleep awakening (30% vs. 6.3%). One serious adverse event was reported. A patient in the treatment group became verbally and physically aggressive, requiring police involvement, subsequent inpatient psychiatric hospitalization, and discontinuation of guanfacine treatment.[43]

Seizures

Currently the FDA[44] has approved one cannabis-derived pharmaceutical for use in the pediatric population. Epidiolex is a cannabidiol (CBD)-derived oral solution for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome, two rare and severe forms of epilepsy. The prevalence of comorbid epilepsy is ~12% in childhood and 26% in adolescence in ASD patients.[45] The pathophysiology of both ASD and epilepsy share several synaptic plasticity pathways.[46] Although not FDA approved to address such symptoms, many antiepileptic drugs are prescribed for irritability or emotional regulation in ASD, due to their stabilizing and sedative properties.

In a 2009 survey conducted by the Autism Research Institute,[47] the antiepileptic drugs (AEDs) Depakote and carbamazepine showed net benefits for both seizures and behavioral symptoms. In contrast, adverse side effects outweighed benefit for the AEDs, clonazepam and diazepam. Similarly, a review of seizure medications for the ASD population found Depakote to be effective for both seizures and behavioral symptoms, whereas carbamazepine, clonazepam, and lamotrigine effective for seizures only.[48] The anticonvulsant oxcarbazepine and antiseizure medication, gabapentin, were both minimally effective for seizures, with no benefit for behavioral symptoms.

Sleep problems and anxiety

Sleep problems and anxiety are common comorbid diagnoses in the ASD population, appearing in 50–80% and 42–56%, respectively.[4] Common management techniques for sleep often focus on nonpharmacologic methods, such as establishing bedtime routines and promoting positive sleep patterns for young children.[49] Melatonin has been used as a pharmacologic option. A study by Andersen et al.[50] found eradication of sleep problems in 25%, improved sleep in 60%, and no change in 13% of 107 children with ASD using melatonin. Of note, only three children experienced side effects, morning sleepiness, and increased enuresis, and no patients experienced increased or new-onset seizures.

In support of these findings, a meta-analysis of 18 studies measuring melatonin use in the ASD population by Rossignol and Frye[51] found significant improvements in sleep duration and sleep onset latency when compared with placebo. Additionally, a 2019 systematic review of drug interventions for sleep disorders in children with ASD found melatonin to significantly improve sleep latency, total sleep time, reduced insomnia symptoms, and was a safe long-term treatment option for children with ASD and insomnia.[52]

Anxiety symptoms are typically managed by SSRIs in the ASD population with varying efficacy and sometimes with concerning side effects such as increased anxiety and agitation.[7] A study by Thorkelson et al.[53] measured the effect of monotherapy with the SSRIs sertraline, citalopram, or fluoxetine specifically for improvement of anxiety in 29 ASD children and adolescents. Overall, 55.2% of patients experienced improvement of symptoms after 7–12 months on the same SSRI and 13.8% experienced no change or worsening of anxiety symptoms. Seven patients reported treatment-related side effects of vivid dreams, increased emotional lability, and irritability, and four patients discontinued treatment before study conclusion.[53]

Biologic Plausibility of Cannabis as a Treatment Option for ASD

Currently, we do not possess a clear understanding of the fundamental pathophysiology or etiology of ASD. Although progress has been made identifying genetic or environmental factors, difficulties still remain surrounding development or investigation of possible treatments.[54] However, recent studies have shown a link between ASD and the endocannabinoid system.[55–57] The endocannabinoid system comprises lipid neuromodulators produced in the body, and their cellular receptors. These endogenous cannabinoids (eCBs) regulate synaptic transmission in nerve cells and play an important role in many behavioral functions.[56]

Cannabis produces physiologic effects mainly through action by Δ9-tetrahydrocannabinol (THC) and CBD at the same receptors as eCBs, cannabinoid type 1 receptor (CB1R).[58] More specifically, THC has high affinity at CB1R, whereas CBD is an allosteric modulator of CB1R, potentially decreasing the effects of CB1R agonists such as THC, and inhibits the enzyme fatty acid amide hydrolase (FAAH) leading to increased levels of eCBs and eCB-like molecules; anandamide (AEA), n-palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA).[59,60]

