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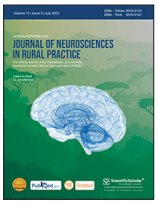

Original Article

Efficacy and tolerance profile of risperidone use in people with autism spectrum disorder in a clinic in Santarém, Pará, Brazil. A retrospective study

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ABSTRACT

Objectives: This study aimed to obtain the profile of efficacy and tolerance of risperidone in the treatment of people with autism spectrum disorder.

Materials and Methods: This research was a cross-sectional and retrospective study. The medical records of 100 patients diagnosed with ASD according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) were analyzed and measures of central tendency and correlation between variables such as gender, age at diagnosis, symptoms, daily dose, comorbidities, polytherapy, adverse drug effects, and outcome (improvement, worsening, and drug discontinuation) were calculated using Pearson's R test with a level of statistical significance $P < 0.05$.

Results: The male gender was the most affected, corresponding to 80% of the participants. The mean age at diagnosis was 6.88 ± 6.24 and the mean dose was 1.89 ± 1.68 mg/day. The use of risperidone for patients with aggressiveness, hyperactivity, insomnia, or self-harm improved in 76% of patients and adverse effects were reported in 27% of cases. The presence of self-harm implied lower chances of improvement ($P = 0.05$/r = −0.20). Adverse effects were strong predictors of discontinuation ($P = 0.01$/r = 0.39), and epileptic patients were more likely to have them ($P = 0.02$/r = 0.20). Male gender was associated with dosages lower than 2 mg/day ($P = 0.05$/r = 0.23).

Conclusion: Risperidone is a good option in the management of secondary symptoms of ASD, generally requiring low doses and presenting an acceptable profile of adverse effects. The age of diagnosis does not affect the drug's efficiency, but it can make the management of ASD difficult.

Keywords: Autism, Treatment, Risperidone

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent impairments in communication and social interaction and by repetitive and/or restrictive behaviors. In the United States, it is estimated that one in every 54 children is affected by the disorder, with males being more affected, in a ratio of approximately 4:1, causing an annual social cost of the disease that exceeds billions.[1,2]

In Brazil, epidemiological studies on ASD are still scarce, generally limited to specific populations, with divergent findings. A study carried out in 2006, in Santa Catarina, found a prevalence of 1.31/10,000 inhabitants. In 2016, another study carried out in the south of the same state evaluated 1,134 medical records from the neurogenetics outpatient clinic of UNISUL and of these 10.76% had a diagnosis of ASD.[3] Male predominance is a common feature in most surveys.[1,4]

Diagnosis can be difficult because there are no tests that detect or confirm it, being based on observation and clinical judgment and screening scales. The heterogeneity of the spectrum presentation contributes to some cases being detected early, while others, unfortunately, are not. Delayed diagnosis of the disorder implies that the child may not receive early interventions essential for managing the disorder.[5]

There is still no specific treatment, which is mainly based on cognitive-behavioral interventions, with greater effectiveness

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if implemented in early childhood, hence the importance of early diagnosis. They aim to encourage the development of appropriate skills and habits. Complementary measures such as speech therapy for language delays should be adopted.[6,7]

Pharmacological therapy is usually based on two drugs, risperidone and aripiprazole, atypical antipsychotics. Both substances appear to be effective in treating irritability, with the side effect profile as a limiting factor.[8] However, recently, olanzapine has also been shown to be useful.[9]

Risperidone works by blocking limbic dopamine receptors and, more weakly, cortical serotonin receptors.[10] The drug has been used with a good success profile in controlling ASD symptoms such as irritability or aggression. However, there are still no medications indicated for the management of core symptoms, such as impaired communication and social interaction or tendencies toward restrictive and/or repetitive behaviors.[11] The most reported side effects include hyperprolactinemia, drowsiness, weight gain, and gynecomastia, in addition to extrapyramidal impregnation.[12]

This study aimed to determine the efficiency and tolerance profile of risperidone use in children and adolescents through exploratory analysis of data from patient records.

MATERIALS AND METHODS

This research was a cross-sectional, quantitative, and retrospective study. The authors collected and analyzed data from the medical records of 100 patients diagnosed with ASD treated between 2004 and 2022 at Unineuro Tapajós, a private clinic located in the city of Santarém, state of Pará, Brazil. The medical records were randomly chosen through a convenience sample in numerical order of the medical records. Data were taken from paper records made by the neurologist during the medical consultation. All information came from previously collected reports, and there was no contact or follow-up of the patients to carry out the research.

Patients diagnosed with ASD according to DSM-5 criteria were included.[13] The variables studied were: Gender, age, ASD severity, symptoms that led to the use of risperidone, dose (in monotherapy or polytherapy), whether the dose was <2 mg/day or more, comorbidities such as attention deficit disorder and hyperactivity or epilepsy, adverse effects and treatment outcome (improvement, no improvement), and adverse effects, in addition to the reasons for discontinuing the medication, when it occurred.

