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Serotonin Transporter Polymorphisms and Efficacy of SSRI Therapy in Pediatric and Adult Patients with Autism Spectrum Disorder

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Introduction

Selective serotonin reuptake inhibitors (SSRIs), such as fluvoxamine and escitalopram, are commonly utilized medications to treat symptoms associated with autism spectrum disorder. Conflicting data is available on the importance of polymorphisms in the serotonin receptor gene and efficacy of SSRIs in patients with autism spectrum disorder.

Summary of Findings

A systematic review was completed that included 3 studies (n=120) which compared SSRI (escitalopram, fluvoxamine) efficacy and genetic variations in 5-HTTLPR in subjects with Autism Spectrum Disorder (ASD). 5-HTTLPR is the promoter region of the 5-HTT gene, which codes for the serotonin transporter (5-HTT). Polymorphisms of the promoter region, long (L) and short (S) allele variations, regulate the expression of 5-HTT [1]. Prior studies have reported that selective serotonin receptor inhibitors reduce reuptake of 5-HT at the 5-HT transporter site, thus minimizing symptoms of ASD, such as insistence on sameness, anxiety, and self-injurious behaviors [2,3]. Such examples of ASD-related symptoms are typically scrutinized with behavior assessments. Of genotypic alleles, prior studies suggest that the L allele variant was associated with positive outcomes with SSRI use (i.e. L/L genotype showed the greatest expression of serotonin transporter, compared to S/S genotype, which showed the least). Therefore, the selected studies examine the effect of 5-HTTLPR polymorphisms on the efficacy of SSRIs in the treatment of ASD.

In 2005, Sugie et al [1] published a double-blind study assessing the efficacy of fluvoxamine, an SSRI, in children with ASD, in correlation to 5-HTTLPR polymorphisms. Correlation analyses between clinical global expressions (CGI) and allele variation found that fluvoxamine showed greater positive outcomes in the L/L and L/S genotypes, with increased efficacy being statistically significant in the L allele variant, compared to the S allele variant. However, when correlated against Behavioral Assessment Scale, the S allele variant was associated with statistically significant improvement of language abilities and flighty eye movements with fluvoxamine use.

A 2010 prospective, open-label study performed by investigators Owley, et al, analyzed genotypic variation of serotonin transporter polymorphisms, and their response on escitalopram treatment of pediatric patients with ASD [2]. While the aforementioned study utilized the Behavioral Assessment Scale to determine changes in behavior among subjects, Owley et al instead utilized the Irritability Subscale of the Aberrant Behavior Checklist-Community Version (ABC-CV-IRR), examined at a weekly basis. The study concluded that the greatest amount of behavioral outcomes between genotype groups occurred significantly earlier in time, with least SSRI responsiveness in the S/S genotype group. Genotypes showed no difference in final dose.

The third component of this systematic review covers a 2015 study published by Najjar, et al, who sought to determine the effect of polymorphisms on serotonin transporter and serotonin-2A receptor genes, and their link to the efficacy of escitalopram in treatment of patients with ASD [3]. ABC-CV-IRR and Repetitive Behavior Scale Revised Compulsive/Ritualistic Behavior Subscales (RBS-R-CRS) were significantly improved in symptoms of insistence on sameness and irritability over the course of 6 weeks for all genotype groups. Unlike the previously mentioned studies, the results of this study conveyed higher ABC-CV score changes in the S/S genotype group, however data was not statistically significant. Improvements in time and dosing trajectories showed no statistical significance.

Discussion

The combined evidence of the three studies does not confirm or suggest a clear association between polymorphisms and the efficacy of SSRI medications in the treatment of ASD. While Sugie et al and Owley et al observed the least responsiveness to SSRI therapy in patients exhibiting the S/S genotype of serotonin transporter 5-HTTLPR, Najjar et al found the greatest amount of responsiveness in their group of patients with the S/S genotype. However, the latter study included a S/S genotype group which had higher irritability scores at baseline, therefore possibly magnifying the trajectory of change in behavior in the S/S genotype group when compared to the L/L and L/S genotypes. Najjar et al also included patients of a greater age variety than the

previous two studies; the average age of subjects was 13, however the eldest patient, an outlier, was 44 years of age, which may have skewed data. Overall, the selected studies, while providing insight about the possibilities of genetic effect on treatment outcomes, carried limitations of population sizes and baseline characteristics.

