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Cannabis Treatment of Autism in Children: A Literature Review

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N695 Alternate Plan Paper

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Abstract

Objectives: This literature review aims to summarize the effects of medical cannabis use in children on Autism Spectrum Disorder (ASD) symptoms, side effects and provide recommendations for practice, education, and research. **Background**: ASD is characterized by core behaviors of significant impairment in social communication and interaction and restricted and repetitive patterns of behavior, interests, or activities (APA, 2013). In addition to these core behaviors, individuals with ASD often have noncore behavioral disorders and several medical comorbidities. Treatment for ASD symptoms includes Cognitive Behavioral Therapy (CBT), aripiprazole (Abilify) and/or risperidone (Risperdal). As of this review, 14 states have added ASD as a qualifying condition in their medical cannabis program. **Methods**: Key terms related to the clinical question were entered into eight different databases to search for studies on cannabis use in children with ASD. **Findings**: The findings suggest improvement in ASD symptoms, such as social communication (core symptom), noncore behaviors (self-injury, restlessness, rage attacks, agitation, aggressiveness, irritability), and comorbid conditions (anxiety, epilepsy, sleep problems/dysregulation, ADHD/hyperactivity/concentration). An additional benefit with the improvement in comorbid conditions is the reduction of medications used in some participants. Common side effects include sleep disturbance, somnolence, and decreased appetite, restlessness, and a single episode of psychosis requiring treatment. These studies' positive outcomes warrant the use of cannabis as an adjunct treatment in children and provide the impetus for further research studies with large randomized controlled trials to provide higher evidence literature to support the treatment of ASD symptoms with cannabis.

Limited Studies on Cannabis Treatment of Autism in Children: A Literature Review

Cannabis was first legalized for medical use in 1996 when California passed Proposition 215 (National Conference of State Legislatures [NCSL], 2021). Since then, 35 states, the District of Columbia, Guam, Puerto Rico, and the U.S. Virgin Islands, have enacted similar laws (NCSL, 2021). Medical cannabis use is limited to qualifying conditions established by each state/territory, resulting in differing qualifying conditions (Boehnke et al., 2019). As of this review, autism is a qualifying condition for medical cannabis in 14 states (Colorado, Delaware, Georgia, Illinois, Iowa, Louisiana, Michigan, Minnesota, Missouri, New Mexico, Pennsylvania, Rhode Island, Texas, Utah) and the Territory of Puerto Rico (Mothers Advocating Medical Marijuana for Autism [MAMMA], n.d.).

The literature has established the human endocannabinoid system (ECS) as a significant regulator of multiple functions in the brain and throughout the body (Blessing et al., 2015; Chakrabarti et al., 2015; Meyer et al., 2018; Zou & Kumar, 2018). The ECS regulates emotional behaviors (Blessing et al., 2015), stress, fear, anxiety (Blessing et al., 2015; Meyer et al., 2018), behavior reactivity to context, social interaction (Chakrabarti et al., 2015), learning, memory, cognition, appetite, reward and addiction, sleep, immunity modulation, pain (Brigida et al., 2017; Chakrabarti et al., 2015; Zou & Kumar, 2018) and many other functions. Rodent models have demonstrated that alterations in the ECS produced ASD-like symptoms (Zamberlettie et al., 2017; Wei et al., 2016) such as "attention and working memory deficits, hyperactivity, repetitive behaviors, anxiety-related phenotypes, altered social behaviors, and increases susceptibility to audiogenic seizures" (Zamberlettie et al., 2017, p. 3). Modulation of the ECS in these rodent models improved behavioral deficits, anxiety (Blessings et al., 2015) and promoted social behaviors (Brigida et al., 2017; Zamberlettie et al., 2017; Wei et al., 2016). The results from

these rodent studies and the established literature on the ECS make the use of exogenous

phytocannabinoids, such as cannabidiol (CBD) and Delta (9)-tetrahydrocannabinol (THC),

appealing treatment options for Autism Spectrum Disorder (ASD) symptoms.

The safety of early-onset and long-term use of exogenous cannabinoids on the developing

adolescent brain is unclear. This is primarily due to conflicting evidence (Burnett, 2016; Jacobus

& Tapert, 2014; Lubman et al., 2015). Some studies suggest that adolescents frequently exposed

to cannabis are at risk for cognitive impairment and increased risk of psychosis (Burnett, 2016;

Lubman et al., 2015). Other studies report that cognitive impairment fully recovers after

prolonged abstinence (Fried et al., 2005; Lubman et al., 2015). Teichner et al. (2000) reported no

relationship between marijuana use severity and cognitive performance among cognitively

impaired and unimpaired adolescents. The cognitive effects of cannabis on the developing brain

are uncertain, due to the inconsistent reports. The ECS is a critical regulator in normal brain

remodeling during adolescence (Lubman et al., 2015). Evidence indicates structural changes

from prolonged cannabis exposure in the adolescent brain, such as alteration in synaptic pruning

and white matter development (Battistella et al., 2014; Lubman et al., 2015). Changes in white

matter tract integrity and abnormalities of neural functioning were also reported (Jacobus &

Tapert, 2014), and reduced gray matter in regions of the brain functionally associated with

motivational, emotional, and affective processing (Battistella et al., 2014). These studies suggest

prolonged exposure during adolescence may be harmful to normal brain remodeling.

Despite the uncertainty in the safety of cannabis use in adolescents and the developing

brain, the preclinical data and literature on the ECS suggest a therapeutic potential in treating

ASD symptoms with exogenous cannabinoids. This literature review aims to summarize the

effects of cannabis on ASD symptoms (core behaviors, noncore behaviors) in children,

associated ASD comorbid conditions, cannabis side effects, and recommendations for practice, education, and research based on the evidence presented in studies selected for this systematic review.

Background

ASD is characterized by core symptoms of social and communication deficits and repetitive and restrictive sensory-motor behaviors (American Psychiatric Association, 2013). In addition to these core behaviors, behavioral problems (irritability, aggression, self-injury) and comorbid conditions (intellectual disability, anxiety, depression, attention-deficit/hyperactivity disorder [ADHD], sleep disorders, epilepsy, gastrointestinal dysfunction, immune deficiency) are often associated with ASD at higher incidence rates (Lukmanji et al., 2019; Neumeyer et al., 2019; Rosen et al., 2018; Soke et al., 2016; Thomas et al., 207; Tye et al., 2018).