The degree of symptoms, as well as their improvement or worsening, was evaluated according to the caregivers' report on the day of the consultations, whether the episodes referring to the verified symptoms increased or decreased. Attitudes such as hostility, direct physical aggression towards people, objects, or animals, as well as verbal aggressions, were considered as aggressiveness. Constant restlessness, difficulty concentrating, at home or school, was considered hyperactivity. Insomnia was related to recurrent difficulty falling asleep. Self-harm was acts of hurting oneself on a regular basis.

The project was approved by the Research Ethics Committee of the State University of Pará under number 5,364,579.6 and all procedures were in accordance with international bioethical norms for research with human beings. Data were collected by the authors, were double-checked, and analyzed using the statistical software Stata for Windows 10®, version 14.0 (Stata Corp, USA). Numerical variables were analyzed to calculate measures of central tendency and categorical variables were analyzed in terms of proportions in the sample. The correlation between the variables was performed using a correlation matrix generated using the Pearson R test. The *t*-test was used to analyze whether there were significant differences between the means, when necessary. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age at diagnosis was 6.88 years, with the mean age among girls being significantly higher than among boys (9.4 vs. 6.2) years ($P = 0.001$). The male gender predominated, corresponding to 80% of the research participants. The most common severity level was 2, corresponding to 56%. The most reported symptoms were aggressiveness (74%) and hyperactivity (80%), and some patients had more than one symptom. The average daily dosage was 1.89 mg/day. Among the 100 participants, 76% improved, 27% had adverse effects, the most common being drowsiness (15%). Other descriptive variables are shown in [Table 1].

In the studied sample, it was not possible to determine improvement predictors. However, it was observed that patients with a history of self-harm are less likely to improve ($P = 0.05$, r = −0.20), and this improvement is a crucial factor for not discontinuing the drug ($P = 0.01$, r = −0.28).

It was also observed that the presence of an adverse effect had a statistically significant influence on drug discontinuation ($P = 0.01$, r = 0.39), and participants with epilepsy were more likely to develop side effects ($P = 0.02$, r = 0.20). In the analyzed sample, male gender was associated with the use of lower doses of risperidone ($P = 0.05$, r = 0.23). The severity of the disorder did not statistically influence the chances of improvement [Table 2].

DISCUSSION

Most patients were male, which is consistent with the extensive literature.[14] In addition, boys had a lower mean age at diagnosis when compared to girls. This may be because diagnostic tools are based on male social development. For

Table 1: Descriptive statistics.

Variable	ASD *n*=100	Description
Gender		
Male	80	80%
Female	20	20%
Age (years)		6.88±6.24
Male		6.25±0.57
Female		9.4±2.05
Dosage (mg/day)		1.89±1.68
Until 2 mg/day	72	72%
>2 mg/day	24	24%
Follow-up (years)		4.29±3.70
Severity level		
1	22	22%
2	56	56%
3	22	22%
Symptoms		
Aggressiveness	74	74%
Hyperactivity	80	80%
Insomnia	46	46%
Self-harm	23	23%
Outcome		
Improvement	76	76%
Worsen	5	5%
No effect	19	19%
Comorbidity		
Epilepsy	22	22%
ADHD	23	23%
Polytherapy		
Valproate	11	11%
Carbamazepine	24	24%
Adverse effects		27%
Drowsiness	15	15%
Anxiety	8	8%
Gastric intolerance	5	5%
Gynecomastia	6	6%
Weight gain	13	13%
Discontinuation	32	32%

ASD: Autistic spectrum disorder, ADHD: Attention deficit hyperactivity disorder. Mean±standard deviation and percentage in the group

example, when analyzing the restrictive pattern of interest, it would be more common to notice in boys a preference for the wheel of a wagon or for trains, than to notice the exacerbated fixation of girls for certain princess movies. In addition, there is the fact that autistic girls may present a development pattern similar to that of "typical" boys, and culturally, the feminine would be associated with quietness and shyness, masking deficits in social interaction in the gender.[15,16]

The mean age at diagnosis was 6.88 years, higher than reported in other studies, where children are commonly diagnosed at around 4.5 years, and the optimal age for initiation of therapies and good prognosis would be 18 months.[17] Late diagnosis of ASD is a worldwide problem associated with lack of information, which causes caregivers to confuse spectrum symptoms as coming from other diseases or development itself, such as aggression or agitation, as supposedly inherent to the male gender. In girls, late diagnosis would also be caused by the development of compensatory measures, such as the act of observing and imitating neurotypical children.[18,19] This may also have influenced the fact that we found a significantly lower mean age at diagnosis in boys than in girls in our study.

