5-2021

Cannabidiol: An Adjunctive Therapy to Risperidone for Autistic Children Experiencing Behavioral Outbursts

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A Scholarly Project

Submitting to the Graduate Faculty of the University of North Dakota

In partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2021

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Abstract

The purpose of this systemic literature review was to evaluate the safety, efficacy, and tolerability of medical cannabis in the treatment of aggression, irritability, and self-injurious behaviors in autistic children that are currently receiving risperidone. For this literature review, DynaMed, Cochrane, PubMed, ClinicalKey, and CINAHL were searched using various keywords and phrases. Studies that were included in this review were published after 2005, were peer-reviewed, and included systemic reviews, journal articles, clinical trials, randomized control trials, and meta-analyses. Studies that did not directly discuss autism and behavioral issues; autism treatment with risperidone, medical cannabis, or cannabidiol; that did not specifically address the pediatric or adolescent population; or that did not directly discuss human subjects were excluded. Ten resources were selected for this review. Risperidone treatment effectively decreases symptoms of aggression, irritability, and self-injurious behaviors, by half, in autistic children. However, with long-term use weight gain, extrapyramidal symptoms, and hypersomnia are common. Rare cases of metabolic syndrome have occurred. Research regarding cannabidiol treatment in autism is limited. Recent studies show a lessening of aggression and self-injurious behaviors when treated with cannabidiol; however, decreased appetite, somnolence, and restlessness are common. One case of psychosis has occurred. Current research regarding cannabidiol use in treating behavioral outbursts in autistic children shows promise; however, more large-scale, double-blind studies should be performed before treatment with cannabidiol can be considered a safe and effective adjunctive therapy to risperidone treatment.

Keywords: cannabis, cannabidiol, risperidone, autism spectrum disorder, behavioral outbursts

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Introduction

Autism spectrum disorder (ASD) is a disability associated with development that may cause challenges that affect behaviors, social interactions, and communication skills of those with this disease. Problem-solving skills, thought processing, and learning abilities of the autistic can range from severely challenged to incredibly gifted. Some may not require much help with daily living, while others may need substantial support. ASD is diagnosed via the Diagnostic and Statistical Manual of Mental Disorders, 5th ed., as a diagnosis of medical conditions that used to be considered separate disorders; these include: Asperger syndrome, autistic disorder, childhood disintegrative disorder, and pervasive development disorder. Screening for autism typically begins at nine months of age and may be reassessed at each well-child visit through the age of 30 months (Sanchack, & Thomas, 2016). Most everyone diagnosed with autism suffers from core symptoms, which include difficulties with social behavior, social interactions, communication, adapting to change, and behaviors that are repetitive or restrictive in nature (Chandler, et. al., 2015). There are a multitude of other symptoms that patients with autism may experience, which may include but are not limited to: anxiety; depression; attention-deficit/hyperactivity disorder; insomnia; intellectual disabilities; abdominal pain; diarrhea; constipation; gross motor delays; toe walking; and, epilepsy. According to Aran, Cassuto, Lubotzky, Wattad, and Hazan (2018), approximately 50% of children that have been diagnosed with autism will experience behavioral outbursts, tantrums, violence, and may partake in self-injurious behaviors. These behaviors can interfere with how they interact with friends, family, and caregivers. All patients that have autism are encouraged to engage in behavioral therapy. When behavioral therapy alone is not

successful in reducing symptoms, medications may be added. Risperidone is currently one of the most prescribed antipsychotic medications used to treat these behaviors, and patients usually notice improvements. However, there are patients that do not show improvement with risperidone or do not like the side effects associated with it. Due to these varying outcomes, parents of children with autism who suffer from aggressive, self-injurious, or irritable behaviors are seeking additional treatments that they feel are not only less toxic and have a better safety profile but also alleviate these symptoms. The purpose of this study is to determine if the addition of medical cannabis to behavioral therapy and current risperidone treatment will help to alleviate the aggressive, self-injurious, and irritable behaviors that some of these patients are still experiencing.

Statement of the Problem

Autism affects one in 54 people each year and is typically diagnosed prior to 30 months of age. Many patients with autism experience atypical symptoms such as aggression, irritability, and self-injurious behaviors. Behavioral therapy is a mainstay in the treatment plan for all autistic patients; however, sometimes, that is not sufficient for the reduction of these atypical symptoms. The antipsychotic medication risperidone is approved by the FDA to help in the treatment of those who are experiencing atypical behavioral issues that can be associated with autism. Risperidone is effective in decreasing the frequency of these behaviors by about half in most patients (Stepanova, Dowling, Phelps, & Findling, 2017). Even if daily outbursts are decreased by half, patients could still experience outbursts as often as three to four days per week. This can be very challenging for parents, siblings, teachers, and caregivers to deal with. In addition, there are adverse side effects to risperidone that some patients do not like, the most significant being excessive weight gain. This is concerning to many patients, and some

discontinue treatment with risperidone for this reason alone. More and more parents are searching for and seeking alternative treatment options for their autistic children. Limited research has been done regarding the use of medical cannabis for the treatment of these behaviors in children with autism. This is largely because medical cannabis is a controlled substance, and that marijuana was, and in some states continues to be, an illegal substance. Now that states are changing their laws and allowing medical marijuana to be prescribed, we may see an increase in studies utilizing medical cannabis to determine its safety and efficacy in autism and many other medical disorders. Within the last couple of years, a few studies have been completed. More are in the pre-trial or clinical phases regarding medical cannabis use in treating autism, or symptoms associated with it.

Research Question

In autistic children currently taking risperidone and exhibiting uncontrolled aggressive behaviors, would the addition of cannabis to their current medication regimen decrease the frequency of their behavioral outbursts?

Methods

For the literature review, academic electronic databases were utilized, which included DynaMed, ClinicalKey, Cochrane, CINAHL, and PubMed. The following search strategies were employed and utilized on each database to include these keywords and phrases: cannabis; cannabidiol; risperidone; autism spectrum disorder; Cannabis AND Autism; Risperidone AND Autism; and Cannabidiol AND Autism. Research for Risperidone and Risperidone AND Autism was limited to 2015-2020 on all sites. Research for cannabis, cannabidiol, cannabis AND autism, and cannabidiol AND autism was limited to 2010-2020. Initial search results yielded 197 studies. Studies that did not directly discuss autism and behavioral issues; autism and treatment with

risperidone, medical cannabis, or cannabidiol; studies that did not specifically address the pediatric or adolescent population; or studies that did not include human participants were eliminated. Systemic reviews, meta-analysis, journal articles, and clinical trials were assessed to establish the safety, efficacy and risks of introducing medical cannabis as an alternative or adjunctive therapy for aggressive, self-injurious, and irritable behaviors that may be experienced by children that have autism. Duplicate studies were further eliminated, which left a total of 10 studies that were used for this review.

Literature Review

A review of the literature shows that children with autism who experience aggressive, self-injurious behaviors and increased irritability typically see a decrease in the frequency of these symptoms when treated with risperidone. However, with long-term risperidone treatment, many children experience adverse effects such as weight gain (which may be significant), extrapyramidal side effects, and metabolic syndrome (Loy, Merry, and Hetrick, 2017). There is limited research on the use of medical cannabis for the treatment of aggressive, self-injurious behaviors and increased irritability associated with autism. What research has been completed shows a decrease in the frequency of aggressive and self-injurious behaviors as well as irritability; however, side effects such as decreased appetite, somnolence, and restlessness are common (Aran et. al., 2018).