The clinical phenomenon of interest

There is no treatment for ASD, but core symptoms and behavioral problems are often managed with Cognitive Behavioral Therapy (CBT) for cognitive, language, and adaptive skills training (National Center on Birth Defects and Developmental Disabilities [NCBDDD] & Centers for Disease Control and Prevention [CDC] 2019; Sanchack & Thomas, 2016). Pharmacotherapy is frequently used to treat behaviors not managed with CBT and comorbid conditions associated with ASD (Jobski et al., 2017; Sanchack & Thomas, 2016). The only atypical antipsychotics approved by the U.S. Food and Drug Administration (FDA) for treating ASD-associated irritability, aggression, explosive outburst, and self-injury are aripiprazole (Abilify) and risperidone (Risperdal) (Barnard-Brak et al., 2016; LeClerc & Easley, 2015; Sanchack & Thomas, 2016). Pharmacotherapies such as antipsychotics, mood stabilizers, antiepileptics, stimulants, and SSRIs are used "off label" in treating behaviors and core social

impairments in ASD despite their increased risk for adverse effects in children and little to no evidence to support their efficacy (Barnard-Brak et al., 2007; Jobski et al., 2017; LeClerc & Easley, 2015; McClellan et al., 2016; Yu et al., 2020). To date, there are no FDA-approved medications or conclusive evidence to support any pharmacological agent for the treatment of core social impairment in ASD (Barnard-Brak et al., 2016; McClellan et al., 2016; Sanchack & Thomas, 2016). Since the legalization of medical cannabis, certain patient populations have an additional option for treating ASD symptoms that are not managed with the available therapy and pharmacotherapy.

Clinical question

The following clinical question guided this systematic literature review: *In children (2 to 21 years of age) with autism, does medical cannabis treatment improve ASD symptoms (*core and noncore behaviors, comorbid conditions)*?*

Clinical significance for advanced practice

There are few FDA-approved medications for noncore behaviors and no pharmacotherapy for core behaviors. To access medical cannabis in Minnesota, a provider (medical doctors [MD's], Osteopaths (DO), Advanced Practice Registered Nurses [APRN's]) certifies that the patient has a qualifying condition and follows up with the patient according to that state's regulations (Buppert & Klein, 2021). Qualifying conditions vary between the states, but as of 2021, fourteen states have included autism as a qualifying condition for medical cannabis use (MAMMA, n.d.). Patients rely on the expert knowledge of the provider to assist them in making informed decisions. The certifying provider must know the current state of evidence regarding cannabis treatment of ASD to properly advise the patient on their risk, benefits, and potential adverse side effects.

Method

Search strategies

The search for published literature was completed using the following databases: Academic Search Premier (ASP), CINAHL Plus with Full Text (CINAHL), ProQuest/Medline (PQ/ML), Nursing and Allied Health Database (NAHD), PubMed, Health Source: Nursing/Academic Edition (HS/NAE), Cochrane Central Register of Controlled Trials (CCRCT), and ClinicalTrials.gov (CT). These databases provide a diverse collection of articles from multiple disciplines (medical, nursing, psychology) and cover all medical topics (research, clinical practice, controlled trials, medical studies on human volunteers). Refer to Table 1 in the Appendix for a full description of subjects covered by each database. The literature search was completed on October 20, 2020 (ASP, CINAHL, PQ/ML, NAHD, PubMed, HS/NAE) and December 8, 2020 (ASP, CCRCT, CT). The literature published dates for all databases, except CT, were limited to the past 10 years. All dates were included for studies from CT. All searches were limited to studies published in the English language. Other restrictions varied between the different databases. Refer to Table 1 in the Appendix for listing of complete restrictions.

Study selection

Keywords used for searches in ASP, CINAHL, PQ/ML, NAHD, PubMed, HS/NAE, and CCRCT include medical cannabis, medical marijuana, cannabinoid, autism, ASD, autism spectrum disorder. Additional keywords used for ASP searches include ASD, autism spectrum disorder, children, adolescents, youth, child, teenager, and cannabidiol. Cannabidiol was an additional keyword used for searches in CCRCT. The keywords used for searches in CT include autism spectrum disorder, cannabinoid, and cannabidiol. The number of article 'hits' from the keywords noted above was recorded for each database. The author reviewed study bibliographies

for additional references that may have been missed from the database search. Refer to Table 2 in the Appendix for full details on keyword search combinations and article hits.

Inclusion/exclusion criteria

Studies were included if they were written in English, published as full papers in peer-reviewed journals within the past ten years (since 2010), and met the following criteria: (a) the population included individuals with a diagnosis of autism spectrum disorder, between the ages of 2 to 21 years, (b) the intervention involved cannabinoids, such as cannabidiol (CBD), delta-9-tetrahydrocannabinol (THC), administered at any dose and any form, (c) studies with or without a comparison group (placebo or other forms of treatment), and (d) any outcome was considered, for the purposes of this review. No limits were placed on study designs (case report, case series, retrospective, observational longitudinal, randomized, or controlled clinical trials).

Title and abstract screening were conducted on searches with ten or fewer hits. After eliminating duplicate articles, twelve articles remained for full-text screening. Four articles met inclusion criteria after full-text review. The eight articles were excluded due to one or more of the following reasons: not specific to autism spectrum disorder, not specific to the target ages (two to 21), not specific to CBD or THC treatment, and not a quantitative research design. Refer to Table 3 in the Appendix for the specific inclusion and exclusion rationale used for each study.

Literature review process

The four articles that met the inclusion criteria were reviewed by the author in full, data was abstracted, and findings analyzed. The following variables were abstracted: study purpose, population age and comorbidities, study design and level of evidence, assessment instruments, intervention, key findings, and practice implications. The level of evidence (LOE) was classified according to the hierarchy of evidence described by Melnyk and Fineout-Overholt (2015). The

four studies include one level V prospective cohort study without a control group, one level V

retrospective cohort study without a control group, one level V prospective observational study

without a control group, and one level VI case report. Refer to Table 4 in the Appendix for

further detail on data abstraction of included articles.

