SSRIs or CBT as a treatment method for ASD patients

(Department of Psychiatry, 2019)

Vera Sijbesma; S4825047

Biology, Behaviour and Neurosciences

Faculty of Science and Engineering

University of Groningen

Bachelor's Thesis Life Sciences IIb (WBBY901-05)

Supervisor: prof. dr. Martien J.H. Kas

June 21, 2024

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Abstract

Autism spectrum disorder is a neurodevelopmental disorder characterized by the presence of deficits in social communication and restrictive, repetitive behaviours. It is thought to be present in circa 1% of each country's population. There are different treatment methods used to decrease the presence of ASD symptoms in individuals however, the degree of efficacy has not been truly assessed thus far. One of these treatments is the prescription of SSRIs which block the reuptake of serotonin in the synaptic cleft prolonging serotonin stimulation. The degree of effect of SSRIs appears to be specific for each distinct type of SSRI with only Fluoxetine and Fluvoxamine improving ASD symptoms, whose use is often accompanied by side effects. Another type of treatment used is CBT which combines behavioural and cognitive treatment and focuses on replacing harmful/dysfunctional thoughts and behaviours with more positive ones. It has been shown that CBT is able to reduce ASD symptoms and that it can be used as a treatment for co-morbid disorders.

There is a gap in literature present when looking at the effects of SSRIs on ASD symptoms, therefore while some SSRIs may be able to help with ASD symptoms it is difficult to know if the benefits outweigh the risks. This indicates that SSRIs should probably not be used as a first-line treatment. On the other hand, CBT appears to be effective as an ASD treatment, even though the effect size can be debated due to the lack of big cohort studies and the need for adaptive CBT protocols, as these adapted CBT protocols are able to achieve better results than standard of practice CBT protocols. Nonetheless, this positive view on the effectiveness of CBT and the lack of possible side effects would allow this therapy to be considered as a first-line treatment.

Introduction

Autism spectrum disorder (ASD) is a well-known neurodevelopmental disorder that is characterized by deficits in social communication and the presence of restrictive, repetitive behaviours which can be present in different severities in each individual (Hodges et al., 2020; The American Psychiatric Association, 2013).
The prevalence of ASD is expected to be around 1% of the population of the United States of America. This 1% is also believed to be representative for other country's populations (The American Psychiatric Association, 2013). Diagnosis of ASD is seen more often in males than it is in females. Previously the male-female ratio was thought to be 4:1 (Ratto et al., 2017; The American Psychiatric Association, 2013), however, a more recent study has demonstrated that this ratio is likely to lay closer to 3:1, suggesting that a proportion of females with ASD go unrecognized (Loomes et al., 2017).

As previously mentioned, ASD is defined by deficits in social behaviours. This characteristic is divided into three aspects, namely problems with social-emotional reciprocity, nonverbal communication, and development, maintenance, and understanding of relationships (Lord et al., 2018; The American Psychiatric Association, 2013). Besides deficits in social behaviours, restricted, repetitive behaviours are seen as a characteristic of ASD. This core feature can also be divided into several subcategories, this being the repetition of motor movement, repetitive use of objects, repetition of speech patterns, adherence to routines, presence of patterns both verbal and nonverbal, hyper fixation on different subjects that reach an abnormal level of intensity, and being hyper- or hypo-reactive to sensory input from the environment (Lord et al., 2018; The American Psychiatric Association, 2013).

Even though ASD is characterized by these core features, it is recognized that clinical heterogeneity is present in regard to the aetiology, phenotype, and outcome of the hallmarks of ASD (Lord et al., 2018; Masi et al., 2017). Many factors play a role in the presence of this heterogeneity. One of these factors is genetic variation, which is associated with the development of ASD. Masi et al. (2017) showed that there does not appear to be a specific mutation that is the main cause, but rather that the cause lies by a combinatorial effect of several mutations. However, while it appears to be mainly a combinatorial effect, there are studies that have shown that there are cases where specific mutations play a major role in the development of ASD. So is there under patients with fragile X syndrome, tuberous sclerosis, and Down's syndrome, which are all genetically defined diseases, a high prevalence of ASD (Kohane et al., 2012). Besides genetic variability, comorbidity of other diseases also plays a significant role in the heterogeneity of ASD. Research has shown that over 10% of ASD patients suffer from bowel disorders or epilepsy, another 5% show cases of central nervous system or cranial abnormalities, and 2% of the patients suffer in addition to ASD of schizophrenia (Kohane et al., 2012). Additionally, around 40% of the patients diagnosed with ASD are also diagnosed with at least one type of anxiety disorder (Zaboski & Storch, 2018).