Limitations

All studies included in the systematic review showed discrepancies in baseline characteristics of patients, with all studies including highest percentages of male, Caucasian patients. Furthermore, all studies included a small population size (e.g. Sugie et al had the smallest amount of participants, n = 18), further limiting data relevance [1]. Owley et al included a small population size of patients with S/S genotype (n =9) , which made it difficult to analyze whether the least responsive genotype group (i.e. S/S genotype) would require higher doses of escitalopram than other genotypes to see positive outcomes [2]. An apparent detriment of population age was seen in the study by Najjar et al, where the mean age was 13, with outlying age of 44 included the study; this variety in age may explain why Najjar et al saw greatest behavioral outcomes in the S/S genotype, unlike the other two studies, both of which included only pediatric patients [3]. Furthermore, the S/S genotype group included by Najjar et al showed the highest irritability scores at baseline, which minimized their conclusion that the S/S genotype illustrated the greatest reduction in irritability scores. Finally, Owley et al and Najjar et al were of open-label designs, while also utilizing behavioral assessments conducted by the parents or caregivers of patients, a combination would may introduce bias due to lack of standardization in perception of symptoms.

Comparison with Current Practice Guidelines (average paragraph)

Approximately 45% of children and adolescents who are on the spectrum are treated with psychopharmacological agents [4]. Due to the wide range of behavioral difficulties that can be seen in autism spectrum disorder, SSRIs are routinely utilized in these patients in order to control symptoms such as aggression, anxiety, depression, and repetitive behavior [4]. SSRIs are utilized after it has been ruled out that there are no treatable medical causes as well as modifiable environmental factors and that the behavioral symptoms cause significant impairment. However, if there is a diagnosis of comorbidities such as major depression, bipolar disorder, or anxiety disorder, a patient can then be put on the same pharmacological agents used to treat these conditions in children who otherwise do not have ASD. Guidelines suggest that initial selection of SSRIs is dependent on the target symptom and potential coexisting diagnosis. As per the American Academy of Pediatrics, selected potential medication options include fluoxetine, fluvoxamine, citalopram, escitalopram, paroxetine, and sertraline to address potential coexisting comorbidities of obsessive compulsive disorder or stereotypic movement disorder (target symptoms of repetitive behavior, behavioral rigidity, obsessive compulsive symptoms), intermittent explosive disorder (target symptoms of aggression, explosive outbursts, self-injury), generalized anxiety disorder or anxiety disorder that is otherwise not specified (target symptom of anxiety), and major depressive disorder or depressive disorder that is otherwise not specified (target symptoms of social withdrawal, irritability, sadness or crying spells, decreased energy, anorexia, weight loss, sleep dysfunction). Additionally, the American Academy of Child & Adolescent Psychiatry suggests the use of citalopram or fluoxetine specifically to address the target symptom of repetitive behavior. Unfortunately, evidence lacks when it comes to recommendation of specific treatment for psychiatric comorbidities in patients with ASD, but pharmacogenomics as a field has great potential to impact prescribing of appropriate agents in order to address these issues and optimize therapy.

Areas in Need of Future Study

Future studies may benefit from the inclusion of larger sample sizes with less variety in baseline characteristics among patients. Seeing as that the Najjar et al study may have observed biased data due to outlying adult subjects among a majority of pediatric subjects, future studies may gain greater insight by the separate examination of SSRI therapy in pediatric patients and adult patients with ASD, in association with serotonin transporter polymorphisms. Furthermore, an examination of a wide selection of SSRIs may further elucidate the effects of each, and therefore streamline future recommendations for patients with ASD.

Psychiatry 2014;53:237-57.

Summary of Literature

Study	Population	Objectives	Outcomes
Sugie Y, et al. 2005. [1]	Nineteen Japanese patients ages 3-8 years old	Evaluate the effectiveness of fluvoxamine by focusing on the corre-lation between clinical responses and the genetic polymorphism of the 5-HTT gene	Fluvoxamine was more effective in patients with genotype l/l + l/s than in those with genotype s/s, and was significantly more effective in the l allele variant than the s allele variant.
Owley T, Brune CW, Salt J, et al. 2010. [2]	Fifty-eight patients in the United States ages 4.5-17 years old	Relate the genotype group of 5-HTT gene to response of ABC-Irritability scores after escitalopram, and relate genotype group to final dose of escitalopram.	Genotypes differences made relatively little difference in response of ABC-Irritability scores. Final dose did not differ significantly between the low, intermediate, and high expression genotype groups.
Najjar F, Owley T, Mosconi MW, et al. 2015. [3]	Fourty-four patients in the United States ages 5-44 years old	SLC6A4 5HTTLPR genotypes are associated with response and tolerability to escitalopram in subjects with ASD.	Whole study population experienced improvement in symptoms over 6 weeks (ABC-CV-IRR baseline 19.48+-9.23, end 12.2+-8.16). 5HTTLPR genotype comparison showed no difference in symptom change.

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