Methodological assessment

Relevant studies may have been excluded due to one or more of the following factors:

limiting title/abstract screening to searches with ten or fewer hits, excluding non-English studies,

excluding other forms of cannabinoids (cannabinol, cannabigerol, cannabichromene,

tetrahydrocannabivarin), and excluding the scientific name of cannabis (cannabis Sativa). The

addition of a second reviewer for study selection, data abstraction, and assessment of the

evidence level may decrease author bias and improve the validity and reliability of this

systematic literature review.

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Literature Review

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Study characteristics

This literature review included three level V studies (prospective cohort study,

retrospective cohort study, and prospective observational study) and one level VI case report. All

four studies were published within the past two years. Sample sizes ranged from one (Barchel et

al., 2019) to 188 (Bar-Lev Schleider et al., 2019). The age range of the participants was four to

twenty-two years old. All studies assessed the effect of cannabinoids (cannabidiol and delta-9-

tetrahydrocannabinol) in treating one or more of the following: ASD core behaviors, ASD

noncore behaviors, and comorbid conditions. The ASD core behavior, social communication,

was assessed in three studies (Aran et al., 2019; Bar-Lev Schleider et al., 2019; Ponton et al.,

2020). Barchel et al. (2019) reported social communication deficits in their population but did

not measure the effects of cannabinoids on social communications. Noncore behaviors and comorbid conditions reviewed by one of the four studies include severe behaviors based on the Clinical Global Impression Scale score of 6 or 7 and anxiety (Aran et al., 2019); self-injury, rage attacks, hyperactivity, sleep problems, and anxiety (Barchel et al., 2019); restlessness, rage attacks, agitation, epilepsy, attention deficit hyperactivity disorder, Tourette syndrome, celiac disease, sleep problems, anxiety, and depression (Bar-Lev Schleider et al., 2019); and aggressiveness, irritability, concentration, epilepsy, anxiety, social anxiety, and sleep dysregulation (Ponton et al., 2020).

Cannabinoid treatment contained cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) in a 20:1 ratio in all studies. Bar-Lev Schleider et al. (2019) also included treatment doses of 30% CBD and 1.5% THC, and 3% THC in some cases with severe aggression and violent behaviors. The daily dose given varied based on tolerability and body weight (Aran et al., 2019; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Ponton et al., 2020). Cannabinoid treatment was given as adjuvant therapy in three studies (Aran et al., 2019; Bar-Lev Schleider et al., 2019; Ponton et al., 2020). Barchel et al. (2019) did not indicate concomitant use of medications in their participants. All four studies did not include a control or comparison group (Aran et al., 2019; Bar-Lev Schleider et al., 2019; Ponton et al., 2020). One study compared the improvement in cannabinoid treatment to published conventional treatments and found that cannabinoid treatment was not inferior to the conventional treatments (Barchel et al., 2019).

Symptom assessment tools varied between the studies under review, and some of the assessment tools are not validated. Bar-Lev Schleider et al. (2019) conducted a symptoms inventory and global assessment through structured questionnaires at intake and post-treatment (at one month and six months); symptom improvement was rated as "significant improvement",

"moderate improvement", or "cannabis did not help." Barchel et al. (2019) assessed the ASD comorbid symptom changes with phone questionnaires graded as "improvement", "no change", or "worsening" symptoms. Ponton et al. (2021) assessed noncore and comorbid condition changes with a visual analog scale (0 -10), Children's Sleep Habits Questionnaire, and the Adult Autism Spectrum Quotient score for core symptoms. Aran et al. (2019) measured outcomes with the Caregiver Global Impression of Change scale, the Home Situations Questionnaire-Autism Spectrum Disorder, and the Autism Parenting Stress Index. Three studies reported adverse side effects (Aran et al. (2019; Barchel et al. (2019; Bar-Lev Schleider et al., 2019). Barchel et al. (2019) coded side effects according to the Medical Dictionary for Regulatory Activities. A modified Liverpool Adverse Events Profile was used by Aran et al. (2019) to assess side effects. Bar-Lev Schleider and colleagues (2019) inquired for side effects in their questionnaire. No side effects were reported by Pronto et al. (2020).

Synthesis of research

Core behaviors

Social communication status improved with cannabis treatment, ranging from 30% (Bar-Lev Schleider et al., 2019) to 47% improvement (Aran et al., 2019). Ponton et al. (2020) reported talkativeness improved by four points from a baseline of zero out of 10 scale. These findings suggest a benefit of cannabinoid treatment for social communication, a core behavior of ASD. A review by Karhson et al. (2016) emphasize that current evidence only supports the endocannabinoid signaling role in nonverbal motor-related aspects of social communications. However, they noted that the left hemisphere cortical regions have high concentrations of cannabinoid receptors and are associated with verbal language functions (Karhson et al., 2016), possibly explaining the improvement in communication noted in these studies. Other core

symptoms of ASD, such as restricted and repetitive patterns of behavior, interests, or activities, were not assessed in the studies reviewed. Bar-Lev Schleider et al. (2019) assessed tic disorder in their population and noted 80% of children reported improvement in symptoms. The ECS is involved in motor control (Zou & Kumar, 2018), but due to the lack of data among these studies, it is unclear if motor functions improve with cannabis without further study.

Noncore behaviors

Three studies examined the effects of medical cannabis on specific noncore behaviors. Barchel et al. (2019) examined self-injury and rage attacks. Restlessness, rage attacks, and agitation were the most common behaviors noted by Bar-Lev Schleider et al. (2019). Aggressiveness and irritability were assessed by Ponto et al. (2020). Aran et al. (2019) did not report specific behaviors in their study population, yet behaviors were assessed with the Clinical Global Impression Scale; all participants had a score of six or seven indicating severe behaviors (Aran et al., 2019). All four studies observed improvement in noncore behaviors across studies. Barchel and colleagues (2019) described that of the children who reported self-injury and rage attacks ($n = 34$), 67.6% indicated 'improvement' in those behaviors. Bar-Lev Schleider et al. (2019) reported 'improvement' at six months in 89.8% of the children ($n = 170$) with restlessness, 89.0% of the children ($n = 150$) with rage attacks, and 83.8% of children ($n = 148$) with agitation. Ponto et al. (2019) indicated a decrease in aggressiveness (0/10) and decrease in irritability (2/10). In the study by Aran et al. (2019), behavior problems were described as 'much improved' or 'very much improved' in 61% of the children. The high percentage of children that reported improvement in noncore behaviors in all four studies suggests there are benefits of cannabinoid treatment. However, it is unknown if improvement in noncore behaviors is due to cannabinoid treatment or the result of improved comorbid conditions such as anxiety, ADHD,

and sleep dysregulation. These comorbid conditions can also have similar behaviors as presenting noncore ASD symptoms.

