Comparison of the Effectiveness of Risperidone and Suramin for Autism Spectrum Disorder

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Abstract

Autism spectrum disorder diagnoses are increasing and treatments are limited. The objective of the paper is to compare the effectiveness of risperidone and suramin. Risperidone and suramin will be compared based on cellular function, efficacy, side effects, and limitations. Both risperidone and suramin have previous studies showing its efficiency which will be discussed throughout the paper. Many questions can be answered through the paper such as what is autism and what are some potential causes? What is suramin, and is it an effective drug for ASD? What is risperidone, and is it an effective drug for ASD? In addition, questions that need to be answered are which drug is the most effective? What opportunities could suramin bring to the ASD community? This study was conducted by gathering previous studies done about ASD, risperidone, and suramin and analyzed.

Chapter 1:Introduction

In 2018 CDC data showed that autism spectrum disorder affects approximately 1 in every 44 children in the United States. In 2008 data showed that 1 in 88 children in the United States was affected by autism spectrum disorder (*What Is Autism Spectrum Disorder?*, 2022). The number of children affected doubled from 2008 to 2018. In other words, twice as many children were diagnosed with autism twice the year of 2018 compared to 2008 (*Data and Statistics on Autism Spectrum Disorder*, 2022).

Autism spectrum disorder (ASD) is a developmental disorder caused by neurological differences (American Psychiatric Association, 2022, 56). ASD can impair the individual's social communication and interactions and cause repetitive behaviors or interests. Autism is classified into levels which are separated into level 1, 2, and 3. Level 1 is when the individual requires support. Individuals require support to socialize and communicate because it is hard for

individuals to start communications and social interactions. Making friends can be difficult because the individual is generally seen as shy and has difficulty keeping the conversation flowing (American Psychiatric Association, 2022, 57-58). An individual with level 1 ASD can communicate but have a hard time with to- and-for conversations. Level 2 is when the individual requires substantial support, due to deficiency in verbal and nonverbal social communication skills such as facial expression and eye contact. Individuals with level 2 have difficulty initiating conversations and have reduced or abnormal responses to social overtures from others. Repetitive behaviors are seen in level 2 but not as severe in level 3. Level 3 is when the individual requires substantial support because of severe verbal and nonverbal social communication deficiency. Typically the severe deficiency in communication is caused by severe impairments in functioning, extremely limited initiation of conversations, and minimum responses to social overtures from others (American Psychiatric Association, 2022, 58). Symptoms for ASD vary by each individual case and are not subject to levels of ASD. Some symptoms include but are not limited to hyperactivity, impulsive, gastrointestinal problems, repetitive behaviors, delay in or total lack of development of spoken language, lack of social or emotional reciprocity (Hodges et al., 2020).

One of the significant issues, when diagnosed with autism spectrum disorder(ASD) is finding treatment due to limited treatment options (Hodges et al., 2020). ASD treatments are focused on helping with secondary symptoms instead of core symptoms. Lego therapy is meant to help the individual with communication and social skills (Lindsay et al., 2017, 173-182). As the individual plays with Legos, he or she must practice taking turns and communicating with peers. Another option for treatment are pharmacological treatments. Pharmacological treatments help with symptoms like aggression, behavioral problems, depression, seizures, and anxiety. Only a few drugs have been FDA approved to help treat some ASD symptoms such as risperidone (Hellings et al., 2006).

Risperidone (also known as Risperdal) was the first drug to be FDA-approved for treating irritability in individuals with autism spectrum disorder(ASD) (Hellings et al., 2006). Risperidone was initially developed to treat schizophrenia and, in 2006, was FDA-approved to help treat ASD. Studies have reported significant improvements in individuals with ASD, and it is possible to observe a 43% change in the mean irritability score (score that measures irritability based on observed or reported behaviors) (Mano-Sousa et al., 2021). Some side effects associated with risperidone are weight gain and the development of metabolic syndrome. Weight gain and metabolic syndrome are major concerns because they may lead to type 2 diabetes mellitus. Individuals with ASD and caregivers are often left with few options because of the limited medication available.

Suramin is an old drug used to treat African sickness and river blindness. Suramin is currently in clinical trials as a potential treatment for ASD (Naviaux et al., 2014). Naviaux et al. are attempting to prove that suramin can treat the core symptoms such as impaired communication, reciprocal social interaction, repetitive behavior or interests of ASD. If suramin is proven effective, it will be the first drug to be approved for treating the core symptoms. Suramin is expected to treat the core symptoms of ASD due to its effect in the cell danger response(CDR).

Suramin blocks receptors of the CDR by inhibiting purinergic signaling. Purinergic signaling is a signal that a cell releases, among others that have effect in learning, locomotion, behavior, sleep, and memory (Huang et al, 2021). CDR causes cells to reduce communication with each other. Reduced communication between the cells interferes with brain development and function, which potentially leads to ASD. Blocking the CDR will potentially help with all ASD symptoms (Naviaux et al., 2014).

Statement of the Problem

An individual with severe ASD has severe signs and symptoms such as hand flapping, restricted interests, lack of spoken language or non-verbal, and lack of appropriate developmental play (Hodges et al., 2020). Individuals have more difficulty socializing and communicating with others. Individuals with severe autism could also have issues with irritability and aggression. Some of the signs and symptoms could improve by taking medication (Hellings et al., 2006). Medications such as Risperidone are proven to reduce irritability and aggression, which could help individuals with ASD improve communication and socializing indirectly. However, ASD has limited treatment for its signs and symptoms and no treatment for its core symptoms. Suramin is the first drug to attempt to treat the core symptoms. Suramin is currently in clinical trials and has not been approved by the FDA (Naviaux et al., 2014). Data from previous studies about the efficacy of Suramin and Risperidone in treating ASD will be analyzed, and a conclusion of the more effective drug will be presented.

Background and Needed

Old Classification of ASD

Autism spectrum disorder was once categorized as classic autism, Asperger syndrome, and pervasive development disorder not otherwise specified (PDD-NOS). Classic autism typically affects the individual's social communication and interactions and causes repetitive patterns of behaviors. Asperger syndrome usually does not have major cognittypicallyive difficulties. The individual normally has an average IQ or could have an IQ higher than average. Difficulty in using language usually is absent in Asperger syndrome. PDD-NOS has some symptoms, like classic autism, but not all (Faras et al., 2010).

Diagnosis

Diagnosis usually can be done after sixteen months of age but could be as early as twelve months. The diagnosis is ministrated by asking the parent a list of yes or no questions. If the parent questionnaire score is high, additional evaluation occurs, such as evaluations for hearing

and vision, neurological and psychological evaluation, and testing for genetic defects. In addition to that, during medical checkups, observations are made, such as checking for eye contact, pretend play, and pointing. If the diagnosis confirms that the individual has ASD, treatment plans are put in place (Hodges et al., 2020).

Cause

The cause of autism spectrum disorder is currently unknown. Most research findings have consistently shown that ASD is a multifactorial disorder meaning environmental, genetic, and metabolic factors can cause it. Research has shown a genetic association, but a gene causing ASD has not been discovered. Environmental risk factors such as rubella and high maternal age are also associated with ASD (Hodges et al., 2020).

Cellular Danger Response

Cellular danger response (CDR) is a natural cellular response to stress or injuries, which helps protect the cell and start the healing process. The CDR can get stuck and respond even after the completed healing cycle. CDR getting stuck can cause permanent damage to the way cells respond to the world. The cells then start to behave as if they are constantly injured or in danger, which alters homeostasis and causes a change of behaviors in the host. A cell stuck in cellular danger response creates a pathological metabolic memory, which can lead to chronic disease (Naviaux et al., 2014).

ABC Scale

Aberrant Behavior Checklist(ABC Scale) is a scale where behaviors can be assessed and compared. ABC scale is commonly used to evaluate the efficacy of the psychotropic medication and is used in behavior therapy. In addition, the ABC scale is used for behavioral and psychiatric research because of its high validity. The ABC scale can differentiate between behavioral

phenotypes in individuals with neurodevelopmental disorders such as ASD (Mano-Sousa et. al, 2021).

Purpose of the Study

In 2018 ASD affected roughly 1 in every 44 children in the United States (*Data and Statistics on Autism Spectrum Disorder*, 2022). ASD diagnoses are increasing, and treatments are limited (Faras et al., 2010). The purpose of the paper is to compare the effectiveness of risperidone and suramin. Risperidone and suramin will be compared based on cellular function, efficacy, side effects, and limitations. Both risperidone and suramin have previous studies showing its efficiency which will be discussed throughout the paper.

Research Questions

Many questions arise when trying to understand autism and conclude if the drugs risperidone and suramin are effective. The initial questions would be what is autism and what are some potential causes? What is suramin, and is it an effective drug for ASD? What is risperidone, and is it an effective drug for ASD? In addition, questions that need to be answered are which drug is the most effective? What opportunities could suramin bring to the ASD community?