Diagnosis of ASD has to be based on behavioural deficits, as no reliable biomarkers are known for this disorder (Lord et al., 2018). A study that was able to show why this is the case is one performed by Lenroot and Yeung (2013). In this study, the researchers looked at what neuroimaging was able to tell about the heterogeneity in ASD. The main conclusion given

was that there are patterns of brain abnormalities present in people with ASD, however, there is a lot of inconsistency present between the different study results, which makes it difficult to identify a biomarker that could be meaningful on an individual level.

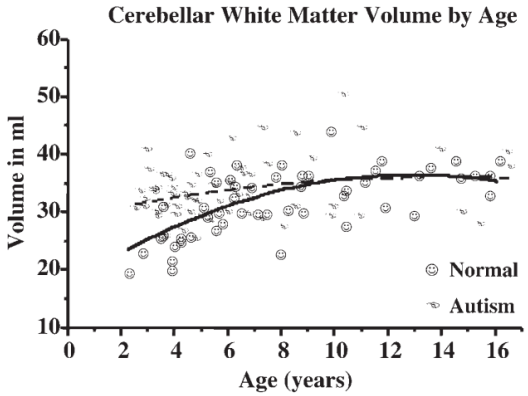

***Figure 1**: Brain volume of cerebellar white matter of children at different ages ranging from 2 to 4 years old. Taken from (Courchesne, 2002).*

While neuroimaging cannot be used as a biomarker for ASD diagnosis as there are no changes in brain pattern that hold for every individual (Lenroot & Yeung, 2013) it is known that brain development happens differently in people who will later be diagnosed with ASD. At birth, brain volume seems to be either smaller or equal to normal (Courchesne et al., 2003; Lainhart et al., 1997). However, children in the age range of two to four years old who have ASD have been shown to have increased brain volumes, specifically in the cerebral cortical grey matter, cerebral white matter, and cerebellar white matter (**Figure 1**) (Courchesne, 2002). After this initial overgrowth of the brain, growth will slow down to abnormal levels in some brain regions, while premature growth arrest happens in other brain regions (Courchesne et al., 2001; Courchesne, 2002; Courchesne, 2004).

Individuals with ASD often struggle with social and repetitive behaviours (The American Psychiatric Association, 2013) and therefore struggle to function in the current society (Bishop-Fitzpatrick et al., 2017). Currently, there is no curative treatment available for people with ASD. Instead, treatment is focused on maximizing functional independence and quality of life. This is done by minimizing the presence and effect of social behaviour deficits and the presence of repetitive behaviour. Additionally, therapy can focus on the facilitation of development and learning, promotion of socialization, and reduction of eventually present maladaptive behaviour in ASD patients. If necessary, education and support can be made available for the families (Shenoy et al., 2017). The types of treatments used to achieve these goals are numerous, including applied behavioural analysis, cognitive behavioural treatment (CBT) and distinct types of medication such as selective serotonin reuptake inhibitors (SSRIs) and antipsychotics (Masi et al., 2017; Shenoy et al., 2017). Since there is such a high degree of heterogeneity among people with ASD personalized treatment and medicine are an important aim as this would create the most effective treatment possible (Frye et al., 2022; Masi et al., 2017).

Even with the current knowledge of heterogeneity in ASD, little has been done to see how this affects the effectiveness of several types of treatment that can be used to treat ASD symptoms. By diving deeper into two specific treatment methods, CBT and the use of SSRIs, it would become clear why these therapies are used and how effective they actually are. With this information, it could be decided if these therapies should indeed be implemented in all cases of ASD and if so, should they be used as a first line of treatment. Additionally, this can help in understanding why some treatments work better in one group of patients than they work in other patients.

Selective serotonin reuptake inhibitors

SSRIs and their mechanism of action

Selective serotonin reuptake inhibitors are commonly prescribed as antidepressants; however, they are also prescribed for several other psychiatric disorders such as social anxiety disorder and, off-label, ASD (Chu & Wadhwa, 2023; Edinoff et al., 2021).