Comorbid conditions

Compared to the normal population, individuals with ASD have higher rates of concurrent medical conditions, including psychiatric conditions (Neumeyer et al., 2018; Rosen et al., 2018; Tye et al., 2019), epilepsy (Lukmanji et al., 2019; Thomas et al., 2016; Tye et al., 2019), sleep disturbances (Neumeyer et al., 2018; Tye et al., 2019), gastrointestinal dysfunction (Neumeyer et al., 2018; Tye et al., 2019), and immune dysfunction (Tye et al., 2019). The common comorbid conditions between the four studies include anxiety (Aran et al., 2019; Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Ponto et al., 2020), epilepsy (Aran et al., 2019; Bar-Lev Schleider et al., 2019; Ponto et al., 2020), sleep problems/dysregulation (Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Ponto et al., 2020), and ADHD/ hyperactivity/ concentration (Barchel et al., 2019; Bar-Lev Schleider et al., 2019; Ponto et al., 2020).

Anxiety. Anxiety is the only comorbid condition addressed in all four studies with improvement in symptoms noted in each of them (Aran et al., 2019; Barchel et al., 2019; Bar-Lev et al., 2019; Ponton et al., 2020). The improvement in anxiety symptoms ranged from 23.5 % (Barchel et al., 2019) to 88.8% (Bar-Lev et al., 2019). Ponton et al. (2020) reported a 7-point improvement in overall anxiety and social anxiety from a baseline of 10/10. The findings of these four studies suggest that cannabinoid treatment may decrease anxiety symptoms in children with ASD. These findings are consistent with evidence from both human and animal studies reporting CBD anxiolytic effects (Blessing et al., 2015; Crippa et al., 2011; Vanessa et al., 2017).

Epilepsy. Epilepsy was assessed in three studies based on medication use before and after initiation of cannabinoid treatment. Aran et al. (2019) reported that 33% of the children received less medication or lower doses after starting on cannabinoid treatment, 24% stopped taking medications, and 8% received more medications or higher doses but did not indicate if those medications were specific to epilepsy. Bar-Lev Schleider et al. (2019) reported antiepileptic use in 26.0% of their participants; follow up at six months found 13% of the participants had stopped taking antiepileptic medications. In the case study by Ponton et al. (2020), the patient trialed a decrease in their antiepileptic medication and was not successful; the medication was titrated back to its initial dose. The findings of the studies reviewed indicate relatively small benefits of combination cannabidiol and THC treatment for epilepsy, likely due to the lower dosing used in these studies. The literature supports high-dose CBD as effective treatment of intractable seizures, which has also been approved by the FDA (Devinsky et al., 2017, Devinsky et al., 2018; FDA, 2018; Thiele et al., 2018).

Sleep problems/dysregulation. Sleep problems/dysregulation was assessed in three studies. Sleep improvement ranged from 58.6% (Bar-Lev et al, 2019) to 71.4% (Barchel et al., 2019) after initiating cannabinoid therapy. Ponto et al. (2020) reported a 1-2 hour increase in the number of hours slept after starting cannabinoid treatment. These findings suggest improvement in sleep problems/dysregulation with cannabinoid therapy. Kesner and Lovinger (2020), Russo et al. (2007), and Shannon et al. (2019) examined the treatment of sleep disorders with CBD and THC combination therapy and also noted improved sleep.

ADHD/hyperactivity/concentration. ADHD/hyperactivity/concentration was measured in three studies that indicated improvement in concentration after starting cannabinoid treatment. Bar-lev Schleider et al. (2019) reported an increase in concentration from 0% to 14% of children;

2 points improvement in concentration was reported by Ponto et al. (2020), and 64.8% reported improvement in ADHD symptoms post starting treatment (Berchal et al., 2019). These findings suggest improvement of concentration in their study population. However, all three studies also report improved sleep problems/dysregulation, which can influence cognition, memory, performance deficits, and behavior problems (Medic et al., 2017).

Two studies reviewed changes in concomitant use of medications and cannabis. They reported 56% (Bar-Lev Schleider et al., 2019) to 82% (Aran et al., 2019) of children taking medications for behavioral problems before the study. Antipsychotics, mood stabilizers, hypnotics/sedatives, and SSRIs are among the most common among their participants. After cannabis treatment was initiated, 33% (Aran et al., 2019) to 34.3% (Bar-Lev Schleider et al., 2019) of children received fewer medications or a lower dosage of the medication. The results of these studies indicate the positive effects of cannabinoid treatment on decreasing concomitant use of medications.

Side effects

The most common side effects include sleep disturbance (Aran et al., 2019), somnolence and decreased appetite (Barchel et al., 2019), and restlessness (Bar-Lev Schleider et al., 2019). Ponto et al. (2020) did not report any side effects. One case of psychosis that requires antipsychotic treatment was reported by Aran et al. (2019). They indicated the psychosis was likely due to a cannabinoid combination with a high THC concentration (Aran et al., 2019). Adolescents have been reported to have an increased risk of adverse effects for psychosis (Ludman et al., 2015), especially in those with a history of schizophrenia or genetic predisposition for schizophrenia (Burnett, 2016).

Quality indicators

The effects of cannabis on ASD behavior symptoms are highly consistent between the studies reviewed. There was abundant literature on the effects of the ECS on human and rodent studies supporting evidence on potential effects caused by alterations in the ECS with exogenous cannabinoids. The conclusions made by the authors of these studies were supported by their data and other published works of literature. The studies in this review provide novel data and insights on the effects of cannabis use in ASD, a topic that lack human research, especially in the pediatric population.