Theme One: Pathophysiology and Pharmacologic properties of Risperidone and Medical Cannabis

The purpose of this review performed by Scott and Dhillon (2007) was to focus on risperidone treatment in autistic children and adolescents as well as discuss the pharmacologic properties of risperidone. The exact mechanism of action of risperidone is not known; however,

it is thought that dopamine D_2 and serotonin 5-HT_{2A} receptor antagonism may mediate its effects. Risperidone and its active metabolite have a high affinity for both the dopamine D_2 and serotonin 5-HT_{2A} receptors, which inhibits dopamine and serotonin significantly. Psychosis is reduced when dopamine D_2 receptors found in the mesolimbic pathway are inhibited in the brain. Deficiency of dopamine within the nigrostriatal pathway may induce adverse effects such as tardive dyskinesia and extrapyramidal effects, whereas when deficits of dopamine occur in the tuberoinfundibular pathway, hyperprolactinemia may occur. There is one theory that proposes when antagonistic actions at the serotonin 5-HT_{2A} receptors occur, that dopamine is released in the nigrostriatal pathway, which would decrease the likelihood that tardive dyskinesia and extrapyramidal side effects would occur. Since the mesolimbic pathway has very few serotonin 5-HT_{2A} receptors, antipsychotic actions of risperidone treatment would not be altered. Therefore, if risperidone has a higher affinity for serotonin 5-HT_{2A} receptors than dopamine D_2 receptors, there would be less adverse motor effects. Weight gain, a common side effect noted with risperidone use, may be due to the actions found at both dopamine D_2 and serotonin 5-HT_{2A} receptors found in the brain (Scott and Dhillon, 2007).

The review performed by Fernandez-Ruiz, Gaive-Roperh, Sagredo, and Guzman, (2020) focused on preclinical and clinical evidence regarding the pharmacological and biochemical effects of cannabis use related to the neuropsychopharmacology field, including autism. They looked more specifically at the endocannabinoid (EC) system. When the EC system is altered in neurological diseases, such as in autism, it may affect one's ability to perform complex cognitive or behavioral tasks. It is then discussed how cannabis may help regulate the malfunctioning endocannabinoid system and relieve the adverse symptoms associated with that (Fernandez-Ruiz et. al., 2020).

The results of the genetic studies found that there are alterations to the endocannabinoid system that may be responsible for the development of autism. 2588 patients with autism and 580 controls were utilized in this study, which found that there were inherited *de novo* mutations found in the CNR1 gene, which encodes for the CB_1 receptor, in those that were diagnosed with autism (Girirajan et al., 2013). This evidence may support the therapeutic benefits of utilizing cannabinoids in the treatment of autism. One study analyzed the effects of prenatal exposure to CB_1 and CB_2 receptor agonists by utilizing 1405 cases and 94,844 controls. This large study evaluated the effects of prenatal exposure to these agonists and found that those exposed were less likely to develop autism than those that were not exposed (Janecka et al., 2018). Another study found that autistic children had lower levels of serum anandamide (AEA), an endocannabinoid secreted at the post-synaptic neuron cell membrane (Aran et al., 2019). When AEA binds to the CB_1 receptor, it modulates neurotransmission in the brain. Finding lower levels of AEA in autistic children suggests that there is a decreased function of the endocannabinoid system in these patients. A prospective study that analyzed 192 autistic individuals, 93 of which were evaluated for six months, found when using cannabis extracts that contained 30% cannabidiol (CBD) and 1.5% Δ9-tetrahydrocannabinol (THC), that 30.1% had reported a significant improvement of their symptoms and 53.7% found that they had moderate improvement of their symptoms, based on their parent's responses to a questionnaire (Bar-Lev Schleider, Mechoulam, Saban, Meiri, & Novack, 2019). Rage attacks, anxiety, hyperactivity, and self-injury were found to be reduced in another study of 53 autistic patients between the ages of 4-22 (Barchel et al., 2019). These individuals were prescribed oral cannabidiol oil, which was found to be effective in reducing those symptoms in 60-70% of the cases. Another study involving 60 autistic children had similar results. It has been found that combining cannabidiol

with THC yields more favorable results than cannabidiol alone (Aran et al., 2019a This may be due to which receptors are targeted by each drug. THC may modulate the excitation/inhibition balance associated with autism, whereas cannabidiol may modulate cortical and subcortical connections as well as many neurotransmission systems (Fernandez-Ruiz et. al., 2020).

In conclusion, the pathogenesis of autism appears to be associated with a hypo-functioning endocannabinoid system. More specifically, it may be due to decreased levels of AEA at the post-synaptic neuron cell membrane that are associated with neurotransmission within the brain. This evidence may suggest that by enhancing decreased endocannabinoid signaling with cannabidiol in autistic patients that they may find relief of core and co-morbid symptoms associated with this disease. The use of THC with cannabidiol was associated with better results when compared to cannabidiol alone; however, THC may cause psychosis in some patients and should be used with caution (Fernandez-Ruiz et. al., 2020).

Limitations to this review are due to the lack of research regarding the clinical application of cannabis or cannabinoid formulations in the treatment of autism specifically. Further large-scale studies are warranted for the evaluation of the safety and efficacy of cannabidiol treatment in patients with autism.

Poleg, Golubchik, Offen, and Weizman et. al., (2019) published a review that summarizes the safety and effectiveness of medical cannabis in young autistic patients. This review compiled information regarding the safety and effectiveness of medical cannabis, utilizing available pre-clinical and clinical patient data. The objective of this review was to research the use of cannabinoids as either monotherapy or adjunctive therapy for symptoms of Autism Spectrum Disorder (Poleg et. al., 2019).

The methods utilized in this review included searching for pre-clinical and clinical

studies that researched the effects of cannabidiol and its use in medicine as well as its effects on neurodevelopment, and symptoms associated with autism such as anxiety, psychosis, sleep disorders, attention deficit hyperactivity disorder, aggressiveness, and impaired social behaviors (Poleg et. al., 2019).

The results of the review included discussions regarding cannabidiol and its use for treating core and co-morbid symptoms of autism in the young. Initially, the discussion focused on the endocannabinoid (EC) system in people with autism. Social interactions, emotional responses, and behavioral reactivity are regulated by the EC system. There are two main endocannabinoids found in humans, anandamide (AEA) and 2-arachidonoyl glycerol (2-AG). There are two g-protein-coupled receptors that AEA and 2-AG bind to that are found within the cell membranes of neurons. They are cannabinoid receptors type 1 (CB1), and cannabinoid receptors type 2 (CB2). When bound, they modulate neurotransmission. Brain neurotransmission is modulated by CB1 receptors; however, CB1 receptors are also found in adipose, cardiac, hepatic, vascular, bone, and reproductive tissues. CB2 receptors are found in the brain as well as in the immune system. Cannabis psychoactivity occurs due to the stimulation of the CB1 receptors. Whereas decreased tissue damage and reduction in inflammation may occur with stimulation of CB2 receptors. Autistic patients that have co-morbidities such as anxiety, sleep disturbances, seizures, and cognitive impairments have been found to have EC systems that show lower levels of AEA in their plasma when compared to healthy controls. This may suggest that impaired levels of AEA may contribute to the development of autism in these patients. The discussion continues with how the use of cannabidiol may help reduce the symptoms associated with a decrease in the amount of AEA present at post-synaptic neuron cell membranes. Cannabidiol has a low affinity for both the CB1 and CB2 receptors, so it should not cause