The mechanism of action of SSRIs is the inhibition of the reuptake of serotonin by blocking the action of the serotonin transporter that is present at the presynaptic axon. This inhibition causes an increase in the amount of serotonin present in the synaptic cleft, allowing for prolonged stimulation of the postsynaptic receptors (Chu & Wadhwa, 2023; Edinoff et al., 2021). A benefit of using this type of antidepressants is that SSRIs only have a small effect on the levels of other neurotransmitters like dopamine and noradrenaline (Chu & Wadhwa, 2023).

However, SSRIs have a delayed effect. Some patients may already feel the effect of the SSRI they are taking at the end of the first week, but in most cases, it will take longer. In the worst-case scenario, they may have to wait up to six weeks before they feel the effects (Chu & Wadhwa, 2023; Edinoff et al., 2021; Taylor et al., 2006). This delay of effect suggests that the acute increase in serotonin that takes place when taking SSRIs is necessary, but insufficient to create the needed effects. While no exact mechanism is known for this, it is thought that the elevated level of serotonin causes a gradual shift of brain homeostasis and neuro-functioning leading to a change in gene transcription and activation. This change may take four to six weeks, which correlates with the maximum time needed to reach the full effectiveness of the SSRIs (Edinoff et al., 2021; Santarsieri & Schwartz, 2015). While this is the main mechanism of action of SSRIs, there will be differences present between the several types of SSRIs: Fluoxetine, Sertraline, Paroxetine, Fluvoxamine, Citalopram, Escitalopram, Vilazodone (Chu & Wadhwa, 2023; Edinoff et al., 2021).

Possible side effects of SSRI treatment

While SSRIs are, in general, better tolerated than other antidepressants, there are still several side effects that a patient may suffer from when taking them. These side effects are often dose-dependent, and a couple of the most common ones are nausea, headache, insomnia, agitation, weight changes, and decreased sex drive (Chu & Wadhwa, 2023; Edinoff et al., 2021; Lochmann & Richardson, 2018).

Besides these common side effects, there are also more rare side effects. One of these is the prolongation of the QT interval (**Figure 2**), which represents the duration of the systolic phase of the ventricles, including depolarization and repolarization (Ambhore et al., 2014). Researchers have shown that Citalopram may cause this QT prolongation in a dose-dependent manner. Additionally, people with risk factors that could lead to QT interval prolongation seem to have an increased

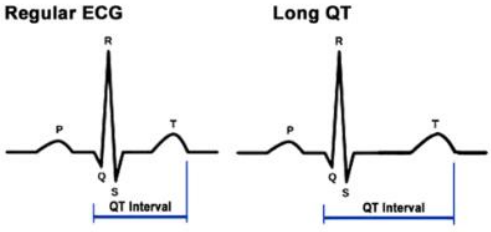

***Figure 2**: Representation of what a prolonged QT interval looks compared to a regular electrocardiogram (ECG). Taken form Thryv Therapeutics (2020).*

vulnerability to this side effect (Cooke & Waring, 2012; Edinoff et al., 2021). Prolonged QT interval predisposes to some arrhythmias such as Torsades de Pointes and could in some cases lead to sudden death (Ambhore et al., 2014; Edinoff et al., 2021).

One of the most debated side effects of SSRIs is an increased risk of suicidality. This is due to the inconsistent results found in the subsequent studies that took place after the initial case reports. With some studies yielding an elevated risk of suicide when taking SSRIs, while others show no significant increase or decrease in suicidality, and another set of studies showing a decrease in suicide risk when taking SSRIs (Li et al., 2024). Therefore, while it is unclear how correct it is to name an increase in suicidality a side effect of SSRIs, it is still important to keep it in mind as a potential side effect as the consequences could be fatal.