Gaps in the literature

Based on the findings from this review, evidence for cannabis treatment of core ASD symptoms is still lacking. Findings suggest that there may be some benefit to social communication and tic disorder, but the evidence is not conclusive on the effectiveness of cannabis for treating social communication or tic disorders. Further studies are needed to address core ASD symptoms specifically.

The dosing of cannabinoids varied between participants and between the studies, which does not provide sufficient data for analyzing dosing safety and efficacy. Most of the participants were using concomitant medications, which leads to the question of whether the participants' side effects were related to the cannabis or perhaps drug-drug interaction.

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Discussion

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The existing literature on ASD treatment with cannabis is limited. Despite the beneficial findings reported in the studies in this review, all were considered low levels of evidence (V-VI) (Melnyk & Fineout-Overholt, 2015). The literature lacks substantial evidence to support cannabinoid treatment of ASD core and noncore behaviors and comorbid conditions in children. The studies in this literature review were observational, with small sample sizes making it is

difficult to generalize the results; despite the absence of strong evidence supporting the use of cannabis for treating ASD symptoms. These studies provide insight into the therapeutic effect of cannabis in treating several ASD symptoms, which is also supported by preclinical findings and understanding of the ECS. The preclinical data along with key studies in this literature review warrant further research with large, randomized controlled trials.

Implications for future research

The findings of this literature review indicate beneficial effects of cannabis in treating ASD symptoms and some comorbid conditions in children, but they do not provide strong evidence due to the low-level study designs of research contained in this review. The finding provides strong support for further random controlled trials to determine safety and efficacy in cannabis use in treating ASD symptoms and comorbid conditions in children, as well as longitudinal studies on the long-term effects of cannabis on the developing brain.

Clinical practice recommendations

The literature is sparse and does not recommend cannabis as an evidenced-based treatment for ASD symptoms and comorbid conditions. However, the potential benefits identified in these studies strongly support further research and consideration of medical cannabis as an adjunct treatment after careful review of risks, benefits, and considerations for accessibility. Key considerations for accessibility include legal status of medical cannabis in the state in which the patient and provider reside, the feasibility of medical cannabis use due to cost and the patient's ability to access a dispensary. Furthermore, providers should use validated tools for symptom assessment in order to obtain reliable data on efficacy of this intervention. Patient's new to medical cannabis should start with low THC products due to the risk of adverse effects

with high THC products (psychosis, hyperemesis) and be titrated carefully based on symptom profile and side effects.

Recommendations for research

Research designs such as large double-blinded research control trials are needed to assess the safety and efficacy of cannabinoid treatment of ASD symptoms in children. Additional research is needed to assess the efficacy and safety of different cannabinoid strains, concentrations, dosing, titration recommendations, and route in children. Further research is needed to determine ASD symptoms assessment tools for assessing the effects of medical cannabis treatment in children. Symptom assessment tools should be objective, standardized, and validated to provide reliable and valid data. Research concerning the drug-drug interactions of cannabinoids is essential as ASD treatment is often accompanied by pharmacotherapy of comorbid conditions. Longitudinal studies are needed to study the effects of cannabis use on the developing brain.

Recommendations for policy changes

At the federal level, marijuana/cannabis remains classified as a Schedule I substance under the Controlled Substances Act. "Schedule I substances are considered to have a high potential for dependency and no accepted medical use, making the distribution of marijuana a federal offense" (National Conference of State Legislatures, 2021). As a result of this classification, health insurances do not provide any coverage or copay for medical cannabis and the burden of cost falls entirely on the patient alone. The high cost of medical cannabis limits its accessibility to only patients with the ability to pay out of pocket.

The state medical cannabis laws only permit possession and use of cannabis within the state where the patient received the certification(Walters, 2021). This can be interpreted to mean

that crossing state lines with medical cannabis is illegal as federal laws supersede state laws (Walters, 2021). Patients will have to use alternative treatments when traveling, which is disruptive to their disease management with medical cannabis. The conflicting state and federal policies on medical cannabis make navigating care difficult for patients and providers.

Conclusion

With the legalization of cannabis for medicinal use, providers will likely encounter patients seeking this treatment option. The few studies that exist report benefits in ASD symptoms and comorbid conditions, with the most common side effects being somnolence and the potential for psychosis with higher THC concentration. There are studies that report potential harm on the developing brain with cannabis use (Battistella et al., 2014; Lubman et al., 2015). RCT studies are needed to assess the safety of cannabis in the pediatric population, as children as young as two years old can qualify for medical cannabis use in some states. There is not enough evidence to support the use of cannabis as a primary or alternative treatment for ASD symptoms in children, yet findings suggest potential benefits for cannabis use as an adjunct therapy in children. The consideration for using cannabis as an adjunct therapy should occur after careful review of the benefits and barriers of the therapeutic use of cannabis with parent(s) and the child. The analysis of this literature review and related recommendations are consistent with two other reviews on the current state of evidence of cannabis use in ASD (Agarwal et al., 2019; Poleg et al., 2018).

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Appendix

Table 1: *Database Search Description*

Database/ Search Engine	Restrictions Added to Search	Dates Included in Database	General Subjects Covered by Database
Academic Search Premier (ASP)	Full Text; Scholarly journals; English Language; all publication type, all document type	January 2000-December 2020	This multi-disciplinary database provides full text for more than 3,100 journals, including full text for nearly 2,700 peer-reviewed titles.
CINAHL Plus with Full Text	Full text; English Language; Peer Reviewed; all clinical queries; Human; All journal subjects; All geographic subset; All publication type; All sex; All age groups; All special interest	January 2000-December 2020	*CINAHL Plus with Full Text* is a robust collection of full text for nursing & allied health journals, providing full text for more than 770 journals indexed in *CINAHL*. This authoritative file contains full text for many of the most used journals in the *CINAHL* index, with no embargo. *CINAHL Plus with Full Text* is the core research tool for all areas of nursing and allied health literature. Full text coverage dates back to 1937.
ProQuest/Medline (PQ/ML)	Humans; English Language; Children, all (0-18 years)	January 2000-December 2020	Provides citations and abstracts to articles covering all medical topics, including "research, clinical practice, administration, policy issues, and health care services.
Nursing and Allied Health Database (NAHD)	Full text, Peer reviewed, English, Scholarly journals; Preschool child (2-5 years), child (6-12 years), Adolescent (13-28)	January 2000-December 2020	Provides citations, abstracts, and selected full text to articles about all aspects of nursing and allied health.
PubMed	Full text, clinical trial, meta-analysis, randomized controlled trial, review, systematic review, English; MEDLINE, Nursing journals	10 years	Provides citations, abstracts, and selected full text to articles about "medicine, nursing, dentistry, veterinary medicine, the health care system, and the preclinical sciences."