Definitions

Autism Spectrum Disorder:

Neurodevelopmental disorder characterized by deficits in social communication with presence of restricted interests and repetitive behaviors (Hodges et al., 2020).

Classic autism:

One of the old categories of autism. Characterized by severely restricted interests, highly repetitive behavior, and severe social interaction and communication abnormalities (Faras et al., 2010).

Asperger syndrome:

One of the old categories of autism is characterized by generally higher functioning and average IQ. Cause some social difficulties and repetitive interest (Faras et al., 2010).

Pervasive development disorder not otherwise specified (PDD-NOS)

One of the old categories of autism that have most ASD symptoms but not all (Faras et al., 2010).

To-and-Fro Conversation

A conversation that requires two individuals to communicate back and forth (Hodges et al., 2020).

Ethical Considerations

The definition of cure is when an individual is relieved from all symptoms of the disorder or condition. A cure for autism spectrum disorder means that the individual will not be deficient in social communication, interaction, and repetitive behavior or interests. The major concern in finding or attempting to find a cure for autism is whether curing autism will be similar to controlling the individual. Ultimately taking their right to choose how much they should communicate and interact with others. By reducing or controlling repetitive behavior or interests might be seen as manipulating the individual to do what others want rather than themselves deciding on their own. Finding or attempting to find a cure for autism is seen as controversial because it can be seen as a way of violating the individual's rights (Graf et al., 2017).

Chapter 2:Introduction

Autism spectrum disorder (ASD) is a neurological and developmental disorder seen in early childhood and persists throughout life (American Psychiatric Association, 2022). ASD can impair the individual's social communication and interactions and cause repetitive patterns of behaviors or interests. ASD has limited treatments, especially when it comes to pharmaceutical drugs. Pharmaceutical drugs are typically used to treat irritability, aggression, and mood swing in

ASD. Pharmaceutical drugs are often seen as a last resort. Pharmaceutical drugs such as risperidone are among the few drugs approved by the Food and Drug Administration (Kent et al., 2012).

Risperidone

In 2006, risperidone was the first drug approved by the Food and Drug Administration (FDA) to treat irritability in individuals with autism spectrum disorder (Hellings et al., 2006). Risperidone is proven to treat irritability in children and adolescents (Kent et al., 2012). Risperidone was designed to resemble haloperidol while minimizing dyskinesia (Hellings J. et al., 2006). Dopamine and serotonin neurotransmitter systems are implicated in aggressive and destructive behaviors. Approximately 30% of individuals with autism spectrum disorder (ASD) have abnormal serotonergic measures. By design, risperidone exerts a serotonin 5HT2a postsynaptic receptor-blocking effect to control serotonin release (Hellings et al., 2006).

Study 1

By 2006, risperidone was proven safe and effective for aggressive and destructive behaviors in short-term studies (Hellings et al., 2006). *A Crossover Study of Risperidone in Children, Adolescents, and Adults with Mental Retardation* by Hellings and colleagues was designed to determine the risperidone effect in a longer duration with a broad sample. Forty subjects participated in this study, ages 8-56 years (mean=22). All subjects who participated in The study had an IQ of less than 70. Subjects with significant aggression or self-injury were included in the study to determine the results better (Hellings et al., 2006).

Setting/Sample

Three hundred forty-three patients were screened, but the study sample consisted of 23 males and 17 females due to ineligibility and drop-outs. In the study, there were 13 children (8-12 years), eight adolescents (13-18 years), and 19 adults (22-56 years) (Hellings et al., 2006). 85% of the subjects were white, 7.5% African American, 2.5% Hispanic, and 5% other. The

levels of MR were 11 mild, nine moderate, 11 severe, and nine profound (Hellings et al., 2006). The study consisted of 28 subjects who met DSM-IV criteria for Autistic Disorder and 8 for Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS) (Hellings et al., 2006).

Procedure

The subjects were randomized into low or high-dose risperidone phase, and over two weeks, the amount of risperidone was gradually increased to a low or high dose (Hellings et al., 2006). The study consisted of a 22-week crossover study and 24 weeks of open maintenance after the crossover study. The low dose was given 1 mg/day for children and adolescents, while adults were given 2 mg/day; all received the dose twice daily. The high dose was calculated by pharmacists who used subjects' baseline weight to calculate each high dose, which was 0.05 mg/kg/day for all groups regardless of age . For children and adolescents, the high dose mean was 2.0 mg/day (range 1.2-2.9 mg/day). For adults, the high dose mean was 3.6 mg/day (range 2.4-5.2 mg/day). The study was based on an automatically blinded dose-halving mechanism to remove subjects who might have severe side effects. Study drop-out was an option for all matters. The results were determined using SAS Proc Mixed to compare the mean of the ABC-C Irritability score and ABC-C subscale (Hellings et al., 2006).

Results

In the acute phase, the Irritability subscale score decreased from 19.16 in placebo 1 to 11.5 for the low dose and 13.31 in the high dose phase (Hellings et al., 2006). The Irritability subscale score of 23 subjects showed a 50% reduction, and 35 subjects showed a 25% decrease. Gender, mood disorder, and antiseizure medications were shown not to alter the response. The dose in the study was not significant, which means that aberrant behaviors were not significantly different between the two dose conditions. Both low and high doses of risperidone were effective, and the difference between the mean was not extremely large. The low and high doses

had significantly different impacts on the adverse events. In the study, almost one-third of the subjects could not tolerate a gradual dosage increase of 0.05 mg/kg/day (over two weeks) because of sedation or gastrointestinal complaints (which were dose-related). Side effects such as increased appetite, weight gain, drowsiness, gastrointestinal complications, and sedation were present in the study (Hellings et al., 2006).

Limitations

The subgroups were small due to the heterogeneous sample (Hellings et al., 2006). The crossover study design can compromise the blind raters because the subjects were given the drug at predictable stages. Other limitations are the broad age group range and that IQ testing was accepted if done within the past three years. The diagnosis of the subjects was based on clinical history rather than the autism diagnostic scales (Hellings et al., 2006).

Study 2

Risperidone improves irritability in children and adolescents (Kent et al., 2012). The primary concern is the long-term safety and tolerability of the drug . Given the need for risperidone long-term use, it is essential to determine the dose that should be administered long-term to lower the adverse side effects. Justine M. and his coworkers held a research study in 2012 called *Risperidone Dosing in Children and Adolescents with Autistic Disorder: A Double-Blind, Placebo-Controlled Study*. The study was done to determine the lowest effective dose to be given to minimize the potential adverse effects risperidone can cause.

Purpose

The purpose of the study *Risperidone Dosing in Children and Adolescents with Autistic Disorder: A Double-Blind, Placebo-Controlled Study* is to find the lowest effective dose in efforts to minimize risperidone effects. Potential adverse effects can include weight gain, dyslipidemia, hyperglycemia, sedation, and tardive dyskinesia.

Setting/Sample

The study populations were children and adolescents aged 5 to 17 from either sex and in total of 96 patients (Kent et al., 2012). The weight limitation was a minimum of 20 kg with a diagnosis of autistic disorder . The diagnosis was determined based on scores on the Autism Diagnostic Interview-Revised. Parents were asked several questions and scored based on answers.

Intervention

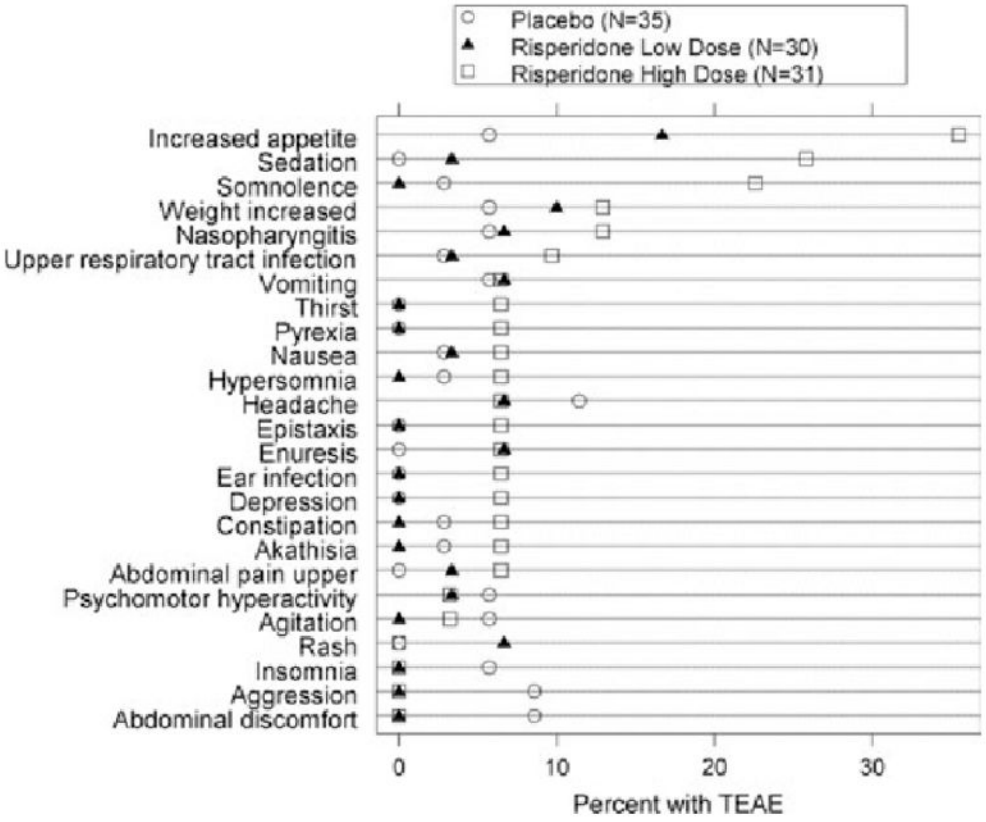
The study included parent-related scores of at least 18 for Aberrant Behavior Checklist-Irritability (ABC-I) (Kent et al., 2012). The participants were required to have a mental age of more than 18 months. Participants with a history of seizures were not allowed to participate if they were not seizure-free for at least six consecutive months. The exception for the previous requirements is if the participant were on a stable dosage of antiepileptic drugs for at least four weeks before screening. Participants were not allowed to take psychotropic medications for at least one week before baseline. Participants were required to have average fasting glucose, creatinine, and liver function test levels less than 1.5 times the upper limit of normal. Pregnant females were not allowed to participate in the study (Kent et al., 2012).