Even though it cannot be classified as a side effect, it is important to mention that SSRIs are metabolized by the cytochrome P450 (CYP) enzymes which are mainly present in the liver and play a role in most cases of drug metabolisms (Chu & Wadhwa, 2023; Zhao et al., 2021). Meaning that in cases of liver diseases doses may have to be adjusted to prevent higher SSRI levels than desired (Corponi et al., 2022; Villeneuve & Pichette, 2004). Besides SSRIs levels being affected by the CYP enzymes, SSRIs themselves also affect them. Most SSRIs inhibit the functioning of the enzyme CYP2D6, with other enzymes being affected in some cases (Brøsen, 1998; Chu & Wadhwa, 2023). Since these enzymes often play such a key role in drug metabolism, their inhibition could lead to an increased level of co-administered drugs, which in turn could cause some adverse effects (Brøsen, 1998; Zhao et al., 2021).

Contraindications

Patients taking SSRIs should be monitored for the presence of side effects. However, there are cases where the use of SSRIs is contraindicated. One of these situations is when patients use any type of medication that would increase the serotonin levels, such as monoamine oxidase inhibitors. The reason this combination is contraindicated is because it could lead to the development of serotonin syndrome, which results from excessive activity of serotonin throughout the nervous system; and the consequences of this syndrome can range from mild to fatal (Chu & Wadhwa, 2023; Simon et al., 2024).

Additionally, there is a Paroxetine-specific contraindication, as this specific SSRI is contraindicated during pregnancy. Paroxetine has been shown to have teratogenic effects when prescribed in the first trimester, causing cardiac malformations in the embryo (Chu & Wadhwa, 2023; Nevels et al., 2016).

Effectiveness of SSRIs as ASD treatment

The mechanism of action of each specific type of SSRI is the same, however, each compound is differently structured, and this often causes differences in the pharmaceutical activity of each compound. Thus, while looking at the effectiveness of SSRIs it is important to look at the individual effects of each type of SSRI. An overview of theses specific effects can be found in **Table 1**.

Fluoxetine

Looking at Fluoxetine, Hollander et al. (2004) found in their controlled crossover trial that giving children and adolescents with ASD liquid Fluoxetine significantly reduced repetitive behaviours. However, they did not find any significant effects on global autism symptoms. Besides the positive effect of Fluoxetine on repetitive behaviour the researchers did not find an increase in side effects when comparing the Fluoxetine and placebo groups. This includes no effects on weight gain and no increased risk of suicidality for the Fluoxetine group.

Adding proof to the positive effect of Fluoxetine, Hollander et al. (2012) showed in a randomized control trial that Fluoxetine given to adults with ASD significantly reduced repetitive behaviour. Additionally, patients treated with Fluoxetine showed greater improvement in the overall severity of the symptoms. Fluoxetine was tolerated well in this trial, with only mild to moderate side effects present in the patients. Additionally, no suicide intentions were found in either the Fluoxetine or the placebo group.

Further research on the effect of Fluoxetine in ASD patients was also done by Reddihough et al. (2019). They performed a randomized clinical trial where they tested the effect of taking Fluoxetine on obsessive-compulsive behaviour in children and adolescents. After primary analysis (adjustment for site, age, and intellectual ability) the researchers found a significant improvement in obsessive-compulsive behaviour in the groups treated with Fluoxetine. However, during secondary analysis (adjusting for additional factors such as sex, and verbal vs. nonverbal) no significant effects of Fluoxetine were found. Side effects were present in 45% of the Fluoxetine groups and 42% of the placebo groups, with these side effects being of mild nature in most cases. It is, however, important to note that the interpretation of these results is limited by a high dropout rate of patients during the course of the trial.

Citalopram

Unlike Fluoxetine, Citalopram was not found to have a significant effect on reducing repetitive behaviour in children and adolescents with ASD (King et al., 2009). The researchers note that this is not likely caused by inadequate sampling or poor adherence to the protocol. They do, however, theorize that the dosing may not have been adequate. Despite the lack of significant results regarding changes in repetitive behaviour, King et al. (2009) did find a significantly increased amount of side effects within the group treated with Citalopram compared to the placebo group. While most of the adverse effects were mild, there were also several cases of moderate side effects and even some serious side effects, namely the experience of seizures. This significant increase in side effects does raise a concern regarding the safety of Citalopram for children and adolescents.