psychotomimetic effects. However, it does help to reduce anxiety, addiction, and schizophrenia, implying that it has psychopharmacological effects. These effects are not habit-forming and should not produce a high. Cannabidiol has neuroprotective properties and may also act as an anticonvulsant, anti-inflammatory, antipsychotic, sedative, and hypnotic. It may also help by aiding in neurogenesis and have antioxidant-like properties too. Cannabidiol may help to prolong the effects of AEA by preventing its reuptake and enzymatic breakdown. It may help to regulate the secretion of vasopressin and oxytocin, or as an agonist at 5HT1a receptors that may then induce anxiolytic, antidepressant, and pro-cognitive like effects. The review further delves into the current acceptable use of medical cannabis in the treatment of adverse effects of cancer treatments such as chronic pain, emesis, and weight loss, as well as in the treatment of children with epilepsy that experience seizures that are resistant to current treatments. Next, the review turned to the use of cannabidiol and psychosis and found when compared to a placebo, cannabidiol showed better results regarding antipsychotic behaviors in schizophrenics as an adjunctive treatment; however, when used alone, it was ineffective. Parkinson-related psychosis also decreased when using cannabidiol treatment. When using cannabidiol for anxiety, the review found that when used by patients with social anxiety disorder, it had an anxiolytic effect. It is believed to be due to cannabidiols effects on the paralimbic and limbic areas of the brain. Some patients with autism partake in addictive behaviors like internet and television use; these behaviors may be lessened in autistic patients that are treated with cannabidiol. Autistic children tend to have difficulty falling asleep, staying asleep, or waking up frequently at night. If difficulty sleeping is associated with pain, cannabidiol may be beneficial. However, extended use may perpetuate sleep disturbances. Autistic patients typically suffer from ADHD. In a randomized placebo-controlled study of an oral cannabidiol spray that contained a 1:1 ratio of

THC: CBD, patients showed marked improvement with hyperactivity, inhibition measures, and impulsivity afterward but did not show significant improvement in cognitive performance. A major concern regarding the use of cannabidiol in children and adolescents is the effect that it may have on brain development. Since the brain is undergoing significant developmental growth at these ages, the use of cannabinoids at this time may be harmful. There are several human studies that show a correlation between major depressive disorder and cannabis use; this may also be seen in schizophrenia and cannabis use. However, it has been shown that cannabidiol, when used in humans, has a very low toxicity and does not have mutagenic or teratogenic effects on pregnancy. Care should be taken when choosing which medical cannabis product to use, as some may contain harmful agents such as pesticides and heavy metals (Poleg et. al., 2019).

The conclusions of the review found that the use of cannabidiol for the treatment of autism spectrum disorder is rapidly expanding; however, further research is needed regarding the therapeutic use of cannabidiol for autism. There is research regarding the use of cannabidiol in treating conditions that are typically associated and found in patients with autism, but further research is needed for patients diagnosed with autism and the associated comorbid medical or mental conditions that they may experience and treatment of such with cannabidiol. Treatment of ASD in adults and children appears to be relatively safe despite insufficient clinical data. Some harmful effects have been reported regarding the use of cannabinoids, some of which were due to additives and lack of regulatory supervision. Further research both pre-clinical and clinical is warranted to better establish the safety and efficacy of cannabidiol treatment of ASD symptoms (Poleg et. al., 2019).

The limitations of this review were due to a lack of research regarding patients diagnosed with autism spectrum disorder and their associated symptoms and co-morbid conditions, as well

as the lack of human versus animal trials.

Theme Two: Safety, Efficacy, and Tolerability of Risperidone in the Treatment of Autism

Aman et.al., (2015) performed an eight-week placebo-controlled trial to assess the safety, efficacy, and tolerability of risperidone treatment in autistic children or adolescents. This study was conducted with a one to two-year follow-up to assess long-term effects.

The methods employed in this study included 84 children and adolescents ranging in age from five to 17 years that were suffering from severe irritability and had been diagnosed with having autism based on the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Severe irritability was determined by having an Aberrant Behavioral Checklist (ABC) – Irritability subscale score ≥ 18. The ABC – Irritability subscale focuses on behaviors such as but not limited to: crying, screaming, and yelling inappropriately; impatience when demanding things; physically or verbally aggressive behaviors; outbursts; temper tantrums; rapidly fluctuating moods; and whininess. Scores are rated from 0-3 with 0 meaning the behaviors never occur, 1 meaning they occur infrequently and are a minimal problem, 2 they occur often and are moderately problematic, and 3 they occur frequently and are severely problematic. After the initial eight-week placebo-controlled study of risperidone use in these patients had been completed, they were further assessed over an average of 21.4 months. If they had shown a reduction in their ABC - Irritability score of > 25%, they could continue with risperidone treatment for four additional months. Those that had received the placebo and did not have any positive results were then offered the same eight-week trial of risperidone treatment. If they too showed improvement with the ABC irritability score, then they could also continue with four additional months of risperidone. The assessment both initially and at follow-up included tolerability, safety, and developmental measures (examples include but are not limited to:

analysis of non-fasting blood work, urinalysis, ECG, vital signs, side effects most often seen with risperidone treatment, neurological symptoms, behavior, and IQ) as well as standardized rating instruments (Clinical Global Impressions-Severity [CGI-S], Vineland Adaptive Behavior Scale [VABS], Children's Yale-Brown Obsessive-Compulsive Scale, ABC, and Modified Real Life Rating Scale for Autism). Whether risperidone treatment continued during the follow-up period was not controlled for. The data was analyzed statistically with the outcome results over time. Each day that the participants were exposed to either risperidone or other antipsychotics were analyzed over time (time = the number of days from the end of the eight-week trial to the follow-up date). T-tests were utilized to analyze the data regarding those participants who returned for the follow-up versus those that did not return for follow-up. Categorical variables were assessed for differences utilizing the chi-square test (Aman et. al., 2015).

The results show that of the 84 initial participants, 56 of them had continued to be treated with risperidone at follow-up. There were 61 participants that responded to risperidone, 12 that did not, and 11 that had no resolution at the end of the 8-week study. Neurological side effects were not found to be significant; however, significant side effects (p-value was considered significant at 0.10) such as excessive appetite (42%, $p=0.08$) and enuresis ($p=0.02$) were noted, while not significant 5.5% of the participants experienced weight gain. Regarding the analysis of non-fasting blood work, urinalysis, and ECG, no significant clinical side effects were noted. A decrease in severe irritability was found to be clinically significant when compared to the initial screening on the CGI-S with a $p < 0.0001$, as well as improvement in some of the core symptoms associated with Autism (socialization skills) (Aman et. al., 2015).

In conclusion, Aman et al. found that side effects related to increased appetite and enuresis increased significantly when risperidone is taken long-term. These side effects may be

offset by the clinically significant decrease in irritability and improvement with socialization skills that these children experienced while taking risperidone long-term (21.4 months at follow-up).