Studies have shown links between the endocannabinoid system and ASD-specific symptoms. Karhson et al.[60] proposed a role for dysregulated cannabinoid signaling in the pathophysiology of the social functioning deficits seen in many brain disorders, including ASD. Supporting this, several animal studies have demonstrated improvements in social functioning through

enhanced AEA signaling by inhibition of its breakdown and increased action at CB1R.[55,61] Additionally, FAAH breaks down AEA (and structurally related compounds, PEA and OEA) leading to decreased concentrations at CB1R and CB2R; while inhibiting FAAH increases levels of AEA, suggesting FAAH may be a novel therapeutic target for ASD.[55]

Karhson et al.[56] conducted the first study to translate these preclinical findings into useful information for human ASD patients. They found that AEA concentrations were lower in the ASD population than in a control population of neurotypical children. A twofold increase in AEA corresponded with a fourfold decrease in the likelihood of ASD. In support of these findings, a 2019 study by Aran et al.[57] found that serum levels of AEA, PEA, and OEA were lower in children with ASD compared with an age, gender, and BMI-matched control group. Furthermore, AEA levels were not statistically associated with age, gender, BMI, medications, or ADHD status, but remained independently associated with ASD status.[57]

These findings suggest low circulating eCBs as a possible biomarker for ASD, providing a potential method for earlier diagnosis. This is of great significance due to the heterogeneity of the disorder and the importance of early behavioral intervention in improving long-term outcomes.[1,57]

In addition, some studies have shown an association between cannabinoids in the neurotypical population and sleep and anxiety. Endocannabinoids have been found to exhibit a circadian rhythm, implicating their association with sleep.[62] A study by Nicholson et al.[63] found cannabinoids to have varying benefits on sleep for neurotypical patients and rarely adverse clinical effects related to sleep. Additionally, various studies have shown improvement of sleep problems with the use of cannabinoids for patients with chronic pain.[64–66] The eCB system has been implicated to mediate anxiety through CBD action at CB1R in the brain.[67] A supportive study, which used CBD for social anxiety disorder, demonstrated improvements in anxiety, cognitive impairment, and discomfort during simulated public speaking.[68]

Cannabis and ASD

Therapeutic effects

As of the date this review was written, there has been one proof-of-concept randomized trial by Aran et al.[69] showing that a 20:1 CBD:THC cannabis product is well tolerated for 3 months in ASD patients. There is also another randomized double-blind clinical trial studying the efficacy and safety of cannabidivarin in children with ASD (https://clinicaltrials.gov/ct2/show/NCT03202303). All other evidence provided about this topic comes from the limited number of existing cohort studies; primarily four studies which had a treatment group, but no comparative control group. These studies all measured response to CBD-rich medical cannabis in diagnosed ASD patients for various categories of symptoms, comorbidities, and side effects.

Aran et al.[70] performed a retrospective study assessing the efficacy and safety of CBD-rich cannabis in 60 children with ASD and severe behavioral concerns. These patients received sublingual oil of whole plant extracts containing CBD and THC in a 20:1 ratio for 7–13 months. Anxiety was "very much improved" or "much improved" in 39% of patients, communication was "very much improved" or "much improved" in 47% of patients, and behavioral problems were "very much improved" or "much improved" in 61% of patients. This study did not evaluate cannabis' effects on sleep problems or seizures.

A prospective study by Bar-Lev Schleider et al.[71] measured response to 20:1, CBD:THC medical cannabis in 93 ASD patients specifically for improvement of agitation and common comorbid symptoms of ASD after 6 months of use. Improvement with outbursts and agitation was reported in 90.3% and 85.2% of participants, respectively. However, 9.5% and 14.7% saw no change or worsening of symptoms, respectively. Positive mood was also found to be improved from 42% of patients at baseline, to 63.5% after receiving treatment.