Using the data recorded by King et al. (2009) Simonoff et al. (2022) looked at the effect of Citalopram on anxiety symptoms of children and adolescents with ASD. The researchers found a decrease in anxiety symptoms in both the Citalopram and placebo group, suggesting some degree of placebo effect. However, a greater improvement in symptoms was found in the group treated with Citalopram. Despite this difference in improvement, the researchers could not conclude that a significant improvement took place in the Citalopram group. Even so, it cannot be said with certainty that Citalopram has no effects on anxiety symptoms in

children and adolescents with ASD. Especially when taking into consideration that the data used in this study did not consist of children and adolescents specifically selected for the presence of anxiety disorders, as this was not the primary goal of King et al. (2009).

Fluvoxamine

McDougle et al. (1996) showed in their research that Fluvoxamine was able to significantly reduce ASD hallmarks in adults. Fluvoxamine was able to reduce repetitive behaviour and aggression and improve social behaviour. This trial lasted 12 weeks, and during this period mild side effects were present in the patients taking Fluvoxamine, indicating that the drug was well tolerated. Important to note is that the sample size of this research is rather small, with 15 subjects in each of the groups, meaning that the sample may not be fully representative of the whole ASD population.

Escitalopram

Owley et al. (2010) looked at the effect of Escitalopram on the Aberrant Behaviour Checklist (ABC), specifically looking at the irritability score category. To do this, the researchers separated the subjects into three groups based on the expression levels of the serotonin transporter (low, intermediate, and high). No significant changes in the results of the ABC irritability score were found in any of the groups, however, the researchers do mention that the groups of low serotonin transporter expression showed a much smaller change in the irritability score than the other groups. While the researchers did mention keeping track of side effects no data was provided on which side effects were present and of which nature they were.

Sertraline

Sertraline has not been shown to have a significant effect on the improvement of ASD hallmarks when compared to placebo treatment in a six-month clinical trial (Potter et al., 2019). However, Potter et al. (2019) also note that there were several limitations present during the research, starting with a limited sample size and possibly a sample bias that was created by the recruitment criteria. Additionally, the researchers mention that subjects were drawn from the same region creating a sample that may not be fully representable. Besides a lack of effect, the researchers also mentioned the lack of significant difference when looking at the presence of side effects in the Sertraline and placebo group, which would indicate that a six-month treatment of Sertraline appears to be safe, but longer-term safety of Sertraline still has to be assessed.

Paroxetine and Vilazodone

Little to no data is available on the effect of Paroxetine or Vilazodone on the hallmarks of ASD, making it difficult to know whether or not the use of these two SSRIs is recommended. What is known so far about Paroxetine is that it appears to be the least safe option of all the SSRIs currently available (Nevels et al., 2016). Indicating that even in the case of Paroxetine being effective, it would probably not be the first recommended treatment as the chances of the benefits outweighing the risks are small.

Vilazodone is an SSRI that has, thus far, been approved by the United States Food and Drug Administration (FDA) in 2011 for the treatment of Major Depressive Disorder (Viibryd (Vilazodone) FDA Approval History, n.d.). It is a relatively new SSRI, however superiority of this new SSRI compared to other SSRIs still has to be demonstrated. Important is to mention that Vilazodone is considered safe and well-tolerated (Wang et al., 2016). Since Vilazodone is such a relatively new drug little is known about possible off-label disorders it could be used in.