Limitations of this study included that a placebo control group was not utilized, developmental effects were not controlled for, tools and rating systems to adequately assess the core symptoms of autism spectrum disorder were not implemented. Since the statistically significant results were reported by parents and not the participant themselves, this poses a risk for bias. Observations of symptoms while taking risperidone were not directly performed, therefore, there is an additional risk of bias and misinterpretation of symptoms changes based on the parent's perception and interpretation of results.

The objective of the review performed by Loy, Merry, and Hetrick, (2017) was to assess the safety and efficacy of atypical antipsychotics against a placebo when treating children that are experiencing disruptive behavioral disorders.

The methods employed by Loy, Merry, and Hetrick, (2017) included five databases, two trial registers as well as CENTRAL, Embase, and MEDLINE. The randomized controlled trials needed to evaluate children and adolescents no older than 18 years of age that had been diagnosed as having a disruptive behavioral disorder. Data was collected and analyzed by two independent review authors. The quality of evidence was determined by utilizing the GRADE approach. Meta-analyses were performed regarding each primary outcome (conduct issues, aggression, side effects, and weight gain/changes) (Loy et. al., (2017).

Two hundred and thirty-eight individuals from three different studies were selected as part of a meta-analysis on aggression determined by the Aberrant Behavior Checklist (ABC) – Irritability subscale. A reduction in aggressive behaviors was found in children that were taking

risperidone as compared to the placebo (mean difference of -6.49, confidence interval of -8.79 to -4.19). Data was then pooled from two separate risperidone trials, which included 190 participants utilizing the standard mean difference. One study utilized the Overt Aggression Scale – Modified (OAS-M), while the other used the Antisocial Behavioral Scale (ABS). The ABS has two aggression subscales (reactive and proactive) to which each subscale was individually compared against the results from the study that used the OAS-M scale. When comparing the Reactive ABS subscale to the OAS-M, the standard mean difference of -1.3 shows a moderate quality of evidence to suggest that 95% of the participants should show improvement in their aggressive behaviors when taking risperidone (95% confidence interval of -2.21 to -0.40). When comparing the Proactive ABS subscale with the OAS-M, the standard mean difference of -1.12 (95% confidence interval of –2.30 to 0.06) which infers uncertainty regarding the efficacy of risperidone in reducing aggression in these children. Weight gain while taking risperidone was also analyzed using two meta-analyses. The two meta-analyses employed were the effects on weight when taking risperidone alone and the effects on weight when taking risperidone as well as a stimulant. There was a moderate quality of evidence to suggest that out of 138 participants (two studies) that were taking risperidone alone, that 95% of them did gain approximately 2.37 Kg more than those taking a placebo (95% confidence interval of 0.26 to 4.49). There was low quality of evidence to suggest that out of 305 participants (three studies) that were taking risperidone as well as a stimulant that 95% of them gained 2.14 Kg more than those taking a placebo (confidence interval of 1.04 to 3.23) (Loy et. al., 2017).

In conclusion, risperidone, when used short-term, may help to reduce aggression in children with disruptive behavior disorders according to the Aberrant Behaviour Checklist (ABC)– Irritability subscale. Due to the differences noted between reactive and proactive

aggression, the authors were unable to say if there was a clinically significant difference noted when taking risperidone or not. Adverse effects regarding weight gain were also discovered; this may be of concern for clinicians and patients alike.

Limitations to this review included a lack of high-quality trials making data interpretation challenging as well as a lack of information regarding children under five years of age.

The purpose of the systematic review performed by Maneeton, Maneeton, Putthisri, Woottiluk, Narkpongphun, and Srisurapanont, (2018), was to analyze data regarding the acceptability, tolerability, and efficacy of risperidone in the treatment of autism in children and adolescents.

The methods employed by Maneeton et. al., (2018) included searching electronic databases for randomized control trials that researched monotherapy treatment with risperidone against a placebo for autism spectrum disorder in children and adolescents. This included Scopus, CINAHL, Cochrane, and PubMed. There were no restrictions placed on language. The results of the standardized rating scales for Autism Spectrum Disorder were utilized to obtain the efficacy of outcome by pooling the response rates and mean changed scores of these standardized rating scales. All participants were 18 years of age or younger and had previously been diagnosed as having autism spectrum disorder. Efficacy was evaluated by utilizing the mean changed score of the data collected from the standardized Autism Spectrum Disorder scale that focused on the rate of response and relapse while using risperidone as compared to the placebo. Acceptability was evaluated by the rate of discontinuation found with the meta-analysis between risperidone and the placebo. Tolerability was evaluated by side effects or adverse events experienced while taking risperidone as compared to the placebo. Relative risks (RR) were calculated using the 95% confidence interval (CI). If the relative risk was exactly one, then there

was no difference between the risperidone and placebo groups. If the relative risk score was more than one, then the treatment increases the risk of results. If the relative risk score was less than one, then the treatment decreases the risk of results. The relative risk values were utilized for response rates and discontinuation between those treated with risperidone and those treated with the placebo (Manteen et. al., 2018).

The results included seven randomized controlled trials in which 372 participants were randomly selected. Participants were under the age of 18 and had to have met the criteria for the diagnosis of ASD. For those participants that received short-term treatment (six to eight weeks) with risperidone, the results of the Aberrant Behavior Checklist for irritability subscale (ABC-I) were analyzed, and a pooled mean change score was obtained. It was found that for those that were being treated with risperidone, a significantly greater response rate was noted when compared with those who had received the placebo (relative risk score of 2.57 and a 95% confidence interval of 1.35 to 4.86). For those participants that received long-term treatment (six months) with risperidone, the results of the Childhood Autism Rating Scale (CARS) were analyzed, and a pooled mean change score was obtained. It was found that for those that were being treated with risperidone, a significantly greater response rate was noted when compared to those that had received the placebo (Weighted Mean Difference -4.62, 95% CI of -7.84 to -1.40). Analysis of the pooled relapse rates showed that those that had received risperidone were significantly less likely to experience a relapse than those of the placebo group (relative risk of 0.30 and a 95% confidence interval of 0.13 to 0.68). No significant differences were found between either group regarding discontinuation due to adverse effects. Weight changes were more significant in those taking risperidone both short term and long term when compared to the placebo (weighted mean difference of 1.75 [95% CI 1.25 to 2.25] and 1.57 [95% CI 0.38 to 2.76]

respectfully). Other adverse effects that were reported included increase appetite (RR 2.64, 95% CI 1.76 to 3.96), somnolence, drowsiness, fatigue, hypersalivation, anxiety, and elevations in prolactin levels (Manteen et. al, 2018).

In conclusion, risperidone appears to be effective against and well-tolerated by adolescents and children with autism that experience core or co-morbid symptoms.

A limitation of this review was that it did include one small scale study. Some of the larger studies had received financial support by a company that holds a patent for risperidone. There were concerns regarding bias, more specifically relating to selective reporting, and publication bias may also be present. Some of the studies included in this review had received financial support by companies that hold a patent for risperidone. Large-scale randomized controlled studies should be implemented in the future to further assess the safety and efficacy of risperidone use in children with autism.

The purpose of the review performed by Oshikoya, Carroll, Aka, Roden, and Van Driest, (2019) was to address adverse events of risperidone treatment when used in children.