Procedure

Risperidone was given in two doses (Kent et al., 2012). The low-dose group was administered 0.125 mg/day for those who weighed < 45kg. The weight for the low-dose group ranged from 20 to <45 kg. Those who weighed >45kg received 0.175 mg/day. The high-dose group was administered 1.25 mg/day for those who weighed < 45kg. Participants who weighed > 45 kg received 1.75 mg/day. Risperidone was treated from day 1 to day 4 for both groups (the initial dose from 1 to 3 days was the same but was increased on the fourth day). The drug was administered in the morning or the evening if sedation occurred during the day. Results were determined by treatment-emergent adverse event (TEARs), virtual signs measurements, Physical examination discoveries, EPS rating scales, 12 lead electrocardiograms, clinical laboratory

parameters, Simpson-Angus Rating Scale, Abnormal Involuntary Movement Scale, changes from baseline due to growth hormone factors, prolactin, insulin resistance. Plasma concentration and 9-hydroxy-risperidone and active metabolite were checked in week 6 (Kent et al., 2012).

Figure 1: TEAE treatment-emergent adverse



(Kent et al., 2012)

Results

Participants were randomized per group; 80 percent of the randomized patients completed the six-week double-blind phase. (Kent et al., 2012). The median duration of the treatment ranged from 42 and 43 days. The results of the high-dose and low-dose groups were compared to the placebo. The high-dose group response rates were significantly higher than the low dose compared to the placebo, whose scores were based on Clinical Global Impressions-Severity Scale (CGIS). Irritability scores also improved significantly in the high-dose group but not in the low-dose groups. In the ABC subscales, patients were shown improvements in

hyperactivity subscale scores in the high-dose group. In the low-dose group, there were improvements in the stereotypic behavior subscale scores compared to the placebo. Low-dose and high-dose groups had side effects such as somnolence, sedation, and increased appetite. In the low-dose groups, the side effects happened more frequently than in the high-dose groups (Kent et al., 2012).

Study 3

The use of psychotropic drugs for autism spectrum disorder (ASD) has been growing (Aman et al., 2015). One of the significant issues in this thesis is the lack of knowledge of its long-term effect. Some previous studies, such as Vitiello B. in 2003, noticed that younger patients pose additional concerns with psychotropic exposure, which includes effects on growth, the timing of puberty, brain development, and cognitive effects. The study *Tolerability, safety, and Benefits of Risperidone in Children and Adolescents with Autism: 21-Month Follow up After 8-Week Placebo-Controlled Trial* by Aman M. and coworkers was done to determine the effects of risperidone exposure over 1-2 year follow up period. The study gathers follow-up samples from previous trials that earned FDA approval for risperidone to see if the patient report and assessments show any adverse side effects.

Setting/Sample

Eighty-four subjects (of the originally studied 101 subjects) participated in the study and were assessed for at least some measures (Aman et al., 2015). Of the 84 subjects, 17 were girls, and 67 were boys. The baseline age mean was 8.82 years, and the follow-up was 10.61 years. The ABC Irritability subscale score of the baseline was 26.01, and the follow-up was 26.20 for the sample of 101 (Aman et al., 2015).

Procedure

Families who participated in the original RUPP risperidone protocol were asked to return and do an assessment for about 5-6 hours (Aman et al., 2015). The assessment included clinical

non fasting laboratory tests for complete blood count (CBC) with differential, urinalysis, ECG, vital signs, side effect review form, height and weight, the Simpson-Angus rating scale for extrapyramidal symptoms, the abnormal involuntary movement scale (AIMS), physical examination, medical history, and IQ test. In addition to that, parents were interviewed, which included VABS and the children's Yale-Brown Obsessive Compulsive Scale Modified for PDD. VABS was used to assess the child's performance of daily tasks such as social skills, communication skills, and daily living skills. CY-BOCS-PDD was used as a severity scale from 0-4 on repetitive behavior, level of resistance to repetitive behaviors, control over repetitive behaviors, and interference with ongoing events. The parents were also asked to rate their children using the ABC (used to assess treatment effects in subjects with autism) and the Modified Real Life Rating Scale for Autism. Both were used to rate/scale behaviors such as sensory-motor behaviors, social withdrawal, social relatedness, etc. Parents were also asked about other medications the subject uses (Aman et al., 2015).

Figure 2:

Side Effects That Exceeded Baseline Severities For Risperidone (N=57) And Non-Risperidone (N=27) Groups (Rates >9% of Risperidone or Non-Risperidone Groups)

SIDE EFFECTS THAT EXCEEDED BASELINE SEVERITIES FOR RISPERIDONE (N=57) AND NON-RISPERIDONE (N=27) GROUPS (RATES ≥9% OF RISPERIDONE OR NON-RISPERIDONE GROUPS)

	Risperidone		*No risperidone*		
Side effect	**n**	**%**	**n**	**%**	**p *value (Fisher exact test)***
Sleep Problems	6	10.5	2	8.0	1.00
Tired during the day	13	23.2	7	28.0	0.78
Difficulty awakening	7	12.3	6	24.0	0.20
Constipation	5	8.9	5	20.0	0.28
Diarrhea, loose stools	9	15.8	1	4.0	0.27
Dyspepsia	5	8.9	2	8.0	1.00
Nausea or vomiting	6	10.6	2	8.0	1.00
Anxiety	7	12.3	7	28.0	0.13
Excessive saliva, drooling	10	17.5	2	8.0	0.33
Excessive appetite	24	42.1	5	20.0	0.08
Dry mouth, increased beverage intake	6	10.6	4	16.0	0.48
Urinary problems (enuresis)	11	19.6	0	0.0	0.01
Rhinitis (runny nose)	7	12.5	2	8.0	0.71
Skin rash	3	5.4	3	12.0	0.37
Peculiar eating habits	4	7.1	3	12.0	0.67

(Aman et al., 2015)

Results

Overall, the CGI-S score over the 21-month interval did show improvement in global severity, except for three subjects (Aman et al., 2015). The adverse effects of risperidone were reported, and 42% of the subjects had an excessive appetite. In addition, subjects treated with risperidone had a higher incidence of urinary complications. 3.7% of the subjects reported new seizures, whereas those not treated with risperidone did not report any seizures. Blood counts, chemistries, urinalysis, ECG, or medical history showed no clinical significance. Social skills improved with risperidone. Core symptoms and maladaptive behaviors were improved regardless of group. Height and weight were higher in the risperidone group than in the non-risperidone group. Irritability scores were lower in the risperidone group compared to the non-risperidone group (Aman et al., 2015).

Limitations

The study's limitations included no control group free of treatments, inadequate control for developmental effects, and limited rating instruments (Aman et al., 2015). The study had to rely on parent reports, which may have been biased. No outside information or direct observations could have impacted the results. There was also a difference between those who enrolled in the study and those who declined (Aman et al., 2015).

Chapter 3: Introduction

Autism Spectrum Disorder has limited pharmaceuticals for treatment (Hodges et al., 2020). The available pharmaceuticals are used to treat symptoms such as aggression, irritability, and rapid mood swing. Medications that help individuals with ASD do not treat ASD core symptoms, which include social interactions and communication, nor do they treat the underlying cause. Suramin is currently in clinical trials to attempt to prove it can treat ASD's core symptoms. The core symptoms, such as social interaction deficiency, are not treatable currently by pharmaceutical drugs (Naviaux et al., 2014).