***Table 1**: Overview of the studies examining the effectiveness of the diverse types of SSRIs as an ASD treatment.*

Type of SSRI	Study	Subjects	Study type	Duration	Outcome	Side effects
Fluoxetine	Hollander et al. (2004)	n = 44 with 5 not included in final analysis	Controlled crossover trial	1st treatment = 8 weeks Washout period = 4 weeks 2nd treatment = 8 weeks	Reduction of repetitive behaviours in children and adolescents No effect on global ASD symptoms	No increase found in the Fluoxetine group
	Hollander et al. (2012)	n = 37	Double-blind placebo-controlled fluoxetine trial	12 weeks	Reduction of repetitive behaviours in adults and improvement of overall symptom severity	Tolerated well with only mild to moderate side effects
	Reddihough et al. (2019)	n = 146	Randomized clinical trial	16 weeks	Improvement of obsessive-compulsive behaviour in children and adolescents after primary analysis Secondary analysis showed no effect	45% of the Fluoxetine and 42% of the placebo group presented side effects, these being mostly of mild nature
Citalopram	King et al. (2009)	n = 149	Randomized controlled trial	12 weeks	No effect on reducing repetitive behaviours in children and adolescents	Increase in side effects of mild, moderate and severe nature in the Citalopram group
	Simonoff et al. (2022)	n = 149	Secondary analyses of the double-blind, placebo-controlled RCT from King et al. (2009)	12 weeks	Decrease in anxiety symptoms in children and adolescents of the placebo and Citalopram group, with a larger non-significant increase in the citalopram group	No explicitly mentioned but taken form King et al. (2009) there was an increase in side effects in the Citalopram group
Fluvoxamine	McDougle et al. (1996)	n = 30	Double-blind, placebo-controlled trial	12 weeks	Reduce repetitive behaviour and aggression, and improve social behaviour in adults	Fluvoxamine was well tolerated, with side effects of mild nature
Escitalopram	Owley et al. (2010)	n = 58	Open label in terms of medication, but blind in terms of genotype	10 weeks	No changes in ABC irritability score were found in any of the three genotypes, with low serotonin transporter expression showing the smallest difference.	Side effects were measured, but not specific data was provided
Sertraline	Potter et al. (2019)	n= 58	Randomized, double-blind, placebo-controlled trial	6 months	No effect on ASD hallmarks	No differences found in presence of side effects

Cognitive behavioural treatment

What is cognitive behavioural treatment?

The basic idea behind CBT is that thoughts, behaviours, and feelings are closely related and that these factors play a significant role in the well-being of a person. As the name suggests CBT is a combination of cognitive and behavioural therapy. Cognitive therapy is focused on recognizing and changing beliefs that are untrue and/or distressing, as often the situation is not the only cause of the problem and the exaggerated importance attached to it also plays a significant role. Behavioural therapy is based on the theory that behaviour is learned and therefore it can be changed. It aims to find which behavioural patterns make problems worse or make life more difficult and once these patterns have been found individuals can work towards changing them (Institute for Quality and Efficiency in Health Care, 2022).

The combination of cognitive and behavioural therapy leads to a type of treatment that focuses on letting the patient work on current thoughts and behaviours which are characterized by making the patient feel bad about themselves. The goal is for the patient to be able to help themselves, therefore being able to return to their daily lives without therapy. This is done by challenging their current harmful and/or dysfunctional behaviours and beliefs and subsequentially replacing them with behaviours and thoughts that do not have the same negative effect on the patient. Additionally, patients will learn to adapt and reflect on situations that would normally cause a feeling of anxiety (Beck, 2020; Institute for Quality and Efficiency in Health Care, 2022; Wang et al., 2021).

Possible side effects of CBT

Following some types of psychological treatment may lead to the presentation of side effects (Institute for Quality and Efficiency in Health Care, 2022). However, it is important to notice that these side effects are different from the ones that are seen when using pharmacological treatments, as they are not caused by influencing biological pathways.

The side effects that may be seen in psychological treatment are feelings of distress at first as facing personal problems and anxieties is often very confronting. Additionally, in some cases, relationships with other people can be negatively affected. However, there is not much literature available on the possible side effects of this type of therapy (Institute for Quality and Efficiency in Health Care, 2022).

Effectiveness of CBT as ASD treatment

In a meta-analysis performed by Weston et al. (2016), it was shown that CBT as a treatment for co-morbid disorders in ASD and symptoms of ASD had a small to medium effect size in children, adolescents, and adults. These results were affected by the method used to obtain the data, this being either self-report, informant-report, clinician-report, or task-based measurement. An overview of these results can be found in **Table 2**.

Focusing on CBT as a treatment for co-morbid disorders in ASD it has been shown that analysis completed with self-report measurements yielded a small and non-significant effect size with the presence of significant heterogeneity. Once correct for this, the effect size was still small and non-significant. When looking at data collected through informant- and

clinical-reports a medium effect size was found, also with a significant presence of heterogeneity. Correction for this yielded a medium effect size. No data was provided on the effects seen when using task-based measurement (Weston et al., 2016).

When looking at the effectiveness of CBT for symptoms of ASD instead of co-morbid disorders comparable results were found. When looking at self-reported data the effect size was small and non-significant, however in this case heterogeneity was also non-significant. The researchers still decided to correct for this, which led to a further decrease of the effect size. Analysis using informant-report measurements resulted in a small, but significant effect size, and after taking heterogeneity into account it increased to medium. The use of clinical-reports resulted in a medium significant effect size, however after correction of heterogeneity it changed to a non-significant medium effect size. Task-based measurement resulted in a small significant effect size, but correction for heterogeneity resulted in a non-significant effect (Weston et al., 2016).