The methods employed in this retrospective review occurred at Vanderbilt University Medical Center and analyzed data collected from 371 children from either an outpatient or inpatient setting, who were between the ages of four weeks and 17 years when they had received their first dose of risperidone. Data was collected utilizing REDCap (an electronic data capture tool). The data was de-identified and further evaluated based on sex, race/ethnicity, psychiatric or behavioral diagnoses, comorbidities, medication dose/route/frequency/duration, and adverse effects via MedEx data. If they had received risperidone treatment outside of the facility, had not had sufficient follow-up, or if data was missing from their records, they were excluded from the review. Adverse effects of risperidone treatment had to be reported by either the patient, their

parent, observed by the clinician, or found via laboratory results. Pearson's Chi-squared, Fisher's exact test, and the Mann-Whitney U tests were utilized to assess adverse effects between those that had adverse effects and those that did not. P values < 0.05 were defined as statistically significant, and statistical tests were two-tailed (Oshikoya et. al., 2019).

The results that specifically address adverse effects that were experienced when greater than four weeks of risperidone monotherapy therapy treatment had occurred were found in 156 children. Weight gain being the most common, with 32 children experiencing these effects. Twenty-three children had extrapyramidal symptoms (akathisia, dystonic movement, spastic rigidity, and tremor), which was the second most common adverse effect that had been reported. Other adverse effects reported included but were not limited to daytime hypersomnia, hyperphagia, elevated blood glucose regardless of DM or not, hypersalivation, and abnormal thyroid function. When comparing the likelihood of having an adverse effect in relation to comorbidities of self-injurious behavior, aggression, and irritability, the following results were found: for those taking risperidone in hopes of decreasing self-injurious behavior, there was a significant risk of developing an adverse effect ($p < 0.001$; adjusted odds ratio 3.1; 95% CI 1.7-5.4); for those taking risperidone in hopes of decreasing aggression, there was a significant risk of developing an adverse effect ($p = 0.030$); and, for those taking risperidone to decrease irritability, there was a significant risk of developing an adverse effect ($p = 0.042$) (Oshikoya et. al., 2019).

In conclusion, in children who receive more than four weeks of risperidone monotherapy treatment, a significant risk of developing at least one adverse side effect is very likely. For those children that receive risperidone treatment for self-injurious behaviors, the risk of developing

adverse effects from the treatment is significant. When prescribing risperidone to children with this behavioral issue, extra caution should be taken.

Limitations to this study include: that the study was performed based off of one medical center; therefore, this may not be an adequate sample of the public as a whole; some of the patients included in this study were taking another medication that may also increase sedation and weight gain, this may cause these participants to have a greater risk of having these adverse effects; electronic medical records were used to determine adverse events with risperidone use, the information provided in the electronic health record may not be accurate or may be incomplete; and, the small sample size may not have enabled them to assess for additional risk factors and adverse events that may occur with a more large scale study.

Theme Three: Safety, Efficacy, and Tolerability of Cannabis in the Treatment of Autism

Aran, Cassuto, Lubotzky, Wattad, and Hazan, (2018), performed a study based on cannabis use in autistic children that were experiencing severe behavioral problems. The purpose of this study was to analyze the efficacy and tolerability of cannabidiol in a group size of 60 children that are currently experiencing severe behavioral problems associated with an autism spectrum disorder.

The methods utilized in this study included patient profile, treatment options, and outcome measures. The 60 patients were children ranging in age from five to 18 years with an average age of 11.8, give or take 3.5 years; of these, 83% of the patients were males. 77% of these patients had low cognitive functioning, and all the children were to attend special education programs throughout the study duration. According to the Clinical Global Impression Scale, all children that were part of the study received a severity score of six or seven and were all experiencing severe behavioral problems. All patients received a whole plant extract with a 20:1

ratio of cannabidiol (CBD) to Δ9-tetrahydrocannabinol (THC). If the responses were not adequate, lower doses of CBD were tried. The lowest dose attempted had a 6:1 ratio of CBD:THC. Doses were dissolved in olive oil and given sublingually either two or three times daily. Doses were titrated from one mg/Kg/day of CBD to 10 mg/Kg/day over a period of two to four weeks (Aran et. al., 2018).

The results are as follows: for the 44 patients that received three doses per day, the average daily dose of CBD was 3.8 mg/Kg/day with doses ranging from a low of 1.2 and high of 6.4, and the average daily dose of THC being 0.29 mg/Kg/day with doses ranging from a low of .07 and a high of 0.51. For the 16 patients that received two doses daily, their average dose of CBD was 1.8 mg/Kg/day with doses ranging from a low of 0.2 and a high of 3.4, and the average dose of THC was 0.22 mg/Kg/day with doses ranging from a low of 0.08 and high of 0.36. Forty-four children remained at the end of the study (73%), and 16 dropped out early. Of the 16 that dropped out early, three had quit after two weeks due to irritability issues, five quit as they did not experience the desired effects of treatment, and seven quit due to side effects as well as lack of desired effects. One participant, after six months of treatment, had a psychotic event. This occurred after she had increased the THC to 0.72 mg/Kg/day while the CBD remained at 6.5 mg/Kg/day. Fifty-seven patients experienced side effects of which hypervigilance was the most reported, and it often led to sleep disturbances. Other side effects of note were restlessness, irritability, and loss of appetite. The Homes Situation Questionnaire – Autism Spectrum Disorder (HSQ-ASD) and the Autism Parenting Stress Index (APSI) were utilized in determining whether improvements had been noticed in disruptive behaviors. HSQ-ASD baseline scores had a mean improvement of 1.38 with a range of -0.41 to 3.17. Whereas the APSI baseline scores had a mean improvement of 0.66 with a range of -0.08 to 1.4. Concomitant use of other medications

occurred in 49 (82%) patients, of which antipsychotics were the most used (17%). After treatment, 16 were taking lower doses or less medications overall (33%), 12 had stopped taking all other medications (24%), and four were taking higher doses or more medications (8%) (Aran et. al., 2018).

In conclusion, 61% of the patients in this study showed improvement of their disruptive behaviors after six months of treatment, of which 16 patients were receiving less or lower doses of medications, and 12 had completely quit taking other medications; only 4 needed to increase dosage or take more medications. Care needs to be taken when higher doses of THC are being prescribed as psychotic episodes may occur. Based on the results of this study, controlled studies should occur to further research the efficacy and tolerability of cannabis in the treatment of disruptive behavior in autistic children and that clinical use be postponed until further research can be obtained. The authors of this study will be launching a new study of 150 children with autism and disruptive behaviors in a placebo-controlled cross-over trial (NCT02956226) as well as another study with 100 children with autism using cannabidivarin (NCT03202303) (Aran et. al., 2018).

The limitations of this study include the use of various strains of cannabis that were from different growers and large ranges of CBD and THC dosages. With the small sample size, a true depiction of the evaluation of cannabis for autism treatment did not adequately cover all subgroups.

The objective of the study performed by Barchel et.al. (2019) was to analyze data collected from parents of children with autism that have been treated with oral cannabinoids in hopes of relieving symptoms of aggression, anxiety, and hyperactivity.