Suramin

Suramin is the oldest manufactured drug still in medical use. Suramin was once used to treat African sickness, and now it is being tested to treat autism spectrum disorder. Suramin has many actions, and one of its actions is an inhibitor of purinergic signaling. Purinergic signaling is a signal that a cell releases, among others that have effect in learning, locomotion, behavior, sleep, and memory (Huang et al, 2021). Suramin is the first clinical trial drug with the goal of treating the core symptoms of ASD (Naviaux et al., 2014). Suramin is proposed to help with social interactions and communication by maladaptive cellular danger response (CDR). The CDR is a natural response that helps protect the cell in response to physical, chemical, metabolic, and psychological danger. If the CDR persists once the danger is gone, biochemical pathways of several cellular metabolites can remain disrupted, leading to mitochondrial and plasma membrane damage. ASD is one of many multifactorial disorders with a maladaptive CDR

proposed as an underlying cause. Some others are rheumatoid arthritis (Sahu et al, 2012), multiple sclerosis (Novales-Li, 1996), and diabetic kidney disease (Korrapati et al., 2012).

Study 1

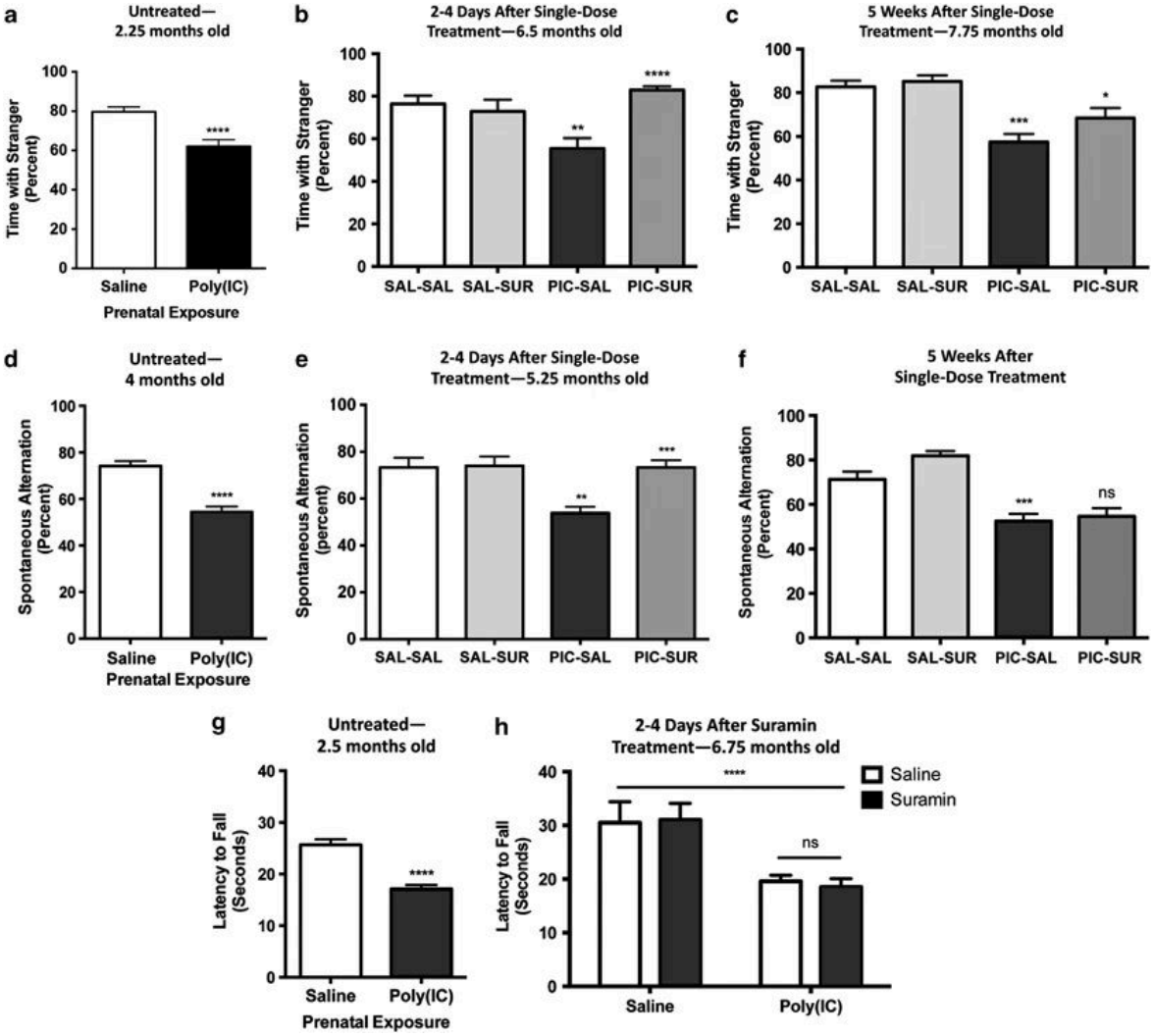
Autism spectrum disorder has many potential causes, which include genetic, environmental, and metabolic factors (Naviaux et al., 2014). Despite all these potential causes and risk factors, there could be a common underlying problem shared by the behavioral and cognitive features. Dr. Naviaux and his co-workers believe that the cell danger response is the underlying cause of autism. They think that by using suramin to block the cell danger response, the core symptoms of autism will improve. The study, *Reversal of autism-like behaviors and metabolism in adult mice with single-dose antipurinergic therapy,* by Dr. Naviax and co-workers, was created to determine the study of a single dose of the suramin on the behavior and metabolism of adult animals.

Procedure

The maternal immune activation (MIA) mouse model was used to determine the side effects of a single dose of suramin (Naviaux et al., 2014). The MIA mouse model of neurodevelopmental disorder was chosen because it produces symptoms similar to autism spectrum disorder. The single dose of suramin was 20 mg kg which was given to 6-month-old male adult mice. Initial behavioral testing occurred at nine weeks of age and was tested for social approach, T maze, rotarod (motor test for mice), light-dark box, and absence of abnormal behaviors. If the mouse had abnormalities in these behaviors, treatment with suramin or saline was started at 21 weeks and continued. Metabolomic analysis was also present to show the metabolic problem/pathway of ASD, which could potentially be the cell danger response (Naviaux et al., 2014).

Figure 3

Antipurinergic therapy of ASD



(Naviaux et al., 2014)

Results

The social approach was contrasted by observing an MIA mouse that showed social decisions early on and presented it with a stranger mouse (Naviaux et al., 2014). Once the MIA mouse received a single dose of suramin, its behavior changed entirely to normal. There was then a suramin washout after five weeks, and a few social changes seen previously remain present (after suramin). Metabolomic benefits were still present after five weeks, indicating that there could be a potential connection with the cause of autism (which was not examined further). The T-maze was administered to measure memory and spontaneous alternation of behavior. The measurement was concluded by comparing whether the rodent would present a novel preference

or have it suppressed (Naviaux et al., 2014). Novel preference is a feature of normal rodents and human behavior; it can predict socialization and communication in children with an autism spectrum disorder. Novelty preference was referred to as spontaneous alternation behavior. Before rodents were provided a single dose of suramin, about 50% showed deficiency in novelty preference by chance. After a single dose of suramin, the rodents' deficiencies were standardized. A suramin washout was also done after five weeks, resulting in a return of deficiencies. Comprehensive metabolic analysis showed that purine metabolism is the fundamental model and that correction of purine metabolism normalized 17 to 18 metabolic pathways. Plasma concentrations were measured before and after suramin to show the uptake of suramin of the central nervous system. The results showed a good uptake of suramin into the central nervous system (Naviaux et al., 2014).