The presence of disruptive symptoms in children with ASD is quite common, with aggressiveness and agitation prevailing in the research. Aggressiveness may be related both to underactivity of the neural circuits responsible for social relationships and to intolerance to routine changes. Agitation is commonly associated with the concomitant presence of ADHD.[20,21] Sleep problems were present in less than half of the participants; however, it is known that changes in the sleep-wake cycle can influence both the central symptoms and the intensification of the other disruptive symptoms mentioned above, such as aggression and agitation.[22,23]

In the evaluated sample, approximately 40% had epilepsy or ADHD. The prevalence of epilepsy increases in autistic people when compared to normal individuals, ranging from 5% to 40%. Some epileptic conditions can cause autism-like findings; however, ASD is characterized by a persistent disorder, unlike epileptic seizures.[24,25] It is estimated that 70 out of 100 children with ASD will have some comorbidity, among which the most common are mood disorders and ADHD.[26]

The use of risperidone was fundamental in the management of the analyzed patients, 76% had improvement of symptoms with the treatment. It was not possible to establish predictive factors for improvement, that is, regardless of sex, age at diagnosis, dose, or comorbidities, the patient may improve with the use of the medication. However, it was observed that participants who suffered from self-harm were less likely to benefit from the treatment. It was also noted that males required smaller doses.

The presence of side effects was a strong predictor of drug discontinuation, mainly weight gain and drowsiness. It was also observed that the presence of epilepsy was associated with its higher occurrence. This may be related to a more severe phenotypic expression of ASD, implying higher doses of risperidone, as well as the need for polytherapy with drugs such as carbamazepine or valproate, which would increase the chances of such adversities.[27-29]

In the analyzed sample, no correlations were found between higher doses and adverse effects, but another study concluded that the effects of risperidone are dose-dependent and, for

Table 2: Correlation matrix of the explanatory and dependent variables by Pearson R.

	Improvement	Age ≤5 years	Male gender	Severity level	Dosage ≤2 mg/d	Aggressiveness	Hyperactivity	Insomnia
Improvement	1.00	-	-	-	-	-	-	-
Age ≤5 years	−0.09	1.00	-	-	-	-	-	-
Male Gender	0.03	−0.13	1.00	-	-	-	-	-
Severity	0.15	0.10	−0.13	1.00	-	-	-	-
Dosage ≤2 mg/d)	0.13	**0.29**	**0.23**	0.00	1.00	-	-	-
Aggressiveness	0.09	**0.41**	−0.11	0.07	0.13	1.00	-	-
Hyperactivity	0.07	0.00	0.14	−0.14	0.10	−0.18	1.00	-
Insomnia	0.12	0.08	**−0.24**	0.13	0.10	0.02	0.09	1.00
Self-harm	**−0.20**	0.17	−0.10	0.12	0.09	0.16	**−0.44**	−0.01
Comorbidity	0.10	0.04	0.01	−0.03	−0.01	−0.01	0.13	0.05
ADHD*	0.02	0.10	0.13	**−0.24**	−0.02	0.09	**0.21**	−0.03
Epilepsy	0.13	0.05	−0.11	**0.28**	0.10	−0.02	−0.04	0.16
Polytherapy	0.09	0.04	−0.10	0.17	0.18	0.12	−0.02	**0.25**
Adverse effects	−0.09	0.18	0.00	−0.07	0.11	−0.01	0.13	0.03
Discontinuation	**−0.28**	−0.11	0.10	−0.11	**−0.22**	0.00	0.01	−0.16

	Self-harm	Comorbidity	*ADHD	Epilepsy	Polytherapy	Adverse effects	Suspension
Improvement	-	-	-	-	-	-	-
Age ≤5 years	-	-	-	-	-	-	-
Male Gender	-	-	-	-	-	-	-
Severity	-	-	-	-	-	-	-
Dosage ≤2 mg/d	-	-	-	-	-	-	-
Aggressiveness	-	-	-	-	-	-	-
Hyperactivity	-	-	-	-	-	-	-
Insomnia	-	-	-	-	-	-	-
Self-harm	1.00	-	-	-	-	-	-
Comorbidity	−0.18	1.00	-	-	-	-	-
ADHD*	−0.18	**0.63**	1.00	-	-	-	-
Epilepsy	0.00	**0.58**	−0.11	1.00	-	-	-
Polytherapy	0.19	**0.38**	−0.01	**0.53**	1.00	-	-
Adverse effects	0.00	0.10	0.13	**−0.20**	0.09	1.00	-
Discontinuation	−0.01	0.01	0.06	0.01	−0.08	**0.39**	1.00

*ADHD: Attention deficit hyperactivity disorder. Statistically significant values in bold. $P<0.05$.

example, with each additional milligram increasing the risk of weight gain by more than 5%.[30]

The study was limited by the retrospective nature of the data, not being able to measure behavioral changes with specific scales.

CONCLUSION

The treatment of disruptive symptoms of ASD is still a challenge for family members, clinicians, and caregivers, but risperidone may be an acceptable option due to its tolerability profile and relative efficacy. Prospective and randomized studies are needed to confirm these findings, minimizing the confounding effects of other therapeutic approaches. The mean age at diagnosis, although high, did not influence the effectiveness of the medication, but it may be associated with greater difficulties in managing the ASD itself.

Author's contributions

All authors were involved in the writing and approval of the study, all also participated in data collection and analysis, read, and approved the final draft.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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