This study was conducted in Israel on children to young adults (3-25 years of age) who had been diagnosed as having autism spectrum disorder based on DSM IV or V criteria. The participants continued with follow-up for a minimum of 30 days after initial therapy with cannabidiol. Symptom response and adverse effects were analyzed by a team of specialists that ranged from pediatric neurologists who specialized in autism spectrum disorder as well as pharmacists and clinical pharmacologists. There were four comorbid symptoms of autism that were addressed self-injury, sleep problems, anxiety, and hyperactivity. For each of these co-morbid symptoms, they assessed the parent's reports for worsening of symptoms, no change, or marked improvement when compared to baseline. Participants were selected based on a registry of parents that had received a license to give their children cannabidiol from the Ministry of Health in Israel. Tikun Olam was the company that prepared and supplied the cannabidiol oil at a concentration of 30% with a concentration ratio of 1:20 cannabidiol (CBD) to Δ9-tetrahydrocannabinol (THC), with a daily dose of CBD of 16 mg/Kg (not to exceed 600mg daily) and a daily dose of THC of 0.8 mg/Kg (not to exceed 40 mg daily). Participants were excluded if they had used cannabidiol previously. Parents were taught how to administer the CBD oil by a provider, and biweekly telephone follow-ups were employed. Parents were further asked to describe what they were observing regarding their children's comorbid symptoms. This included whether they saw improvement, worsening, or no improvement of symptoms. Parents were also questioned as to whether their children were exhibiting side effects to the CBD oil and if other medications had been used. The Medical Dictionary for Regulatory Activities was utilized to code for adverse effects experienced by the children. Changes in comorbid conditions, when treated with cannabidiol, were evaluated against patients who were being treated for the same symptoms but in a conventional method. Frequency and percentage were utilized to describe

categorical data; histograms and Q-Q plots were utilized to describe continuous variables; mean and standard deviation were utilized to describe continuous variables that had a normal distribution; and median and interquartile range were utilized to describe skewed variables. Binomial testing was utilized to describe and compare the results obtained regarding comorbid conditions with cannabidiol treatment to those that had been treated by conventional therapies (Barchel et. al., 2019).

Forty-five males and eight females for a total of 53 participants were used in this study. The median interquartile range (IQR) daily dose of CBD and THC was 90 mg/Kg/day and 7 mg/Kg/day respectfully. The results regarding self-injury, hyperactivity, sleep problems, and anxiety are as follows. There were 34 participants that had been experiencing self-injurious behavior at the beginning of treatment with CBD; of these, 8.8% had worsening symptoms, 23.5% had no improvement, and 67.6% noticed improvement. Those that experienced improvement were then compared to those that had been treated conventionally and had also shown improvement; however, with a $p = 0.063$, only a borderline significance was noted. For those that had worsening of symptoms with CBD treatment when compared to conventional treatment, no significant difference was noted ($p = 0.307$). Regarding hyperactivity, sleep problems, and anxiety no significant differences were noted between CBD and conventional treatments ($p = 0.125$; $p = 0.4$; $p = 0.232$) respectfully. Overall improvement was found in 38 participants, where only two reported worsening of symptoms with CBD treatment (two participants had missing data and could not be included in the overall numbers). The most experienced adverse side effects were somnolence reported by 12 participants, and six reported decreased appetite (Barchel et. al., 2019).

In conclusion and based on reports from parents, cannabidiol may prove to be effective in relieving comorbid symptoms associated with autism, such as self-injury, hyperactivity, anxiety, and aggression. However, further research is warranted with large-scale clinical trials to better analyze the safety and efficacy of CBD for this purpose (Barchel et. al., 2019).

Limitations to this study were that there was no control group, objective tools were not utilized for assessment of changes of symptoms, and data was based on the parent's perception of symptom management by cannabidiol treatment and their reporting of such.

The purpose of the study performed by Bar-Lev Schleider, Mechoulam, Saban, Meiri, and Novack (2019) was to describe the safety and efficacy of medical cannabis in the treatment of patients with autism.

The methods that they used for this study included an analysis of data that had been collected on 188 autistic patients ranging in age of less than 5 to 18 years, from 2015-2017 in Israel. Most of these patients were prescribed cannabis mixed in oil that contained 1.5% THC and 30% CBD. They were evaluated at one- and six-month durations. The safety analysis included side effects that were experienced that were either physiological or cognitive in nature. Parents were asked to describe the duration, severity, and incidence of each side effect that was reported. Efficacy was analyzed by having the parents answer this question: "How would you rate the general effect of cannabis on your child's condition" (p. 5)? Their options for response were significant/moderate/slight improvement, no change, slight/moderate/significant deterioration. Assessment of symptoms included but were not limited to rage attacks, restlessness, agitation, and cognitive impairment. Statistical analysis was performed utilizing continuous variables with normal distribution, which were presented utilizing means with standard deviations. Ordinary or continuous variables that had abnormal distributions were given

as medians with interquartile range (IQR). Counts and percent of the total were given for categorical variables. Continuous variables with normal distributions were analyzed utilizing t-test and paired t-tests. If parametric assumptions were not able to be satisfied, the non-parametric Mann-Whitney U test and paired Wilcoxon test was implemented. Age, gender, number of chronic medications currently being used, and the total number of symptoms were included as variables in this study, as well as the three most common symptoms of rage attacks, agitation, and restlessness. The p-value of <0.05 was regarded as statistically significant (Bar-Lev Schleider et. al., 2019).

The results at one and six months are as follows. Initially, there were 188 patients that were participating in this study. After one month, eight had stopped using the treatment (4.2%), one person had switched to a different supplier of cannabis (0.5%), the 179 remaining had continued with treatment (94.6%). Of those that continued treatment, 119 had answered and submitted the questionnaire (66.4%). The results of which are as follows: 58 of them were experiencing significant improvement (48.7%), 37 had moderate improvement (31.1%), seven were experiencing side effects (5.9%), and 17 had no improvement (14.3%). The side effects that were reported are as follows: 1.6% - sleepiness, 1.6% - bad smell and taste, 0.8% - restlessness, 0.8% - reflux, and 0.8% - loss of appetite. At six months, there were an additional 15 patients that had stopped treatment (8.3%), nine switched suppliers (4.9%), and 155 that were currently still receiving treatment (86.6%). Out of the 155 participants still receiving treatment, 93 had answered and submitted the questionnaire (60.0%). Based on the results of the questionnaire, 28 patients stated that they had experienced significant improvement (30.1%), 50 had moderate improvement (53.7%), six claimed to have slight improvement (6.4%), and eight that had no improvement (8.6%). None of the variables utilized to determine the success of treatment proved

to be statistically significant. Side effects that were found to be most common after six months of treatment were: 6.6% - restlessness, 3.2% - sleepiness, 3.2% - psychoactive effects, 3.2% - had increased appetite, 3.2% - problems with digestion, 2.2% - experienced dry mouth, 2.2% - had loss of appetite. There was a total of 23 patients that had experienced side effects. Of those that had discontinued treatment, 17 had answered the questionnaire. Of these, 12 patients dropped out due to not experiencing any improvement (70.6%); the remaining five dropped out due to side effects (29.4%). Seven of these patients had expressed interest in trying the treatment again. Of the 93 that responded to the questionnaire, 67 of them were using chronic medications prior to starting this trial. Of the 67, six of them had to increase their initial medications (8.9%), 38 remained at their initial doses (56.7%), and 23 decreased their initial doses (34.3%). The chronic medications that were more commonly used were antipsychotics, antiepileptics, antidepressants, hypnotics, and sedatives. Fifty-five patients were taking antipsychotics initially (33.9%), 41 of them were taking the same dosage at six months (75%), three had decreased their dosage (5.4%), and 11 had stopped their medication entirely (20%). Both quality of life and positive mood were shown to have significant improvement after six months of treatment, each with a p-value < 0.001. Where quality of life had improved from 31.3% initially to 66.8% at six months, and positive mood had improved from 42% initially to 63.5% after six months of treatment (Bar-Lev Schleider et. al., 2019).