Study 2

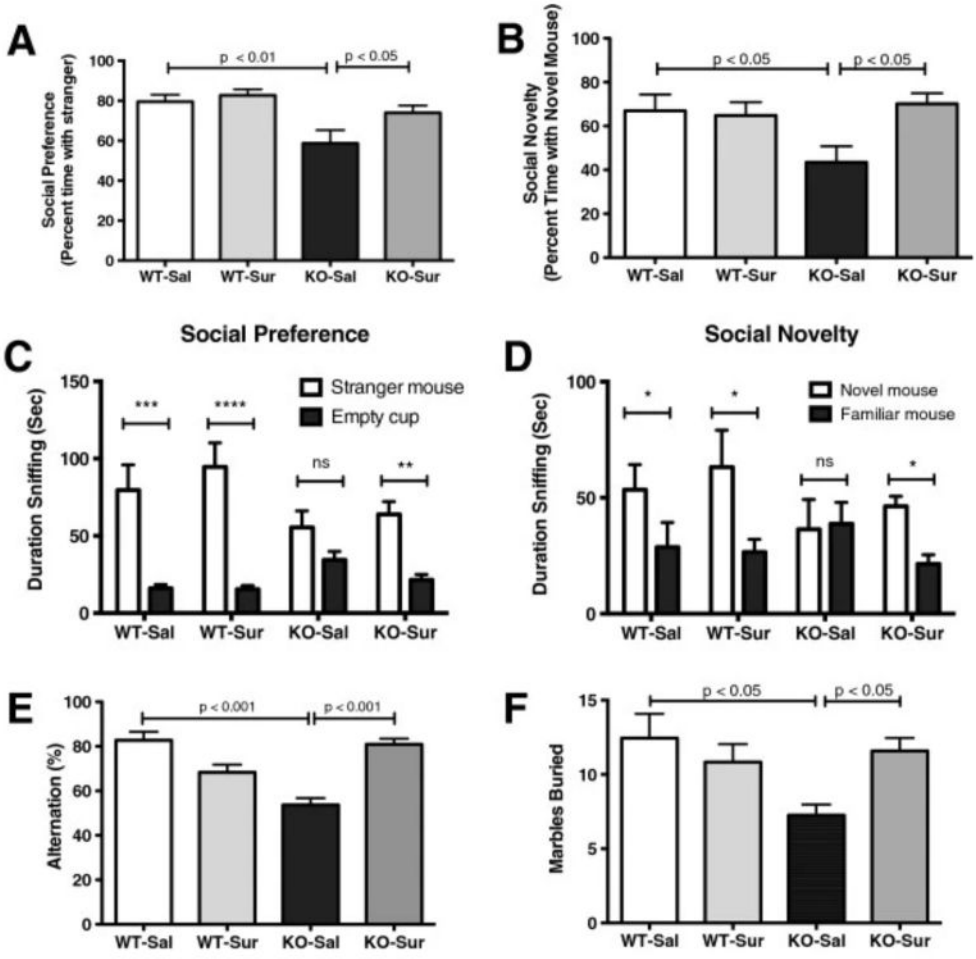
As previously mentioned, the cause of autism spectrum disorder (ASD) is unknown, but studies have shown an association with environmental and genetic factors (Naviaux et al., 2015). The previous study in 2014 found that Fmrl protein (FMRP) was downregulated by 50%. FMRP was restored to normal with suramin, as well as the behaviors in the mouse immune activation mouse model. FMRP is an mRNA and ribosome binding protein that binds to DNA repair proteins involved in cell danger response. In Fragile X models are known to be mechanistically distinct examples of genetic causes of ASD, while MIA is considered an example of environmental causes. The connections found indicate that the cause of ASD could be an underlying metabolic cause (potentially cell danger response) (Naviaux et al., 2015).

Procedure

Behavioral analysis, metabolomics, electron microscopy, and western analysis were used to determine whether suramin can treat disturbance in social behaviors, novelty preference, metabolism, and synapse structure (Naviaux et al., 2015). The behavioral analysis started 13

weeks after taking suramin weekly for one month. Tests such as T-maze, locomotor activity, marble burying, acoustic startle, and social approach were tested on mice for analysis of behaviors. In each test, the mice's social preference was observed, and later on, a stranger mouse was added to observe social novelty. After receiving 16 weeks of suramin or saline (control group), the mice were sacrificed at the age of 25 weeks for the collection of cerebral samples. The cerebral samples were viewed in a transmission electron microscope(TEM) to see the effects of suramin. Western blot was used to separate and identify proteins (Mahmood & Yang, 2012). Twenty micrograms of cerebral synaptosomal proteins were loaded on gels and transferred to a polyvinylidene difluoride (PVDF) membrane for identification (Naviaux et al., 2015).

Figure 4



(Naviaux, 2015)

Results

Western blot analysis showed that there was an absence of the Fragile X protein (FMRP) expression in Fmrl knockout mice (Naviaux et al., 2015). Fmrl knockout are mice that display similar symptoms in human condition such as extremely active, repetitive behaviors, and seizures (Naviaux, 2015;Dolan, 2013). 17 of 54 proteins were found to be changed after suramin treatment of 25 weeks of age. Restoration of normal social behavior was determined by behavioral analysis which showed 26% of Fmrl null male mice improved in social preference, which was measured by time spent interacting with a stranger mouse compared to objects. A 35% reduction in social novelty was shown and was measured by comparing interactions with a novel mouse compared with a familiar mouse. Spontaneous alterations, such as the willingness

of rodents to explore new environments, were measured in the T maze. Suramin improved spontaneous

alterations in the Fmrl knockouts, but no improvement was seen in the FVB controls (FVB is a strain of mice with sensitivity to Friend leukemia virus B strain) which presented a p-value of $p< 0.0001$ (Taketo et al., 1991;Naviaux et al., 2015). Suramin improved marble burying resulting in p-value score of $p<0.05$. Cerebral synaptosome structure was improved by suramin and in addition to that 17 of 54 proteins that were interrogated in cerebral synaptosomes were changed due to suramin. 20 biochemical pathways were associated with symptom improvements and 17 were shared with individuals with autism spectrum disorder. These pathways found were to be related to cell danger response which indicates an association with CDR and autism.

Study 3

Suramin was first synthesized in 1916, making it the oldest manufactured drug still used in medicine (Naviaux et al., 2017). One of the suramin's uses is as an inhibitor of purinergic signaling; blocking the purinergic signaling stops the cellular danger response. It ultimately suppressed the core symptoms potentially caused by the cellular danger response. Although suramin is a very promising medication, it does have its concerns on safety. The case study *Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial* by Dr. Naviaux and co-workers was created to determine whether suramin was safe to treat autism spectrum disorder in children.

Purpose

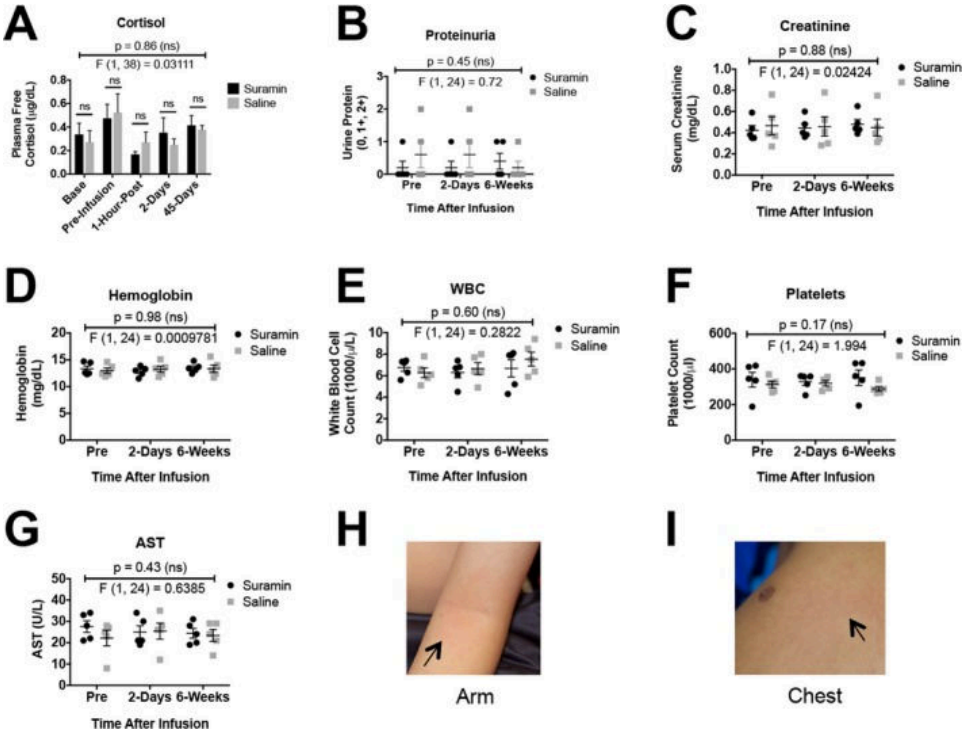
This clinical trial aims to determine whether or not suramin is a safe medication to treat children with autism spectrum disorder (Naviaux et al., 2017). In addition to safety, the case study will also examine the activity of single-dose suramin. If proven true, the drug suramin could then be approved for other clinical trials on humans to determine if it genuinely improved ASD core symptoms.

Procedure

The clinical trial was done with ten male subjects with ASD, ages 5-14. These ten males were matched based on age, nonverbal IQ, and ADOS scores into five pairs (Naviaux et al., 2017). The study was double-blind, and the placebo and the tested group were determined by a randomized sequence generated electronically. The suramin dose of 20 mg/kg or saline was the placebo. Samples of blood urine were collected five times throughout the study to monitor toxicity. The National Cancer Institute Common Terminology Criteria for Adverse Events scale were used to grade in severity the adverse events. Scripted phone calls monitored adverse effects until the end of the case study. A neurological examination was done before and at the end of the case study. The primary outcomes of behaviors were measured by ADOS-2 comparison scores and the Expressive One-Word Picture Vocabulary Test (EOWPVT). The secondary outcomes were measured by an aberrant behavior checklist, autism treatment evaluation checklist, repetitive behavior questionnaire, and clinical global impression questionnaire (Naviaux et al., 2017).