This study also measured changes in comorbid symptoms of ASD: hyperactivity/restlessness, cognition, attention, seizures, sleep problems, and anxiety. At study commencement, 90.4% of patients reported issues with restlessness, 48.4% reported issues with cognitive impairment, and 0.0% reported good concentration with daily tasks.[71] After 6 months of treatment, 91.0% experienced improvement of restlessness, 27.2% saw improvement in cognition, and 14.0% reported at least good concentration on daily tasks. Overall, 84.6% of patients with comorbid seizures experienced improvement and 15.3% experienced complete symptom disappearance after treatment with CBD-rich medical cannabis. Sleep problems were also measured, showing improvement in 78.3% of patients, where 19.5% had complete symptom disappearance. Anxiety showed improvement in 88.8% of patients, while 11.1% experienced no change or worsened anxiety.

A prospective study by Barchel et al.,[72] also using 20:1 CBD:THC medical cannabis, compared outcomes in 53 ASD patients with outcomes seen with commonly used pharmaceuticals. This study focused on comorbid symptoms, such as outbursts/self-injury, hyperactivity, sleep problems, and anxiety.

Outbursts and self-injury were experienced by 34 patients at study initiation and were found to be improved in 67.6%, no change in 23.5%, and worsened in 8.8% with CBD-rich cannabis. These results were compared with those of aripiprazole seen in the study by Marcus et al.[31] Cannabis showed greater improvement in outbursts and self-injury than aripiprazole and there was no difference in worsening effects.[72] Of the 38 children with hyperactivity symptoms, 68.4% saw improvement after receiving treatment and 2.6% saw worsening of symptoms. This improvement was on par with traditional treatment with methylphenidate according to a study by Handen et al.[73]

Additionally, the study on CBD-rich cannabis found that 71.4% of patients experienced improved sleep, 23.8% saw no change, and one patient had worsened symptoms.[72] This was not statistically different from outcomes seen with melatonin use ($p=0.400$). Anxiety improved with cannabis use in 47.1% of the 17 patients who had anxiety at study initiation. This was not statistically different from improvements seen with SSRIs ($p=0.232$).

The fourth study by Fleury-Teixeira et al.[74] observed response to using 75:1 CBD:THC cannabis extract in 18 children with ASD for 9 months. Results were collected monthly through guardians or caretakers completing questionnaires on the estimated severity of eight symptom categories: ADHD symptoms, behavioral disorders, motor deficits, autonomy deficits, communication and social interaction deficits, cognitive deficits, sleep disorders, and seizures. Of the 15 patients that completed the treatment plan, 60% of patients saw improvements of 20% or more in ADHD symptoms, motor deficits, communication and social interaction, behavioral disorders, sleep disorders, and seizures. The most significant improvements were seen in ADHD symptoms, sleep disorders, and seizures, with 80% of participants having improvements equal or greater than 30%.[74]

Of note, a number of patients in these studies stopped using other medications. In the study by Aran et al.,[70] 49 children were using medications and cannabis concomitantly at the beginning. However, by study conclusion, 33% had lowered the dose of their medications, 24% completely discontinued medications, and only 8% increased dose of medications. Similarly, Bar-Lev Schleider et al.[71] reported that of the 67 patients who were taking medications at onset of the study, 34.3% decreased or stopped concomitant medication use and only 8.9% received higher doses of medications after introduction of cannabis. Of the 10 patients taking neuropsychiatric medications at study onset for Fleury-Teixeira et al.,[74] 8 patients were able to decrease or discontinue use of these medications. Barchel et al.[72] did not report concomitant medication use or discontinuation of medications.

Side effects

As with the other commonly prescribed medications for ASD, it is important to mention side effects experienced during treatment with medical cannabis. Aran et al.[70] found sleep disturbances resulting from hypervigilance in 14% of patients as the most common side effect. However, these symptoms resolved in most patients by altering the evening dose given. Other common side effects were restlessness, nervousness, and loss of appetite, all seen in 9% of patients.