Health Source: Nursing/Academic Edition (HS/NAE)	Full text; Peer Reviewed; Academic Journals	January 2000- December 2020	This database provides nearly 550 scholarly full text journals focusing on many medical disciplines. *Health Source: Nursing/Academic Edition* also features the *AHFS Consumer Medication Information*, which covers 1,300 generic drug patient education sheets with more than 4,700 brand names.
Cochrane Central Register of Controlled Trials (CCRCT)	English	January 2000- December 2020	Cochrane Controlled Trials Register is a bibliography of controlled trials identified by contributors to the Cochrane Collaboration and others, as part of an international effort to hand search the world's journals and create an unbiased source of data for systematic reviews.
ClinicalTrials.gov (CT)	Child (birth -17)	All dates	Contains information about medical studies in human volunteers.

Table 2: *Data Abstraction Process*

Date of Search	Key Words	ASP	CINAHL	PQ/ML	NAHD	PubMed	HS/NAE	CCRCT	CT
10/20/2020	Medical cannabis	2,721	795	110	1,061	1,138	1,052	914	X
	medical cannabis or medical marijuana or cannabinoid	6,994	1,796	302	2,667	3,117	2,029	1,812	X
	Title: medical cannabis or medical marijuana or cannabinoid	2,048	562	374	31	418	478	270	X
	Title: medical cannabis or medical marijuana or cannabinoid AND autism	7	5 (4)	7 (4)	2 (2)	3 (1)	6(2)	1 (1)	X

	Title: medical cannabis or medical marijuana or cannabinoid AND autism or asd or autism spectrum disorder	7 **(2)**	X	X	X	X	X	X	X
	Title: medical cannabis or medical marijuana or cannabinoid AND All Text: autism or asd or autism spectrum disorder AND children or adolescents or youth or child or teenager	10 **(3)**	X	X	X	X	X	X	X
12/8/2020	Cannabidiol AND autism	6 **(1)**	X	X	X	X	X	9 **(2)**	X
12/8/2020	Autism spectrum disorder AND cannabinoid	X	X	X	X	X	X	X	2**(2)**
12/8/2020	Autism Spectrum disorder AND cannabidiol	X	X	X	X	X	X	X	4 **(3)**

*BOLD = articles reviewed for match with systematic review inclusion criteria (parentheses indicate those articles meeting inclusion criteria). X= key words not searched in database

Table 3: *Characteristics of Literature Included and Excluded*

Reference	Included or Excluded	Rationale
Aran, A., Cassuto, H., Lubotzky, A., Wattad, N., & Hazan, E. (2019). Brief report: Cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems—A retrospective feasibility study. *Journal of Autism & Developmental Disorders*, *49*(3), 1284–1288. https://doi-org.ezproxy.mnsu.edu/10.1007/s10803-018-3808-2	**Included**	Retrospective study on medical cannabis use in children with ASD and disruptive behaviors.
Bar, L. S. L., Abuhasira, R., & Novack, V. (2018). Medical cannabis: aligning use to evidence-based medicine approach. *British Journal of Clinical Pharmacology*, *84*(11), 2458–2462. https://doi-org.ezproxy.mnsu.edu/10.1111/bcp.13657	Excluded	Only reviewed information on clinical trial NCT02956226; completed, results pending. Not quantitative design study.

Reference	Included or Excluded	Rationale
Barchel, D., Stolar, O., De-Haan, T., Ziv-Baran, T., Saban, N., Fuchs, D. O., Koren, G., & Berkovitch, M. (2019). Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. *Frontiers in Pharmacology*, *9*, 1521. https://doi.org/10.3389/fphar.2018.01521	**Included**	Prospective study on children with ASD.
Bar-Lev Schleider, L., Mechoulam, R., Saban, N., Meiri, G., & Novack, V. (2019). Real life experience of medical cannabis treatment in autism: Analysis of safety and efficacy. *Scientific Reports, 9*(1), 200. http://dx.doi.org.ezproxy.mnsu.edu/10.1038/s41598-018-37570-y	**Included**	Prospective observational study; cannabis use for ASD in children.
Bou Khalil, R. (2012). Would some cannabinoids ameliorate symptoms of autism? *European Child & Adolescent Psychiatry*, *21*(4), 237–238. https://doi-org.ezproxy.mnsu.edu/10.1007/s00787-012-0255-z	Excluded	Provides summary of literature regarding the action of CBD, delta9-THC, and cannabinol as TRPV2 agonists, which increase the release of both oxytocin and vasopressin; potentially improving symptoms of ASD. Not quantitative design study.
Efron, D., & Freeman, J. (2018). Medical cannabis for paediatric developmental-behavioural and psychiatric disorders. *Journal of Paediatrics & Child Health*, *54*(7), 715–717. https://doi-org.ezproxy.mnsu.edu/10.1111/jpc.13902	Excluded	Referenced clinical trial NCT02956226 and single cases study by Kurz and Blass (2010). Not quantitative design study.
Hadland, S. E., Knight, J. R., & Harris, S. K. (2015). Medical marijuana: review of the science and implications for developmental-behavioral pediatric practice. *Journal of Developmental & Behavioral Pediatrics*, *36*(2), 115–123. https://doi-org.ezproxy.mnsu.edu/10.1097/DBP.0000000000000129	Excluded	Literature review for short- and long-term consequences of marijuana use in adolescents. Not quantitative design study.
Kurz R, Blass K. (2010). Use of dronabinol (delta-9-THC) in autism: a prospective single-case-study with an early infantile autistic child. *Cannabinoids*. 2010; 5(4), 4-6.	Excluded	Single case study of dronabinol in autism. Dronabinol is synthetic THC.
Mostafavi, M., & Gaitanis, J. (2020). Autism spectrum disorder and medical cannabis: Review and clinical experience. *Seminars in Pediatric Neurology*, *35*, N.PAG. https://doi-org.ezproxy.mnsu.edu/10.1016/j.spen.2020.100833	Excluded	Retrospective analysis of children dx with ASD, comorbid epilepsy, aggression on cannabis-based treatment. The analysis included the age range of ASD diagnosis but not the current ages of the participations.
Ponton, J. A., Smyth, K., Soumbasis, E., Llanos, S. A., Lewis, M., Meerholz, W. A., & Tanguay, R. L. (2020). A pediatric patient with autism spectrum disorder and epilepsy using cannabinoid extracts as complementary therapy: a case report. *Journal of Medical Case Reports*, *14*(1), N.PAG. https://doi-org.ezproxy.mnsu.edu/10.1186/s13256-020-02478-7	**Included**	Case presentation; 15 y/o with ASD and epilepsy. Cannabinoid trial to replace seizure medications; unanticipated positive effects on behavioral symptoms and core social deficits.
O'Brien, K., & Clark, P. A. (2002). Mother and son: The case medical marijuana / commentaries. *The Hastings Center Report, 32*(5), 11-3.	Excluded	Addressed ethical issues involved with medical THC in a pediatric patient. Not quantitative design study.