Figure 5

Safety Monitoring



(Naviaux et al., 2017)

Results

The case study revealed that suramin has no severe toxicity or adviser effects. Patients had their blood pressure and other vital signs changed during the study, and no significant change was present (Naviaux et al., 2017). Hemoglobin, cortisol, white blood count, platelets, liver transaminases, creatinine, and urine protein showed no significant difference. However, five children developed a rash over 1-20% of their body, which peaked one day after drug administration and disappeared in 2-4 days. ADOS-2 comparison scores improved by 95% in the suramin group at week 6, while there was no change in the placebo group. EOWPVT scores did not change for both groups. There were improvements in language and social interaction and decreased restricted or repetitive behaviors, which increased for three weeks, then dressed slightly over the next three weeks (Naviaux et al., 2017).

Limitations

The size of the study was small, which is a more massive study that could bring forth a greater perspective of safety (Naviaux et al., 2017). The reports on behavior improvements were

reported by parents, which could have been biased. The parents reported improvements after three weeks and then gradually decreased in improved behavior afterward. The blood tests showed that suramin levels decreased from 12 to 4 umol/L after three weeks. The parents reported rash and scripted phone interviews, which could have caused the improvements to be either more significant or lower than they should have been. Another limitation was the ADOS scores, usually used for diagnosis and not having a repeated outcome measure (Naviaux et al., 2017).

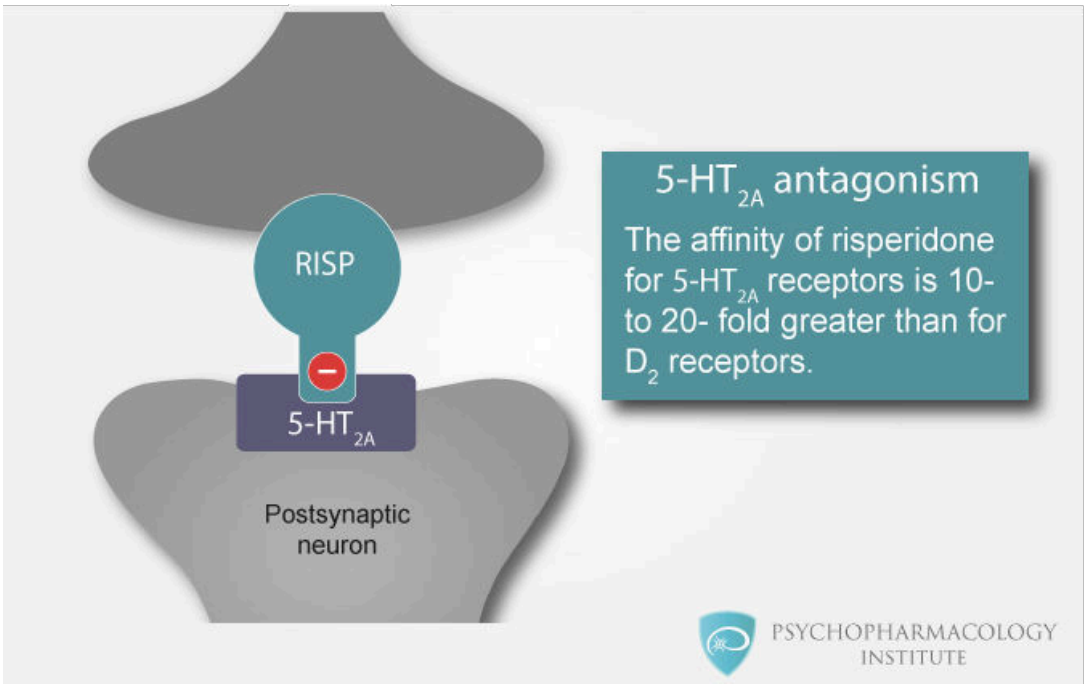
Chapter 4: Comparison

Studies have shown that risperidone and suramin are pharmaceutical drugs that can be effective to treat autism spectrum disorder(ASD) (McNeil et al., 2022;Naviaux et al., 2014). Risperidone is currently FDA approved to treat ASD. Risperidone has been FDA approved since 2006. Many studies have shown risperidone efficiency. Risperidone works by inhibiting 5-HT2A serotonergic receptors and D2 dopaminergic receptors. Suramin is currently in clinical trials in an attempt to prove it can treat ASD's core symptoms, by controlling the cell danger response (Naviaux et al., 2014). The cell danger response could be a potential underlying cause of ASD. In this chapter the function, efficiency, side effects, and limitations of the two pharmaceutical drugs will be discussed.

How does Risperidone work?

Figure 6

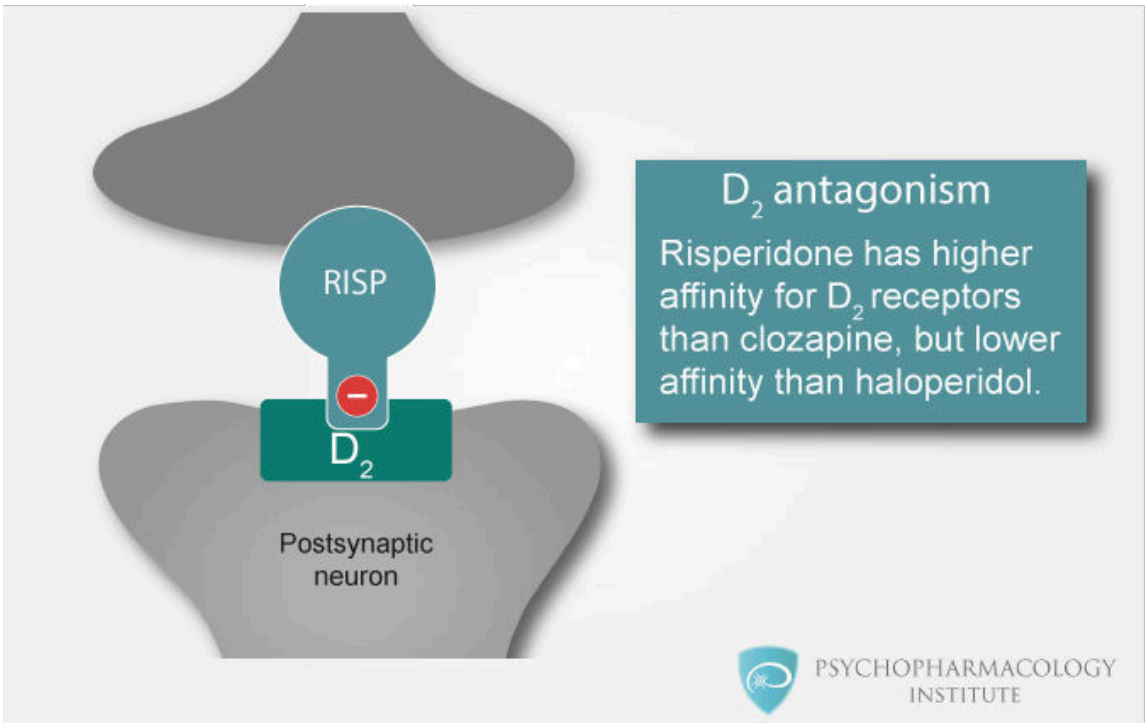
5-HT2A Antagonism



(Guzman, 2014)

Figure 7

D2 Antagonism

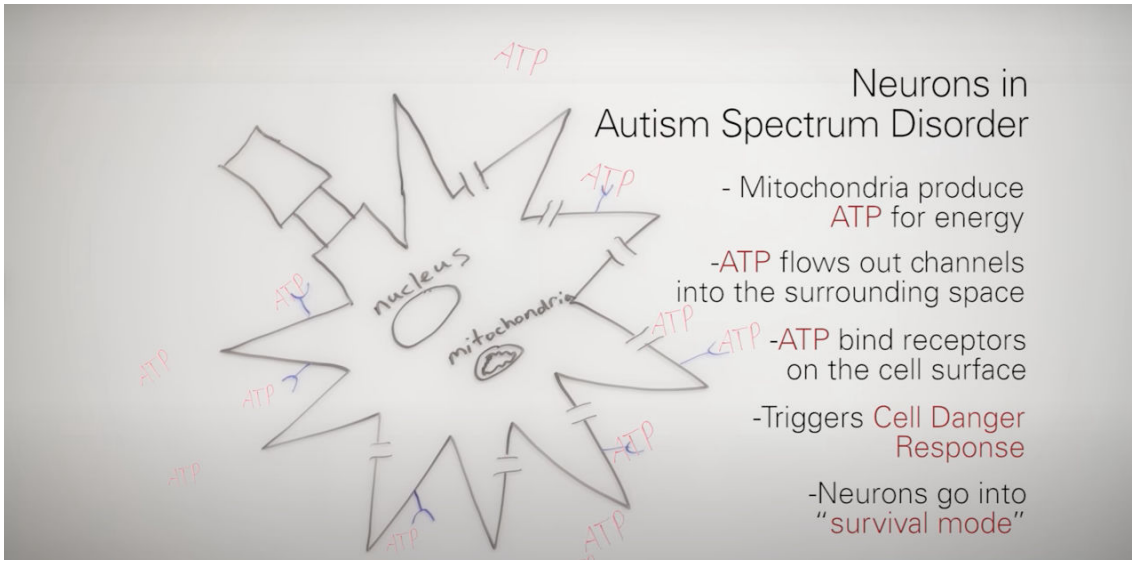


(Guzman, 2014)