Results from Bar-Lev Schleider et al.[71] showed similar results, with the most common side effect being restlessness in 6.6% of patients and somnolence, psychoactive effect, and increased appetite appearing in 3.2% of patients each. Barchel et al.[72] found the most reported side effects being somnolence in 22.6% of patients and changes in appetite in 18.9%. Finally, Fleury-Teixeira et al.[74] reported sleepiness and moderate irritability as the most common adverse effect experienced in three patients.

Other important measures include the number of patients who maintained treatment with medical cannabis, the number that discontinued use, and their reasoning. Retention rates in all studies were high with 73% of patients still using medical cannabis in the study by Aran et al.,[70] 86.6% in the study by Bar-Lev Schleider et al.,[71] and 83.3% in the study by Fleury-Teixeira et al.[74] The most commonly cited reason for discontinuing treatment was low efficacy, followed closely by side effects.[70–72]

According to Aran et al.,[70] 16 children (27%) stopped treatment for the following reasons: a combination of low efficacy and side effects ($n=7$), low efficacy ($n=5$), irritability when beginning treatment ($n=2$), unsuccessful administration of treatment ($n=1$), and transient psychotic event ($n=1$). Bar-Lev Schleider et al.[71] cited 23 patients discontinuing treatment. Seventeen provided explanation for discontinuation: 12

discontinued due to low efficacy and 5 due to side effects. However, seven patients stated they intended to return to the treatment. The Barchel et al.[72] study lost five families to follow-up. Two stopped treatment because of low efficacy, two continued treatment but changed their medical cannabis provider, and one patient's license for medical cannabis expired. Across all three studies, only one serious adverse event led to discontinuation of medical cannabis, the transient psychotic episode in an adolescent girl.[70]

Risks of Cannabis Use

Youth

Cannabis use among adolescents and children remains controversial due to possible physical and mental health consequences, especially as children are still developing.[75] Of importance to the ASD population are investigations on cannabis' effects on cognition and psychosis as these are the main risks studied regarding cannabis use in youth. Typically, this implies the use of recreational cannabis, which is traditionally high THC with very low CBD levels, in contrast to studies in the ASD population, which typically use high CBD, low THC products.

Evidence has shown clear acute cognitive effects after recreational cannabis use. However, a more relevant outcome of interest is the residual cognitive effects. Several studies have found an association between adolescent recreational cannabis use and cognitive and academic impairment lasting up to 28 days after last use.[76–78] Findings have indicated a potential linear relationship between the frequency of recreational cannabis use and performance on cognitive function tests; showing adolescents with higher lifetime use scoring lower. However, a recent meta-analysis by Scott et al.[75] found no significant difference in cognitive function between recreational cannabis users and nonusers after an abstinence period of at least 72 h since last use ($d = -0.08$, 95% CI -0.22 to 0.07; $p = 0.29$).

Current research has provided substantial evidence that adolescents who use cannabis daily or near-daily are more likely to develop future psychotic disorders than nonusers.[79–81] In a longitudinal cohort study of over 6000 participants, 5 or more instances of cannabis use by age 15–16 was associated with greater odds of psychotic disorder by age 30 (adj OR 3.02, 95% CI 1.14 to 7.98).[80] Research has also displayed evidence that adolescent cannabis users are more likely than nonusers to develop future psychotic symptoms, and this increases with more frequent use and is directly related to THC concentration.[79,82,83] However, it remains unclear how cannabis may interact with other risk factors for psychosis, particularly within the ASD population.

Adult

Research has failed to show an association between less-than-weekly cannabis use in adults and psychotic symptoms or disorders.[84] However, substantial evidence has been found indicating that THC intoxication in adults can cause acute psychotic symptoms, following a positive linear correlation with higher doses.[85,86] A study by Di Forti et al.[87] found that individuals who smoked every day had 3.04 (95% CI 1.91 to 7.76) greater odds of having first episode psychosis compared with those who had never used cannabis.