From these results, it can be seen that treatment efficacy is dependent on the type of measurement that is used, but that there may be a positive effect of CBT present. Weston et al. (2016) do note that there are several limitations to this meta-analysis, one important one is the fact that most studies included in the analysis had only small samples, therefore the conclusions reached in this analysis are probably limited.

***Table 2**: Overview of the effect of the measurement method used on the reported effectiveness of CBT as an ASD symptoms treatment or as a co-morbid disorder treatment (Weston et al., 2016).*

	Self-report	**Informant-report**	**Clinical-report**	**Task-based measurement**
Co-morbid disorders	Small, non-significant effect size	Medium, significant effect size	Medium, significant effect size	n.a.
Heterogeneity correction	Small, non-significant effect size	Medium, significant effect size	Medium, significant effect size	n.a.
ASD symptoms	Small, non-significant effect size	Small, significant effect size	Medium, significant effect size	Small, significant effect size
Heterogeneity correction	Further decrease of effect size	Medium, significant effect size	Medium, non-significant effect size	Small, non-significant effect size

Similar results were found by Wang et al. (2021), who showed in their analysis that children and adolescents who received CBT had a significant improvement in symptoms of ASD and social-emotional problems when data was collected using informant- or clinician-reports, but no significant effects were seen when using the self-report method.

A more specific example of the positive effect of CBT on ASD symptoms can be seen in a study performed by Kurz et al. (2018) where nine drug-naïve male children went through a standardized CBT protocol. Behaviour was scored using the ABC at baseline and after 12 months. The results obtained showed a significant change in several behaviours namely irritability, lethargy, and hyperactivity. However, it is important to note that the sample size in this study is small and that there is no control group present, making interpretation limited.

It becomes clear that CBT can be beneficial for ASD patients, however, CBT has several different protocols that can be used, of which some may be more or less effective when treating a specific group of patients. Wood et al. (2020) have been able to show this in their research where they formed three groups out of a cohort of ASD patients with maladaptive and interfering anxiety. One group followed the standard of practice CBT protocol, while another followed an adapted CBT program, and the last group followed the treatment as usual protocol. In each group, the changes in anxiety symptoms were measured. The

researchers concluded that both CBT protocols outperformed treatment as usual in reducing anxiety symptoms in children with ASD; however, the adapted CBT protocol proved to be superior in reducing these symptoms when compared to the standard of practice CBT protocol.

While little literature is available on the effect of CBT on brain structure in ASD patients, there is literature available its effects on brain structure in anxiety, which is a disorder often present in ASD patients (Zaboski & Storch, 2018). Haller et al. (2024) have found that CBT normalized the hyperactivation in the fronto-parietal regions of the brain that is normally seen in children and adolescents with anxiety disorders. This change was however not seen in certain frontal regions and in the right amygdala, but the authors point out that the effect that is seen in this study is an acute effect of CBT, and therefore theorize that longer-term follow-up may still show a normalization in the amygdala. These changes found in patients with anxiety disorders suggests that CBT could also cause brain structural changes in ASD patients, however more research is needed to confirm this.

Discussion

From the literature that is currently available, it can be said that the effectiveness of SSRIs to treat ASD symptoms is dependent on the type of SSRI that is used. Fluoxetine and Fluvoxamine show a decreasing effect on some symptoms of ASD (Hollander et al., 2004; Hollander et al., 2012; McDougle et al., 1996; Reddihough et al., 2019). On the other hand, Escitalopram, and Sertraline have not been shown to have any kind of improving effect on the symptoms of ASD (Owley et al., 2010; Potter et al., 2019). Citalopram is a bit of a special case as it does not seem to have an effect on ASD characteristics, but it may have some effect on the anxiety symptoms that are often present in ASD patients (King et al., 2009; Simonoff et al., 2022). For other SSRIs there is little to no literature available in which effectiveness for ASD is assessed, thus no conclusions can be drawn for them.