In conclusion, treating autistic patients with cannabis may be not only safe and effective for reducing symptoms such as rage attacks but well-tolerated, too, with 80% showing moderate to significant improvement of symptoms at the end of the six-month study. With only 15% of the total number of patients dropping out within the first six months of the study, it appears to be something that patients can remain compliant with as well (Bar-Lev Schleider et. al., 2019).

Limitations to this study were that since it was observational in nature, there was no control group to compare results with. There may be bias as parents of these children may have been seeking treatment with cannabis; therefore, it may not be a good representation of the population. All children had received a previous diagnosis of autism; however, they were not reevaluated for that diagnosis prior to the initiation of treatment. The questionnaires were answered by the parent of the child and not by the patient themselves; therefore, answers are based on the parent's opinion and may be biased. Further research is suggested utilizing a double-blind placebo-controlled format analyzing the effects of cannabis on those with autism.

Discussion

Pathophysiology and Pharmacologic properties of Risperidone and Medical Cannabis

There are several theories regarding the pathogenesis of autism and which medications may work best at alleviating the core and co-morbid symptoms of this disease. The review performed by Scott, and Dhillon, (2007), focused on the theory surrounding dysfunction of the serotonin 5-HT_{2A} and dopamine D_2 receptors in the mesolimbic and nigrostriatal pathway. The authors found that risperidone may elicit its effects by binding with serotonin 5-HT_{2A} and dopamine D_2 receptors. When risperidone is bound to dopamine D_2 receptors in the mesolimbic pathway, risperidone may decrease the incidence of psychosis in patients with autism by inhibiting that pathway. Unfortunately, when bound to dopamine D_2 receptors in the nigrostriatal pathway, inhibition of dopamine release may cause adverse motor effects such as tardive dyskinesia and extrapyramidal side effects. Risperidone has antagonistic properties when bound to the serotonin 5-HT_{2A} receptors in the nigrostriatal pathway, resulting in a release of dopamine, which decreases the likelihood of experiencing adverse motor effects. When risperidone that is used in the treatment of autism has a higher affinity for the serotonin 5-HT_{2A} versus dopamine

D_2 receptors, then the patient may experience the benefit of lessened symptoms of psychosis without the addition of tardive dyskinesia and extrapyramidal side effects (Scott and Dhillon, 2007).

Another theory focuses on a hypo-functioning endocannabinoid system with decreased levels of anandamide (AEA) at the post-synaptic neuron cell membrane, which is associated with neurotransmission within the brain. This may affect one's ability to perform complex tasks. Evidence may suggest that by enhancing decreased endocannabinoid signaling with cannabidiol, that autistic patients may find relief of core and co-morbid symptoms associated with this disease. The use of THC with cannabidiol was associated with better results when compared to cannabidiol alone. However, THC may cause psychosis in some patients and should be used with caution (Fernandez-Ruiz et. al., 2020). Poleg, Golubchik, Offen, and Weizman, (2019), discussed how the endocannabinoid system works by further explaining that there are two main receptor types located within the endocannabinoid system, CB1 and CB2. CB1 receptors modulate neurotransmission, where CB2 receptors are found within cells that make up the immune system and within the brain. Therefore, when CB1 receptors are activated by cannabis, they are responsible for the psychoactivity that occurs, whereas activation of the CB2 receptors by cannabis helps to decrease inflammation and tissue damage. They, too, found that autistic children often have a hypo-functioning endocannabinoid system and decreased levels of anandamide (AEA) at the post-synaptic neuron cell membrane, which may contribute to the core and co-morbid symptoms of this disease. What they found in their review was that research has been done regarding the use of cannabidiol in treating conditions that are typically associated with and found in patients with autism (anxiety, sleep disturbances, seizures, cognitive impairments, hyperactivity, and addictive behaviors), but that minimal research has been

conducted on these behaviors in those that are actually diagnosed with ASD. Therefore, further research is needed for patients diagnosed with autism and the associated co-morbid medical conditions that they may experience and the effectiveness of treatment with cannabidiol (Poleg et. al., 2020).

Safety, Efficacy, and Tolerability of Risperidone in the Treatment of Autism

Severe irritability was found to be significantly reduced in patients that were treated with risperidone long term, when compared to the control group, based off of their initial and final screenings with the CGI-S ($p < 0.0001$), according to the study performed by Aman et. al., (2015). Similar results were found in the review performed by Loy, Merry, and Hetrick, (2017) regarding aggressive behaviors. They concluded that when risperidone was taken short-term for disruptive behavior disorders, that those children scored lower on their ABC-Irritability subscale by 6.49 points than those that were taking a placebo. However, they advise caution when interpreting these results, as it was difficult to ascertain if there was a clinically significant change when looking at reactive versus proactive aggression in clinical practice when utilizing the ABS subscales. Maneeton, Maneeton, Putthisri, Woottiluk, Narkpongphun, and Srisurapanont, (2018) found that risperidone appears to be an effective treatment against the core and co-morbid symptoms associated with autism in children. That one in three children or adolescents may experience lessening of their symptoms as compared to those taking a placebo. However, the tolerability and acceptability of risperidone treatment showed little difference when compared to the placebo when treating these children.

Weight gain and increased appetite were commonly found to be reported as adverse effects of risperidone treatment in each of these studies. Aman et. al., (2015) found that 42% of the children that had received long-term treatment had experienced excessive appetite but did not

find clinical significance regarding weight gain 5.5%. On rare occasions, metabolic syndrome had also occurred. Loy, Merry, and Hetrick, (2017) found that 95% of the participants that had been treated with risperidone monotherapy had incurred a 2.37 Kg increase in weight when compared to the placebo and that 95% of the participants treated with both risperidone and a stimulant had a 2.14 Kg increase in weight when compared to the placebo. Maneeton, Maneeton, Putthisri, Woottiluk, Narkpongphun, and Srisurapanont, (2018) found that when compared to the placebo, weight gain was found to be more significant in the participants that were taking risperidone both short and long-term, as was increased appetite. The most common adverse effects of taking risperidone found in the review performed by Oshikoya, Carroll, Aka, Roden, and Van Driest, (2019) were weight gain, extrapyramidal symptoms, daytime hypersomnia, and hyperphagia. They noted that when children had received more than four weeks of risperidone monotherapy treatment, that weight gain was the side effect that was most reported, with 32 out of 156 participants experiencing this. Interestingly, they also found that when children were taking risperidone for the treatment of self-injurious behavior, aggression, and irritability that the likelihood of developing an adverse effect increased $p < 0.001$; $p = 0.030$; and $p = 0.042$, respectively.