Research has not shown long-term cognitive impairment in adults associated with cannabis use. A meta-analysis found neurocognitive performance in cannabis users to be no different than nonusers after 28 days of abstinence.[88]

Discussion

Diagnostic criteria for ASD have been established, yet difficulties still remain when diagnosing and appropriately treating patients due to the heterogeneity of the disorder. Patients can present with great variability in core symptom severity along with many common comorbidities, such as epilepsy, sleep disorders, ADHD, intellectual disability, and many other psychiatric or medical comorbidities. The heterogeneity of ASD produces great difficulties in appropriately treating this disorder, leading to many medication changes or treatment trials throughout the patient's life.

Currently, only two medications are FDA approved for use in the ASD population, risperidone and aripiprazole, to target comorbid irritability, yet numerous other medications are commonly prescribed in an attempt to control core symptoms or common comorbid symptoms associated with ASD. Common medications have varying levels of efficacy, safety, and tolerability between patients. Social deficits are one of the diagnostic symptoms of ASD. Medications currently prescribed to manage these challenges, Memantine and oxytocin, show mixed results, but appear safe and tolerable.

Another component of symptoms necessary for diagnosis are repetitive behaviors, interests, or activities, which are typically targeted by SSRIs. However, mixed results from various trials indicate that SSRIs have questionable tolerability and safety for use by children or adolescents. Some of the most common side effects cited are

also considered the most troubling symptoms associated with ASD: aggression, anxiety, irritability, depression, weight gain, and negative effects on cognition.

Stimulants are often prescribed to treat comorbid hyperactivity, inattention, and deficits in cognition. While often effective, efficacy and tolerability appear lower in the ASD population than in neurotypical youth. Antipsychotics have proven effective for irritability associated with ASD, however, their safety and tolerability remain questionable, with many patients discontinuing use as side effects often outweigh benefits.

Finally, many patients are prescribed anticonvulsant medications due to the high prevalence of comorbid seizures and in an attempt to control irritability and aggression associated with ASD. Although effective for seizures, benefits regarding behavioral symptoms are mixed. Valproate, however, was uniquely effective for both. Due to the heterogeneity of ASD and the massive variability of medication efficacy in this population, there still remains no proven treatment option for the core symptoms. Additionally, many medications induce side effects that outweigh benefits, and in some cases, perpetuate the most concerning ASD symptoms, such as irritability and aggression.

Recent cohort studies have displayed the potential efficacy, safety, and tolerability of CBD-rich medical cannabis use for treating both core symptoms of ASD and many comorbid symptoms, such as irritability and sleep problems. In support of these findings, some studies have suggested a biologic plausibility behind cannabis due to interactions with the endocannabinoid system. These studies have shown CBD acting as an allosteric modulator to CB1R and inhibiting breakdown of eCBs, which have been found in lower concentrations in the ASD population. Additionally, CBD has been shown to exert its effects in neuropsychiatric disorders through non-CB1 receptors, such as serotonin 5-HT1A, glycine $\alpha 3$ and $\alpha 1$, TRPA1, TRPV1, GPR55, GABAA, PPARγ, and by inhibiting adenosine reuptake.[89–92]

Circulating eCBs have also been identified as a possible biomarker for ASD, providing a possible new method of diagnosis, which would improve long-term outcomes as patients could be identified at a younger age. Further support of CBDs potential in ASD patients can be found in three randomized placebo-controlled trials measuring the effect of CBD on brain connectivity and excitation and inhibition systems through magnetic resonance spectroscopy in adults with and without ASD.[93–95]

Results displayed CBD significantly altered functional connectivity in brain regions implicated in ASD, with no significant change in the control population.[93] More specifically, CBD altered excitatory glutamate response in ASD and control participants, but only altered inhibitory GABA pathways in ASD participants.[94] These findings suggest a theoretical pathophysiological mechanism for CBD as a possible treatment option for ASD and support the rationale for current, ongoing clinical trials of cannabis use in the ASD population.[70]

With the increased interest in medical cannabis among the ASD population, more patients or their caretakers will likely seek advice from physicians. However, an Association of American Medical Colleges (AAMC) survey found 75% of medical school dean's reporting that graduates are either slightly prepared or not at all prepared to answer patients' questions about medical cannabis.[96]