While some SSRIs appear to be effective as ASD treatment, it is important to keep in mind that side effects are common in people using them and that these can range from mild to severe (Edinoff et al., 2021). Besides this, there is little known about the risk of side effects in ASD patients taking SSRIs as long-term treatment studies have not been performed to assess this. Additionally, no studies have been done to look at the effect of heterogeneity on treatment effectiveness, meaning that there may be groups of people diagnosed with ASD who do not respond as expected to SSRI treatment.

The current lack of information regarding the side effects and long-term treatment safety of SSRIs, and the small number of trials performed to see the effectiveness of SSRIs on ASD hallmarks makes it difficult to assess a benefit-risk ratio. Besides this, it is also noticeable that the research performed lacks the necessary quality to draw strong conclusions. While most studies are controlled trials, the sample sizes used are often on the smaller side making interpretation limiting (**Table 1**). On the other hand, the duration of the trials exceeds in all cases the six weeks that may be needed to reach the full effectiveness of the SSRIs (**Table 1**) (Chu & Wadhwa, 2023; Edinoff et al., 2021; Taylor et al., 2006). However, if SSRIs would be prescribed patients would take them for longer periods than the ones used in the different studies, and no studies can be found on the safety of long-term usage of SSRIs. Additionally, it is important to note that some of the studies were open-label or secondary analyses, which would also limit the interpretation of the results.

With the currently available information, it would not be recommended to use any type of SSRI, even Fluoxetine and Fluvoxamine, as a first-line treatment especially because there may be other treatment options with a higher success rate, less risk of side effects, and of which more information is known as currently there is a big gap in the literature regarding this topic.

Literature has shown that CBT seems to be effective in reducing symptoms of ASD and co-morbid disorders (Weston et al., 2016), however the true effect size of CBT is up to debate, as most research done on this topic has made use of small sample sizes and insufficient information regarding the engagement and fidelity of the patients was reported, which indicates the relatively low quality of the studies included in the analysis by Weston et al. (2016). This means that interpretation of the obtained results is limited. Additionally,

research suggests that a standard of practice CBT protocol may be less effective than an adapted CBT protocol. However, these adaptations would be patient-group dependent to achieve maximum effectiveness (Wood et al., 2020).

Since psychological treatments do not have the same degree of side effects as medicinal treatments this would not be a factor of concern when looking at the benefit-risk ratio. While there is plenty of research available about the effects of CBT on ASD this literature is often limited by several factors making it difficult to state a conclusion that would hold for all situations (Weston et al., 2016). However, the combination of the data that is available that indicates positive effects of CBT on ASD symptoms, and the lack of possible side effects would suggest a therapeutic method that can be put as a first line of treatment even with a gap in the literature.

Besides the lack of literature available, especially in the case of SSRIs, it is also important to keep in mind that the diagnostic criteria changed once the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V) came out, as this edition broadened the definition of ASD and reduced the specificity of related symptoms in comparison to the criteria in the DSM 4th edition (-IV) (Masi et al., 2017). This could mean that in literature there may be a severity bias caused by the difference in diagnosis criteria between DSM-V and DSM-IV, making it more difficult to compare studies that used the DSM-IV as a diagnosis guideline and studies that used the DSM-V as a guideline, as some treatment options may only work in more or less severe cases of ASD.

Within the group diagnosed with ASD, there is a large amount of heterogeneity present (Lord et al., 2018; Masi et al., 2017). The presence of heterogeneity means that the effectiveness of a certain treatment will vary between individuals. This means that while research data may show that a treatment is effective this may not be the case for a specific individual. This makes it difficult to create a treatment regimen that could be used for all individuals with ASD and instead points towards the need for personalized medicine (Frye et al., 2022). However, without a proper amount of research it will be impossible to achieve the necessary knowledge to create such personalized regimens that are needed to for maximum treatment effectiveness.

Overall, it appears that CBT could be named an important type of first-line treatment for patients with ASD. On the other hand, some SSRIs could be used as treatment but should not be categorized as a first-line treatment due to their side effects and unclear effectiveness. However, more research is needed to be able to state with certainty that CBT improves ASD symptoms, and that certain SSRIs do indeed improve ASD symptoms while others do not. Additionally, more research will be needed to see how heterogeneity affects these treatments and how treatment regimens can be adapted to it.

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