Risperidone is an atypical antipsychotic; its exact mechanism of action is currently unclear (McNeil et al., 2022). However, it is believed that the primary function is to antagonize the 5-HT2A serotonergic receptors (figure 6) and D2 dopaminergic receptors (figure 7) Serotonin is a chemical that is responsible for carrying messages between nerve cells and the rest of the body (Berger, Gray,& Roth 2008). Serotonin plays a role in mood, sleep, digestion, and more. Risperidone connects to 5-HT2A serotonergic receptors to block the release of serotonin, which controls its function (Figure 6) (McNeil et al., 2022). Dopamine is a chemical that plays a role in emotions, movement, and the reward system in the brain. D2 dopaminergic receptors are one of five receptors of dopamine (Bhatia, Lenchner, & Saadabadi, 2022). Risperidone connects to D2 dopaminergic receptors and blocks dopamine from being released (Figure 7) (McNeil et al., 2022). Studies have shown that individuals with autism have low serotonin levels. Low serotonin levels can worsen repetitive behaviors and increase irritability. Ultimately by blocking the serotonergic and dopaminergic receptors, risperidone can rebalance dopamine and serotonin to improve irritability.

Figure 8

Autism Spectrum Disorder: Cell Danger Response



(UC Health - UC San Diego, 2022)

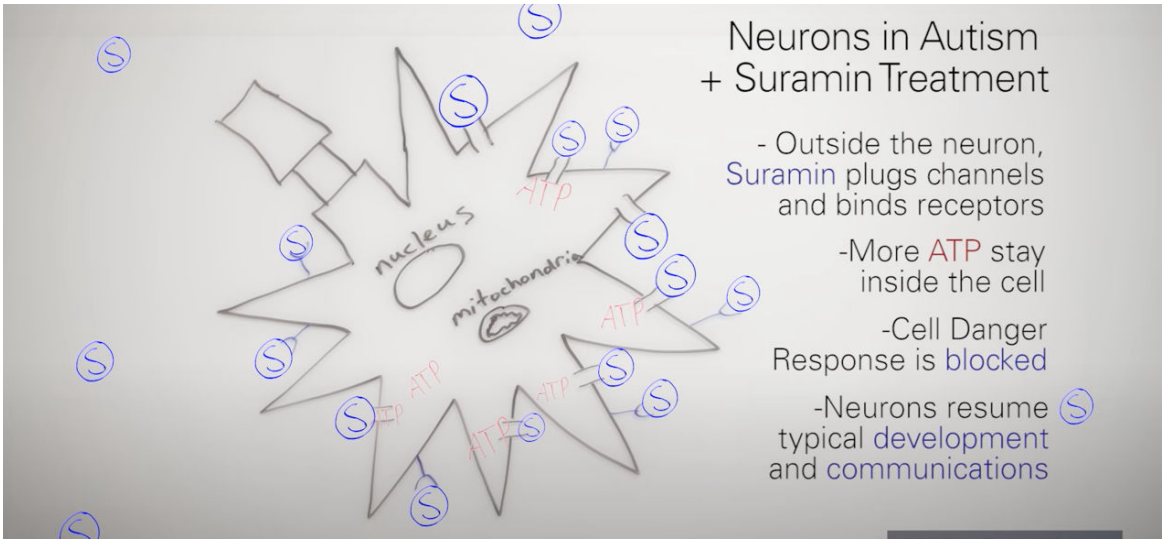
The Cell Danger Response

The cell danger response (CDR) is a metabolic response to danger from chemicals and physical or microbial threats (Naviaux, 2014). Hazards such as psychological trauma can activate the cell danger response, produce chronic inflammation, and increase the risk of many disorders. In addition to that, CDR can lead to altered organ function and behaviors. Once the danger is detected, the mitochondria decrease oxygen consumption to oxidize the cellular environment. They ultimately inhibit monomeric building blocks into polymers and decrease RNA, protein, and DNA synthesis. The membrane of the cell becomes stiffer for protection from invaders. The process of reusing old and damaged cell parts, called autophagy, increases—the decomposition of mitochondria (mitophagy) and mitochondrial fission increases. Mitochondria start releasing ATP, ADP, UTP, and ADP outside the cell resulting in purinergic signaling. Purinergic signaling is released to notify signal danger. In addition, CDR can signal danger and trigger inflammation

and pain. They are ultimately causing persistent CDR activation and ASD, and other disorders. CDR occurs naturally in every cell of our bodies. After CDR, the cell moves on to the healing process, in which the cell will recover from the stress. CDR is believed to cause ASD and several other disorders due to it getting struck and cells under constant stress (Naviaux, 2014).

Figure 9

Autism Spectrum Disorder: Cell Danger Response



(UC Health - UC San Diego, 2022)

How does Suramin control the Cell Danger Response?

Suramin works by inhibiting purinergic signaling. Several ways suramin inhibits purinergic signaling (Naviaux et al., 2014). Suramin can work as a competitive inhibitor of ATP by binding to cell receptors. Suramin can also block the pannexin-P2X7 channels resulting in decreased release of intracellular ATP. By blocking ATP, suramin prevents the cell danger response from being sent out to other cells. Ultimately ending the cell danger response to get the cells back to homeostasis and move forward to the healing cycle (Naviaux, 2014).

Comparison: Efficacy

Risperidone has been FDA-approved since 2006 and due to this has many studies showing its efficacy (Mano-Sousa et al., 2021). The studies presented previously in chapter 2 are great examples of its efficacy. In *A Crossover Study of Risperidone in Children, Adolescents, and Adults with Mental Retardation* by Hellings and colleagues was designed to determine the risperidone effect in a longer duration with a broad sample. Forty subjects participated in this study, ages 8-56 years. The study results showed great significance in irritability scores. The Irritability subscale score decreased from 19.16 in placebo 1 to 11.5 for the low dose and 13.31 in the high dose phase (Hellings et al., 2006). The Irritability subscale score of 23 subjects showed a 50% reduction, and 35 subjects showed a 25% decrease. Justine M. and his coworkers held a research study in 2012 called *Risperidone Dosing in Children and Adolescents with Autistic Disorder: A Double-Blind, Placebo-Controlled Study,* which showed efficiency in irritability and ABC subscales in high dose patients. The study populations were children and adolescents aged 5 to 17 from either sex and in total of 96 patients. Irritability scores also improved significantly in the high-dose group but not in the low-dose groups with a p-value score of <0.001. In the ABC subscales, patients showed improvements in hyperactivity subscale scores in the high-dose group with a p-value score of 0.019. Overall risperidone is effective in reducing irritability in patients which helped them be FDA-approved in 2006.

Suramin is currently not FDA- approved but has two studies that show significant efficacy in improving autism's core symptoms. The study, *Reversal of autism-like behaviors and metabolism in adult mice with single-dose antipurinergic therapy,* by Dr. Naviax and co-workers, was created to determine the study of a single dose of the suramin on the behavior and metabolism of adult animals.The study results showed how suramin can revert the core symptoms of autism to normal in a 6 month old male adult mouse. Before rodents were given a single dose of suramin about 50% showed deficiency in novelty preference. After a single dose of suramin, the rodents' deficiency were normalized. Another example is the study

Antipurinergic therapy corrects the autism-like features in the Fragile X(Fmrl Knockout) mouse model by Jane Naviaux and co-workers which showed restoration of normal social behavior and reduction of social novelty. Based on a behavioral analysis 26% of Fmrl null male mice improved social preference and 35% reduction in social novelty indicating great potential of efficacy in humans. The study *Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial* by Dr. Naviaux and co-workers were created to determine whether suramin was safe to treat autism spectrum disorder in children but also to show the efficacy of suramin. Autism Diagnostic Observation Schedule (ADOS-2) is a standardized diagnostic test for autism spectrum disorder was used as a comparison score. ADOS-2 comparison score improved by 95% in the suramin group at week 6, while there was no change in the placebo group. There were improvements in language and social interaction and decreased restricted or repetitive behaviors. Overall, suramin has proven to be effective in mice that share autic symptoms and is a highly potential medication for individuals with autism as shown in study done by Dr. Naviax in 2017.