Additionally, current recommendations from American Academy of Pediatrics (AAP) on complementary health approaches (such as medical cannabis) are to monitor use with questionable effectiveness and discourage use in those with proven health risks.[97] Specifically regarding cannabis, the AAP opposes medical cannabis use for children, except in situations "that pertain to emerging anecdotal information concerning the medical potential of cannabinoid medications, which may be an option for children who have life-limiting or severely debilitating conditions and for whom current therapies are inadequate."[98]

These recommendations are difficult to interpret and it could be argued that ASD can be life limiting and severely debilitating for some patients. Hopefully with completion of RCTs and continued reports displaying efficacy and tolerability of medical cannabis as a treatment option for ASD, more physicians will feel prepared to discuss cannabis with, and possibly implement as a treatment choice for, their patients.

Of concern is the safety of medical cannabis use among children with ASD. Current studies have shown cognitive impairment and possible psychotic symptoms resulting from recreational cannabis use during childhood or adolescence; however, the magnitude of effect remains questionable. THC has been determined to cause acute psychotic symptoms, whereas CBD has been shown to have no psychoactive properties and to inhibit the psychotomimetic effects of THC.[59,85] It is imperative to note that currently, recreational cannabis products are not regulated based on THC to CBD ratios, unlike the compounds that have been used in current ASD medical cannabis research, which often contain a 20:1 ratio of CBD to THC.

As with current treatment options for ASD patients, providers must take into consideration the patient's history, severity of symptoms, and the established safety and efficacy behind any treatment being considered. However, CBD-rich medical cannabis has shown to be a relatively safe and well-tolerated option to relieve several behavioral and comorbid symptoms of ASD, such as seizures, sleep problems, and irritability. Taking into consideration the risks associated with adolescent recreational cannabis use and the possible efficacy of medical cannabis for the ASD population, as suggested by uncontrolled case series, the benefits may outweigh the risks for many patients.

This review has several limitations. Searches performed were restricted to English-language publications accessed through PubMed, PubMed Central, or Google Scholar. Many studies included regarding commonly used medications only tested for certain side effects or benefits, limiting generalizability to the broader ASD population. All studies included regarding medical cannabis were cohort studies or reports, limiting the strength of conclusions made. Additionally, participation bias may be present regarding medical cannabis use as those in support may be more inclined to participate.

Conclusions

Due to the heterogeneity of ASD, difficulties remain surrounding effective treatment, with many options available, varying in efficacy and safety depending on the symptoms targeted and patient themselves. Some of the most commonly prescribed medications show a risk of side effects and potential to perpetuate troubling symptoms of ASD, like irritability.

Recent studies have found links between the endocannabinoid system and symptoms of ASD, establishing a potential role as a biological marker for ASD and as a target for treatment of ASD symptoms. Furthermore, biologic plausibility for CBD-rich cannabis as an effective and tolerable treatment option for ASD patients has been recently suggested by several reports and studies, however, no completed placebo-controlled studies support this. However, as with other treatments for ASD, cannabis has shown a variation in its effects between different symptoms and patients, so its use may not be recommended for everyone and should be monitored closely by a physician.

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Abbreviations Used

AAMC = Association of American Medical Colleges
AAP = American Academy of Pediatrics
ADHD = attention-deficit/hyperactivity disorder
AEA = anandamide
AEDs = antiepileptic drugs
ASD = Autism Spectrum Disorder
BMI = body mass index
CB1R = cannabinoid type 1 receptor
CBD = cannabidiol
CI = confidence interval
DSM-V = Diagnostic and Statistical Manual of Mental Disorders, fifth edition
eCBs = endogenous cannabinoids
FAAH = fatty acid amide hydrolase
FDA = Food and Drug Administration
MeSH = medical subject heading
OEA = N-oleoylethanolamine
OR = odds ratio
PEA = n-palmitoylethanolamine
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT = randomized controlled trial
SSRIs = selective serotonin reuptake inhibitors
THC = Δ9-tetrahydrocannabinol