Reference	Included or Excluded	Rationale
http://ezproxy.mnsu.edu/login?url=https://www.proquest-com.ezproxy.mnsu.edu/scholarly-journals/mother-son-case-medical-marijuana-commentaries/docview/222388946/se-2?accountid=12259		
Rollins, J. A. (2014). Pot for tots: Children and medical marijuana. *Pediatric Nursing*, *40*(2), 59-60.	Excluded	Not specific to ASD.

Table 4: *Literature Review Table of All Studies Included*

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
Aran, A., Cassuto, H., Lubotzky, A., Wattad, N., & Hazan, E. (2019). Brief report: Cannabidiol-rich cannabis in children with autism spectrum disorder and severe behavioral problems—A retrospective feasibility study. *Journal of Autism & Developmental Disorders*, *49*(3), 1284–1288. https://doi-org.ezproxy.mnsu.edu/10.1007/s10803-018-3808-2	Assess tolerability and efficacy of cannabidiol-rich cannabis in children with ASD and severe behavioral problems.	N = 60 N = 16, excluded; stopped treatment Ages: 5 to 18 y/o Mean age: 11.8 y/o CC: -77% had low cognitive functioning -All had severe behaviors base on Clinical Global Impression	Retrospective cohort Study, without control group (V)	-Caregiver Global Impression of Change (CGIC) scale: ('No change', 'Slightly improved', 'Much improved', or 'Very much improved'), or worsened ('Slightly worse', 'Much worse', or 'Very much worse') -Home Situations Questionnaire-Autism Spectrum	-Cannabis oil containing CBD and THC at a 20:1 ratio -Given sublingual two to three times daily with dose up-titrated over 2-4 weeks	-CGIC Scale: Behaviors: 'much improved' or 'very much improved' in 61%; Anxiety: 'improvement' in 39%; communication: 'improvement' in 47% -HSQ scores improved by 29% -APSI scores improved by 33% -Following cannabis treatment, 33% received fewer medications or lower dosage, 24%	Use of CBD-rich medical cannabis in children with ASD: -improve behavioral outbreaks (61%) -improve anxiety (39%) -improve communication (47%) Decreases medication use or lower dose (33%)Most common SE was sleep disturbance (14%) High THC concentration (6:1

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
		Scale score of 6 or 7		Disorder (HSQ-ASD): 24-item parent-rated measure of noncompliant behavior in children with ASD. -Autism Parenting Stress Index (APSI): 13-item parent rated measure designed to assess the effect of interventions to control disruptive behavior in children with ASD on parenting stress; each item is ranked from 'Not stressful', 'Sometimes creates stress', 'Often creates stress', 'Very stressful on a daily basis', to 'So stressful that sometimes we		stopped taking medications and 8% received more medications or higher dose. -Any adverse events (51%), Sleep disturbances (14%), Restlessness (9%), Nervousness (9%), Loss of appetite (9%), Gastrointestinal symptoms (7%), Unexplained laugh (7%), Mood changes (5%), Fatigue (5%), Nocturnal enuresis (3.5%), Gain of appetite (3.5%), Weight loss (3.5%), Weight gain (3.5%), Dry mouth (3.5%), Tremor (3.5%), Sleepiness (2%), Anxiety (2%), Confusion (2%), Cough (2%),	– CBD to THC ratio) may lead to psychotic episode that require treatment with an antipsychotic

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
				feel we cannot cope' -Medications -Modified Liverpool Adverse Events Profile		Psychotic event (2%)	
Barchel, D., Stolar, O., De-Haan, T., Ziv-Baran, T., Saban, N., Fuchs, D. O., Koren, G., & Berkovitch, M. (2019). Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. *Front iers in Pharmacology*, *9*, 1521. https://doi.org/10. 3389/fphar.2018.0 1521	Record the experience of parents who administered under supervision cannabidiol to their children with ASD.	N = 53 N =6, excluded; stopped treatment Ages: 4-22 y/o Mean: age11 -For all participating children this was their first experience with cannabidiol CC: -Self-injury -Rage attacks -Hyperactivity	Prospective cohort study, without control group (V)	Data obtained from parents using a scale (improvement, no change, worsening). -Symptoms evaluated: -Hyperactivity symptoms -Sleep problems -Self-injury -Anxiety -Overall improvement -Comparison of improvement in symptoms between CBD treatment and published data	Cannabinoid oil at 30% concentration: -CBD and THC at a 20:1 ratio	-Hyperactivity: Improvement: 68.4%; No change: 28.9%; Worsening: 2.6%; improvement not statistically different from conventional treatment (p = 0.125) -Sleep Problems: Improvement: 71.4%; No change: 23.8%; Worsening: 4.7%; improvement not statistically different from conventional treatment (p = 0.4)	Cannabis may be effective in improving ASD comorbid symptoms of hyperactivity, self-injurious behavior, sleep problems, and anxiety Compared to conventional treatments cannabidiol treatment is non-inferior Adverse SE: somnolence and decreased appetite