Safety, Efficacy, and Tolerability of Cannabis in the Treatment of Autism

Cannabidiol, one of the cannabinoids found in the cannabis plant, may have the ability to produce anxiolytic, anti-inflammatory, and antipsychotic properties when used medically. Aran, Cassuto, Lubotzky, Wattad, and Hazan, (2018), performed a study that focused on autistic children that were experiencing severe behavioral problems and treatment of these symptoms with cannabidiol. There were 60 children between the ages of five and 18, each of which received a CBD:THC concentration of whole plant extract that was 20:1. Forty-four of

them received three doses daily with an average daily dose of 3.8 mg/Kg/daily of CBD and 0.29 mg/Kg/daily of THC. Sixteen of them received two doses daily with an average daily dose of 1.8 mg/Kg/daily of CBD and 0.22 mg/Kg/daily of THC. Sixty-one percent of the participants had a lessening of their severe behavioral problems after six months of treatment. Additionally, there were participants that had been on other medications prior to this study, with antipsychotics being the most common. After six months of treatment, 16 were receiving less or had been able to lower their previous dose medication; 12 had completely quit taking their other medications; four needed to increase their current dosage or required additional medications to be added. An important limitation to this study was that the various strains of cannabis from different growers and wide ranges of CBD and THC doses were used (Aran et. al., 2018). Similar results were found in the study performed by Barchel et. al. (2019). The authors of this study focused on the relief of the following co-morbid symptoms of autism: self-injury, sleep problems, anxiety, and hyperactivity. Participants were between the ages of three and twenty-five and had been previously diagnosed with autism based on the DSM-IV and DSM-V criteria. They had one company that prepared a 1:20 CBD:THC cannabidiol oil at a concentration of 30%. The daily dose of CBD was 16 mg/Kg (not to exceed 600 mg daily) and a daily dose of THC at 0.8 mg/Kg (not to exceed 40 mg daily). There were 53 total participants in the study, with follow-up ranging from 30-588 days. There had been 34 participants that had been experiencing self-injurious behavior prior to treatment, 67.7% of which had improvement, 8.8% had worsening of symptoms, and 23.5% had no improvement. When comparing those that showed improvement with CBD to those that showed improvement with conventional therapy, there was only a borderline significance that was noted ($p = 0.063$). When comparing those that had experienced worsening of symptoms with CBD to those that had worsening of symptoms with conventional

therapy, no significant difference was noted ($p = 3.07$). When comparing conventional treatment to CBD treatment for hyperactivity, anxiety, and sleep disturbances, no significant difference was noted. This study lacked a control group, and data collection was based on the parent's perception of symptom management (Barchel et. al., 2019). Bar-Lev Schleider, Mechoulam, Saban, Meiri, and Novack, (2019) performed a study that included 188 autistic participants that were evaluated at one and six months of duration. The participants mostly received cannabis oil that contained 30% CBD and 1.5% of THC. Assessment of symptoms included rage attacks, restlessness, agitation, cognitive impairment, and more. Eight patients had dropped out after one month of treatment. At six months, of the 179 participants that had been previously experiencing rage attacks (150 participants), and those that were continuing with treatment (155 participants) that had then responded to the questionnaire (93 participants), 65 of them had experienced a lessening of rage attacks with CBD treatment. Seventy-one had a lessening of restlessness; 57 had experienced a lessening of their agitation symptoms; 15 had a lessening of their cognitive impairment. In general, each of these studies shows improvement of co-morbid symptoms associated with autism when treated with CBD oil. This study also lacked a control group and required parents to report their observation of symptom management (Bar-Lev Schleider, et. al., 2019).

Adverse effects of CBD treatment were found in all three of the previous studies. According to Aran, Cassuto, Lubotzky, Wattad, and Hazan, (2018), 57 out of 60 participants had experienced side effects, of which hypervigilance was the most reported and often led to difficulty sleeping. Other side effects listed were restlessness, irritability, and loss of appetite (Aran et. al., 2018). Barchel et. al. (2019) reportedly had 12 participants that had experienced somnolence and six that had decreased appetite out of 53 total participants. After six months of

treatment with CBD oil, Bar-Lev Schleider, Mechoulam, Saban, Meiri, and Novack, (2019) found that 23 out of 93 participants had experienced side effects, of which restlessness was most common at 6.6%; sleepiness, 3.2%; psychoactive effects, 3.2%; increased appetite, 3.2%; digestive issues, 3.2%; dry mouth, 2.2%; and loss of appetite, 2.2%.

While each of the above studies showed improvement of co-morbid symptoms of autism, side effects were also noted. Each of the authors felt that further research was required before cannabidiol is routinely used to treat those afflicted with these symptoms.

Conclusion

Autism is a disease that is becoming more commonly seen in the primary care setting, with one out of 54 children being diagnosed yearly. Children with autism may have developmental disabilities that make it challenging for them to interact with others, to communicate with their friends and family, and to control their behaviors. Children may also suffer from aggression, irritability, and self-injurious behaviors. Understanding the pathogenesis of autism and how medications may alter that process is key in the development of a successful treatment plan.

Autism may develop due to dysregulation of dopamine and serotonin in the mesolimbic pathway. If this is true, then risperidone may elicit its effects by acting as an antagonist at the serotonin 5-HT_{2A} and dopamine D_2 receptors found within there. If autism is due to a mutation that has occurred at the cannabinoid receptor type 1 in the endocannabinoid system or if there are lower levels of anandamide present at the post-synaptic neuron cell membrane, then cannabidiol may induce its effects by acting as an agonist at the cannabidiol receptors found there. Since there are several theories regarding the pathogenesis of autism, when treatment with risperidone is not successful in lessening the frequency of behavioral outbursts in these children, then the

addition of cannabidiol may be beneficial. Further research needs to be conducted to evaluate the effectiveness of adding cannabidiol to the treatment plan of children who have already been taking risperidone, who continue to exhibit these behaviors.

It is evident by prior research that risperidone has been successful in reducing aggression, self-injurious behaviors, and irritability in patients with autism. It is also evident that weight gain is a common and significant side effect of this treatment option. For those patients that are taking risperidone for self-injurious behavior, these side effects may be more likely to occur. On rare occasions, metabolic syndrome has occurred, care should be taken when prescribing this medication long term. Approximately one-third of the patients receiving risperidone will show improvements of these behaviors; therefore, risks versus benefits should be discussed with the patient and their families prior to initiation of treatment.

Limited studies have been performed regarding the safety, efficacy, and tolerability of cannabidiol in the treatment of aggression, self-injurious behaviors, and irritability found in patients diagnosed with autism. These studies have shown a lessening of aggressiveness and self-injurious behaviors; however, adverse effects such as psychosis, decreased appetite, and restlessness have been reported. Other studies have focused on behaviors that are commonly associated with autism (cognitive impairments, sleep disturbances, anxiety, hyperactivity, addictive behaviors, and seizures) with promising results; however, further research needs to be conducted focusing, more specifically, on patients that have been diagnosed with this condition.

Applicability to Clinical Practice

Current research shows that there is clinical variability among patients that were being treated with cannabidiol and THC. Patients that were failing current treatment with antipsychotics and behavioral therapy did respond favorably and with minimal risks. However,

inconsistency regarding dosages of cannabidiol within these studies warrants further research. Based on the findings in this review, further research in the form of large-scale double-blind placebo-controlled studies is recommended to adequately determine if medical cannabis or cannabidiol is a safe and effective adjunctive treatment option for those experiencing aggression, irritability, and/or self-injurious behaviors associated with autism, while currently being treated with risperidone.

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