Suramin and Risperidone have both shown efficacy in reducing autism symptoms in studies previously done (Kent et al., 2012;Naviax, 2017). The main difference between them is the mechanism they are inhibiting and the overall results of inhibiting these mechanisms. Risperidone is used to improve irritability in individuals with autism spectrum disorder(ASD). Risperidone improves irritability by antagonizing the 5-HT2A serotonergic receptors (figure 1) and D2 dopaminergic receptors (McNeil et al., 2022). Ultimately, blocking the serotonergic and dopaminergic receptors results in rebalance of dopamine and serotonin to improve irritability. Many studies have shown that risperidone can mostly improve irritability while suramin can potentially improve core symptoms of ASD. Unlike risperidone, suramin inhibited the cell danger response. The cell danger response is believed to potentially be the underlying cause of ASD. Studies such as *Antipurinergic therapy corrects the autism-like features in the Fragile*

X(Fmrl Knockout) mouse model by Jane Naviaux and her co-workers showed 20 biochemical pathways were associated with symptom improvements and 17 were shared with individuals with autism spectrum disorder. These pathways found were to be related to cell danger response which indicates an association with CDR and autism. Suramin inhibits the cell danger response by inhibiting purinergic signaling. By inhibiting the potential cause of ASD, suramin can potentially improve all/most ASD core symptoms (Naviaux et al., 2014).

Side effects

Figure 10

Suramin and Risperidone Common Side Effects

Suramin	**Risperidone**
Cloudy urine	Aggressive behavior
Diarrhea	Agitation
Faintness	Anxiety
Headache	Changes in vision
Increased skin color	Difficulty concentrating
Irritability	Difficulty speaking or swallowing
Itching	Inability to move the eyes
Joint pain	Increase in the amount of urine
Loss of appetite	Loss of balance control
Nausea	Mask-like face
Numbness or weakness in arms, hands, legs, or feet	Memory problems
Skin rash	Muscle spasms of the face. Neck, and back
Stinging sensation on skin	Problems with urination
Swelling on skin	Restlessness or need to keep moving (severe)
Tenderness of the palms and the soles	Shuffling walk
Tire easily	Skin rash or itching

Vomiting	Stiffness or weakness of the arms or legs
	Tic-like or twitching movements
	Trembling and shaking of the fingers and hands
	Trouble sleeping
	Twisting body movements
	Increase appetite
	drowsiness
	sedation

(Mayo Foundation for Medical Education and Research, 2022-a;b)

Medications reduce certain symptoms but could have adverse effects (Mayo Foundation for Medical Education and Research, 2022-a). In the figure - it shows risperidone and suramin common side effects. Risperidone has more common side effects than suramin based on the table. Risperidone improves irritability but may cause aggressive behavior, memory loss, increase in appetite, anxiety, etc (Mayo Foundation for Medical Education and Research, 2022-a). Justine M. and coworkers held a research study in 2012 called *Risperidone Dosing in Children and Adolescents with Autistic Disorder: A Double-Blind, Placebo-Controlled Study* which showed many adviser effects risperidone can cause. Low-dose and high-dose groups had side effects such as somnolence, sedation, and increased appetite. In the low-dose groups, the side effects happened more frequently than in the high-dose groups. In a study by Aman M., 42% of the subjects had an excessive appetite (2015). In addition, subjects treated with risperidone had a higher incidence of urinary complications. 3.7% of the subjects reported new seizures, whereas those not treated with risperidone did not report any seizures. Suramin has some similar side effects to risperidone such as skin rash and weakness in arms or feet. Suramin also has some different side effects such as vomiting, loss of appetite, joint pain, etc (Mayo Foundation for Medical Education and Research, 2022-b). The study, *Low-dose suramin in*

autism spectrum disorder: a small, phase I/II, randomized clinical trial by Dr. Naviaux and co-workers was created to determine whether suramin was safe to treat autism spectrum disorder in children. The study revealed no severe toxicity or adviser effects. However, five children developed a rash over 1-20% of their body, which peaked one day after drug administration and disappeared in 2-4 days. Risperidone and suramin both have side effects which some are similar while others are different from each other (Mayo Foundation for Medical Education and Research, 2022-b).

Limitations

Suramin is the oldest manufactured drug still in medical use. Suramin is the first clinical trial drug to try to help autism spectrum disorder with its core symptoms (Kent et al., 2012). Suramin is currently in clinical trials and due to this has limited studies showing its efficiency for improving ASD symptoms. On the other hand risperidone has many studies proving its efficiency in improving irritability in individuals with ASD. However, there is a lack of studies revealing its long term side effects (Hellings et al., 2006).

Chapter 5: Discussion

Autism spectrum disorder has limited treatments and requires new pharmaceutical therapies (American Psychiatric Association, 2022). Risperidone has been FDA-approved since 2006, but its long-term effects are unknown (Hellings et al., 2006). Studies have tried to determine risperidone's long-term effects, but many more studies are needed. The long-term side effects shown in the studies are weight gain, urinary complications, new seizures, somnolence, sedation, drowsiness, and gastrointestinal complications (McNeil et al., 2022). These immediate side effects could lead to long-term worse complications such as high blood pressure and obesity. Suramin is an old drug that can potentially improve core symptoms. Suramin could be the first drug to be approved to treat the core symptoms, if ongoing small studies show it to be

safe and effective. Suramin could help social interactions and communication by ameliorating the cellular danger response.

Discussion

Risperidone is an atypical antipsychotic; its exact mechanism of action is currently unclear (McNeil et al., 2022). However, it is believed that the primary function is to inhibit the 5-HT2A serotonergic receptors and D2 dopaminergic receptors. Many studies have shown risperidone efficacy (Mano-Sousa et al., 2021). Studies such as *A Crossover Study of Risperidone in Children, Adolescents, and Adults with Mental Retardation* by Hellings and colleagues showed significant improvement in treating irritability in individuals with autism spectrum disorder. The Irritability subscale score of 23 subjects showed a 50% reduction, and 35 subjects showed a 25% decrease. Some studies have also shown suramin's efficiency in treating autism spectrum disorder's core symptoms. Studies such as *Antipurinergic therapy corrects the autism-like features in the Fragile X(Fmrl Knockout) mouse model* by Jane Naviaux and co-workers, showed restoration of normal social behavior and reduction of social novelty. Based on a behavioral analysis 26% of Fmrl null male mice improved social preference and 35% reduction in social novelty indicating great potential of efficacy in humans. Overall both risperidone and suramin have shown efficacy in treating (Mano-Sousa et al., 2012;Naviaux et al., 2014). Risperidone has more studies done to prove efficiency as well as a FDA approval. One important aspect to take note is that risperidone has human studies done while suramin only has a study done for safety to get approval for human studies.

Risperidone and suramin are both medications that reduce certain symptoms but could have adverse effects (Mayo Foundation for Medical Education and Research, 2022-a). Some common side effects for risperidone are changes in vision, difficulty concentrating, mask-like face, problems with urination, and trembling and shaking of the fingers and hands. Risperidone

improves irritability but may cause aggressive behavior, memory loss, increase in appetite, and anxiety. Increase in appetite might be a concern because it might cause obesity and heart conditions in the future. Ama et al. have administered a study that showed side effects from risperidone that 42% of the subjects had an excessive appetite (2015). Kent al did a study showing significant increase in appetite with the highest frequency compared to the other symptoms (2012). These two studies indicate a trend in increased appetite in risperidone, causing concerns for the future. Suramin also has common side effects, although less than risperidone (Mayo Foundation for Medical Education and Research, 2022-a). Suramin's common side effects are headache, loss of appetite, stinging sensation on skin, tenderness of the palms and the soles, and nausea. Suramin common side effects are less than risperidone, which may help individuals with ASD to handle side effects better (Mayo Foundation for Medical Education and Research, 2022-b).

Risperidone and suramin both have limitations. Suramin is currently in clinical trials and due to this has limited studies showing its efficiency for improving ASD symptoms (Kent et al., 2012). On the other hand risperidone has many studies proving its efficiency in improving irritability in individuals with ASD. However, there is a lack of studies revealing its long term side effects (Hellings et al., 2006).

Limitations

The author did not do the studies presented in this paper. The studies were gathered to retrieve information to determine which drug would benefit the individual with autism spectrum disorder and their family. The case studies available are not limited to this paper. The case studies for Suramin mentioned in this paper are currently available case studies for the general public. There are still more case studies about Suramin to come. Future studies should be focused on new case studies that Dr. Naviaux and his co-workers will publish to compare the

two drugs better. In addition to that, studies should be done by other investigators to expand the research.

Conclusion

Despite the limitations to this paper many important aspects of risperidone and suramin have been mentioned. Suramin is a drug that inhibits cell danger response which could potentially be the underlying cause of autism spectrum disorder (ASD) (Naviaux et al., 2014). Fixing the underlying cause of ASD can potentially help treat all core symptoms indicating better results for individuals. Previous studies have shown the potential of suramin efficiency with improvement of 26% in social preference and 36% reduction in social novelty in Fmrl null male mice (Naviaux et al., 2015). Although risperidone has also shown efficacy in improving irritability, it does not help individuals with core symptoms (Hellings et al., 2006). Instead, risperidone helps individuals with secondary symptoms and does not solve the underline problem.

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