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
		-Sleep problems -Anxiety		on conventional treatment was analyzed using binomial test.		-Self-Injury: Improvement: 67.6%; No change: 23.5%; Worsening: 8.8%; improvement borderline statistically significance compared to conventional treatment (p = 0.063), and no statistical difference in worsening symptoms (p = 0.307) -Anxiety: Improvement: 47.1%; No change: 29.4%; Worsening: 23.5%; improvement not statistically different from conventional treatment (p = 0.232) -Overall: Improvement:	

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
						74.5%; No change: 21.6%; Worsening: 3.9% Adverse events: somnolence (n= 12) and decreased appetite (n= 6)	
Bar-Lev Schleider, L., Mechoulam, R., Saban, N., Meiri, G., & Novack, V. (2019). Real life experience of medical cannabis treatment in autism: Analysis of safety and efficacy. *Scientific Reports, 9*(1), 200. http://dx.doi.org.e zproxy.mnsu.edu/ 10.1038/s41598-018-37570-y	Characterize the epidemiology of ASD patients receiving medical cannabis treatment and to describe its safety and efficacy.	N = 188 Mean Age: 12.9 y/o CC: -Epilepsy (27) -ADHD (7) -Tourette syndrome (4) -Celiac Disease (3) -Anxiety (3)	Prospective observational study, without a control group (V)	Assessments completed at intake and 6 months: -Patient global assessment -Symptom inventory -Quality of life -Side effects	Cannabinoid oil containing: -CBD and THC at a 20:1 ratio -30% CBD & 1.5% THC -additional 3% THC in some cases	Global assessment: -After 6 months 155 patients remain in active treatment, of those 93 responded to the questionnaire; 28 patients (30.1%) reported significant improvement, 50 patients (53.7%) moderate improvement, 6 patients (6.4%) slight improvement and 8 (8.6%) having no change in their condition. Symptom inventory (3 most common):	Cannabis may be effective in relieving ASD symptoms: restlessness, rage attacks, agitation. Over 80% pf parents reported significant to moderate improvement in the child global assessment. Cannabis may be effective in improving quality of life. Cannabis is well tolerated; less than 15% stopped treatment at 6 months.

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
						-Restlessness: 170 patients (90.4%) reported symptom prior to treatment and after 6 months 71 (89.8%) reported improvement, 7 (8.8%) reported no change, 1 (1.2%) reported symptom disappeared. -Rage attacks: 150 patients (79.8%) reported symptom prior to treatment and after 6 months 65 (89%) reported improvement, 7 (9.5%) reported no change, 1 (1.3%) reported symptom disappeared. -Agitation: 148 patients (78.7%) reported symptoms prior to treatment and after 6 months 57 (83.8%) reported improvement, 10 (14.7%) reported no change, 1 (1.4%) reported	Cannabis may decrease use of medications such as antipsychotics, antiepileptics, antidepressants and hypnotics and sedatives. Most common side effect was restlessness.

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
						symptom disappeared. Other symptom improvements: sleep problems (58.6%), speech impairment (30%), cognitive impairment (27.2%), anxiety (88.8%), seizures (84.6%), tics (80%), digestion problems (62.5%), depression (100%) Quality of life: -31.3% reported good quality of life prior to treatment and 66.8% after 6 months (p<0.001) -42% of parents reported positive mood prior to treatment and 63.5% after 6 months (p<0.001) -26.4% reported no difficulty in ability to dress and shower independently	

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
						prior to treatment and 42.9% after 6 months (p<0.001) -3.3% reported good sleep and 0.0% reported good concentration prior to treatment and 24% (p<0.001) and 14.0% (p<0.001) during active treatment. Medication use: -Of the 93 patients that responded at 6 months, 67 reported chronic medication use; 6 patients reported (8.9%) increase in their drugs consumption, 38 patients (56.7%) reported drugs consumption remain the same and 23 patients (34.3%) reported a decrease, mainly of the following: antipsychotics, antiepileptics,	

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
						antidepressants and hypnotics and sedatives.

Side effects:
-At 6 months 23 patients (25.2%) reported at least one side effect; the most common was restlessness (6 patients, 6.6%). | |
| Ponton, J. A., Smyth, K., Soumbasis, E., Llanos, S. A., Lewis, M., Meerholz, W. A., & Tanguay, R. L. (2020). A pediatric patient with autism spectrum disorder and epilepsy using cannabinoid extracts as complementary therapy: a case report. *Journal of Medical Case Reports*, *14*(1), N.PAG. https://doi- | This case report describes the clinical presentation of a pediatric, overweight patient with ASD, epilepsy, anxiety, insomnia, and social deficits who benefited clinically with low doses of Cannabidiol-based extract (CBE). | N = 1

Age: 15 y/o

CC:
-Controlled epilepsy
-Selective
-Mutism
-Anxiety | Case report

(VI) | Symptom severity on a visual analog scale (VAS)
  -Overall anxiety
  -Social anxiety
  -Aggressiveness
  -Irritability Talkativeness in social situation
  -Concentration

Children's Sleep Habits Questionnaire (CSHQ) | Cannabidiol-based extract containing CBD and THC in 20:1 ratio | VAS (0 = least severe, 10 = most severe)
-Overall anxiety: initial (10/10), improvement at 9 months (3/10)
-Social anxiety: initial (10/10), improvement at 9 months (3/10)
-Aggressiveness: initial (6/10), improvement at 9 months (0/10)
-Irritability: initial (9/10), improvement at 9 months (2/10) | CBE was beneficial for ASD-related behaviors and social symptoms as well as anxiety, sleep disturbance, and weight. |

Citation	Study Purpose	Pop (N)/ Age /Comorbid conditions (CC)	Design/ Level of Evidence	Variables/ Instruments	Intervention	Findings	Implications
org.ezproxy.mnsu .edu/10.1186/s132 56-020-02478-7				Adult Autism Spectrum Quotient Score (AQ)		VAS (0 = quiet, 10 = very talkative) -Talkativeness in social situation: initial (0/10), 9 months improved by 4 points VAS (0 = unfocused, 10 = very focused) -Concentration: initial (4/10), at 9 months improved by 2 points CSHQ: initial (5 to 6 hours of sleep), at 9 months (7 hours of sleep) Adult (AQ) was a normal score of 10	