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

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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

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.
- 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.**

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Statement of the Problem

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- Autism affects 1 in 54 people each year.
- Atypical symptoms such as **irritability, self-injurious behaviors,** and **aggression** are common.
- Behavioral therapy is a mainstay in the treatment plan for all autistic patients.
- Risperidone is approved by the FDA to help in the treatment of autism, decreasing the frequency of these behaviors by about half in most patients (Stepanova, Dowling, Phelps, & Findling, 2017).
- Alternative treatment with cannabidiol is being sought after by many parents.
- Limited research has been performed regarding cannabidiol and autism.

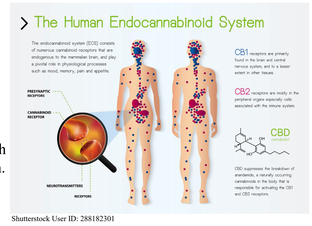
Research Question

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?

Literature Review

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

- 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 (Scott and Dhillon, 2007).
- One theory 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 develop. Since the mesolimbic pathway has very few serotonin 5-HT_{2A} receptors, antipsychotic actions of risperidone treatment would not be altered (Scott and Dhillon, 2007).
- A second theory, regarding the pathogenesis of autism, focuses on a hypo-functioning endocannabinoid system, which may be due to decreased levels of serum anandamide (AEA) at the post-synaptic neuron cell membrane which is associated with neurotransmission within the brain. This alteration may affect one's ability to perform complex cognitive or behavioral tasks (Fernandez-Ruiz, Gaive-Roperh, Sagredo, & Guzman, 2020).



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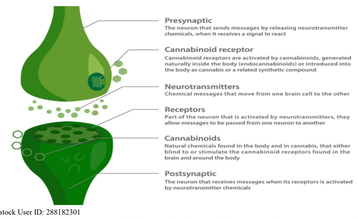

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Theme Two: Safety, Efficacy, and Tolerability of Risperidone in the Treatment of Autism

- According to the study performed by Loy, Merry, and Hetrick, (2017) when risperidone is used short-term, a reduction in aggressive behaviors in autistic children may be significant.
- Out of 138 participants and two studies, they found that of those taking risperidone 95% of them would experience a 2.37 Kg weight increase compared to the placebo group (Loy et. al. 2017).
- The review by Maneeton, Maneeton, Putthisri, Woottiluk, Narkpongphun, and Srisurapanont, (2018) found that out of 372 participants from seven randomized controlled trials that both short-term and long-term treatment with risperidone showed a significant reduction of irritability when compared to the placebo group.
- Weight changes were significant both with short and long-term treatment with risperidone when compared to the placebo (Manteen et. al., 2018).

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

- Aran, Cassuto, Lubotzky, Wattad, and Hazan, (2018) performed a study on 60 children who exhibited severe behavioral problems associated with ASD. These children were treated with sublingual cannabidiol. 61% of the participants showed improvement of their disruptive behaviors after six months of treatment (as shown in Figure 1).
- Fifty-seven out of 60 participants experienced side effects of CBD:THC treatment (Aran, et. al., 2018) (as shown in Figure 2).
- Another study with 53 children of which 34 had been experiencing self-injurious behaviors prior to treatment with CBD:THC found that 67.6% of them noticed improvement with these behaviors, 8.8% had worsening of symptoms. When compared to those that showed improvement with conventional treatment (anti-psychotics) only a marginal difference was noted. When compared to those who had worsening of symptoms with conventional treatment no significant difference was noted (Barchel, et. al., 2019) (as shown in Figure 1).
- 188 children were treated with 1.5% THC and 30% CBD for symptoms such as rage attacks, restlessness, and agitation in the study performed by Bar-Lev Schleider, Mechoulam, Savan, Meiri, and Novack (2019). At one month 79.8% were showing moderate to significant improvement of symptoms. At six months 83.8% showed moderate to significant improvement of their symptoms (as shown in Figure 1).

Discussion

- **Irritability, self-injurious behavior**, and **aggression** are common comorbid atypical behaviors found in autistic children and adolescents, for which treatment is sought.
- There are several theories regarding the pathogenesis of autism.
  - A dysfunction of the serotonin 5-HT_{2A} and dopamine D_2 receptors in the mesolimbic and nigrostriatal pathway (Scott and Dhillon, 2007).
  - 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 (Poleg et. al., 2019).
- Behavioral therapy is a mainstay in the treatment of autistic children but is not always adequate in alleviating these atypical symptoms.
- Risperidone is an FDA approved antipsychotic medication for the treatment of atypical symptoms of autism when behavioral therapy is not sufficient.
  - Frequency of atypical symptoms may be decreased by half in most children (Stepanova, Dowling, Phelps, & Findling, 2017).
  - **One** out of **three** children will continue to experience these atypical behaviors with risperidone treatment.
  - Adverse effects such as excessive weight gain are common and may be increased in those experiencing self-injurious behaviors (Low, Merry, & Hetrick, 2017) (Oshikoya, Carroll, Aka, Roden, & VanDriest, 2019).
  - Metabolic syndrome has also occurred but is rare (Aman et. al., 2015).
- Many families are requesting alternative treatment with cannabidiol for relief of these symptoms.
- Limited research studies have been conducting regarding cannabidiol treatment for atypical behaviors in autistic children.
  - 60-80% of children that were treated with a variation of cannabidiol:Δ9-tetrahydrocannabinol dosages were found to have lessening of frequency of irritability, self-injurious, and aggressive behaviors (Aran et. al., 2018) (Barchel et. al., 2019) (Bar-Lev Schleider et. al., 2019).
  - Side effects most commonly experienced were hypervigilance which caused sleep disturbances (Aran et. al., 2018), somnolence and decreased appetite (Barchel et. al., 2019), and restlessness (Bar-Lev Schleider et. al., 2019).
  - Psychosis occurred in one patient when THC levels were increased (Aran et. al., 2018).

Figures

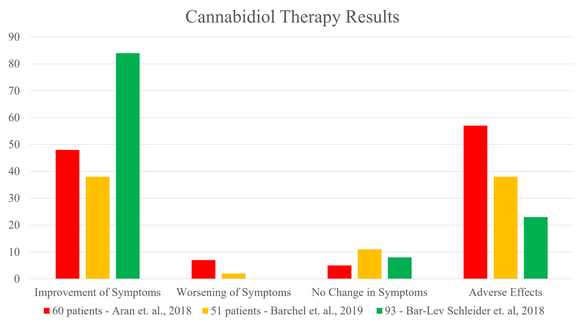

Figure 1. Cannabidiol Therapy Results of Theme Three Studies

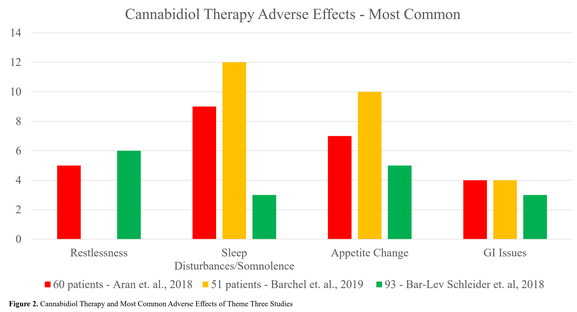

Figure 2. Cannabidiol Therapy and Most Common Adverse Effects of Theme Three Studies

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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