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Risperidone Use in Autism Spectrum Disorders: A Retrospective Review of a Clinic-Referred Patient Population

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Abstract

Risperidone is widely used in children with autism spectrum disorders for behavioral modification. In this study, the authors aimed to (1) describe a clinic-referred sample of patients with an autism spectrum disorder on risperidone, (2) identify differences between the success and nonsuccess groups, and (3) describe our experience with young children (< age 5 years) on risperidone. Eighty patients were initiated on risperidone. Indications included aggression (66%), impulsivity (14%), and stereotypies (4%). Sixty-six percent met criteria for success at 6 months and 53% at 1 year. Sixty-seven percent of the nonsuccess group reported side effects, compared to 47% of the success group. Weight gain was the most common side effect in both groups, followed by somnolence. Somnolence was the most robust predictor of nonsuccess. In our clinic-referred sample, the short-term success rate of risperidone was more than 50%, and side effects limited its use. Although weight gain was common, somnolence more significantly influenced treatment discontinuation.

Keywords

autism spectrum disorders, risperidone, weight gain, somnolence, receptors, serotonin, dopamine

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Background

Behavioral symptoms in children with an autism spectrum disorder present a substantial burden to patients and caregivers. Recent studies have shown the prevalence of aggressive and self-injurious behaviors in children with an autism spectrum disorder to be as high as 32%.¹ This may be particularly problematic for young children (< age 5 years) with a diagnosis of autism, 34% of whom experience clinically significant maladaptive behaviors.² Recent literature suggests that low nonverbal IQ and impaired communication abilities in young children place them at a higher risk for maladaptive behaviors.³ Although these maladaptive behaviors are not a core feature of autism, they can significantly interfere with a child's educational and developmental progress. As a result, there has been a growing interest in pharmacologic interventions aimed at controlling disruptive behaviors.

Haloperidol, a dopamine antagonist, was shown to effectively control the behavioral symptoms associated with autism spectrum disorder in early studies; however, its use was limited by the development of dyskinesias and extrapyramidal symptoms.^{4,5} The development of the atypical antipsychotics led to renewed interest in the treatment of behavioral symptoms in autism spectrum disorders. Atypical antipsychotics, which act on both dopamine and serotonin

receptors, traditionally have fewer side effects than do first-generation antipsychotics.

Risperidone antagonizes both dopaminergic (D₂) and serotonergic (5HT_{2A}) receptors. Several open-label trials have shown risperidone to be safe and efficacious in children with an autism spectrum disorder.⁶⁻¹⁰ Clinical end points, however, varied between trials and were often based on parent report, thus limiting their scope. Two randomized, double-blind trials have shown oral risperidone to be more effective than is placebo in controlling disruptive behavioral symptoms at 8 weeks. In the largest of these trials (N = 101), the rate of positive response was shown to be 69% in the risperidone group, as compared to 12% in the placebo group. In the same trial, two thirds of the positive responders had sustained benefit at 6

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months of treatment.^{11,12} Recent work by Arnold et al explored moderators and mediators of this treatment effect. Of the variables analyzed, only baseline symptom severity moderated treatment response. Weight gain was a clinically significant mediator of poor outcome. Other side effects, including somnolence, were not studied.¹³

Based on several successful clinical trials, in 2006 the Food and Drug Administration approved risperidone pharmacotherapy for the treatment of irritability in children aged 5 to 16 years with an autism spectrum disorder. Since that time, no studies have attempted to characterize the use of this drug in the clinic setting. Furthermore, few data exist on the use of risperidone in young children (< age 5 years), despite its frequent off-label use in clinical practice.

In this study, we sought to characterize differences between children who were successfully treated with risperidone and those who failed the medication. Identifying these differences is critical as we look for ways to better target our use to children who are most likely to benefit from therapy. From a scientific standpoint, treatment efficacy studies may also play an important role in the identification of endophenotypes within the autism spectrum. Children who respond to risperidone pharmacotherapy may represent a subgroup of children with a common underlying pathophysiology and, as a result, a more homogeneous phenotype. We also sought to describe the off-label use of risperidone in young children (< age 5 years) in an effort to better understand treatment efficacy, side effect profile, and prescribing practices in this population.

Patients and Methods

Study Design and Setting

After obtaining Children's Hospital Boston Institutional Review Board approval, we systematically reviewed electronic records of patients with an autism spectrum disorder who were followed in the Department of Neurology at Children's Hospital Boston. We identified relevant records from the hospital's data warehouse through a search engine. All records containing the terms *autism*, *pervasive developmental disorder*, *ASD*, and *PDD* were reviewed manually by one investigator (M. L.).

Routine clinical variables were chosen on the basis of potential clinical relevance and consistent physician documentation. Clinical variables of interest included age, gender, presence of epilepsy, side effects, reason for initiation, reason for discontinuation, and duration of therapy.

Selection of Participants

All children with an autism spectrum disorder treated with risperidone in the past 8 years (2000-2008) were included in the study. Children were either diagnosed by the treating clinician or referred to the Department of Neurology with an established diagnosis of an autism spectrum disorder. Diagnoses made in the Department of Neurology were based on *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition-Text Revision (*DSM-IV-TR*) criteria. Children referred to the clinic with an established diagnosis of autism spectrum disorder did have their diagnoses confirmed by the treating clinician, using *DSM-IV TR* criteria. The year 2000 was chosen as a cutoff because prior to 2000, risperidone use for behavioral symptoms in autism

spectrum disorders was much less common, and therefore, earlier time points yielded few additional data. Further inclusion criteria included (1) age range of 3 to 15 years, (2) documented diagnosis of an autism spectrum disorder, and (3) documented clinical follow-up for at least 6 months after initiation of treatment.

Outcomes and Measurements

The primary outcome of interest was treatment success. Success was defined by: (1) treatment continuation for at least 6 months and (2) clinician documentation of improvement in target symptoms. Treatment failure was, conversely, defined by (1) discontinuation of risperidone within 6 months of initiation and (2) documentation of "no improvement" by the primary neurologist. A secondary outcome of interest was treatment duration in months.

The definition of success was carefully chosen based on outcome measures used in prior studies as well as availability of clinical information. At least 2 studies of risperidone in autism used treatment duration as 1 marker of success.^{14,15} Most clinical trials in the past 5 years have used clinician report of improvement based on the Clinical Global Impressions Scale (Global Improvement subscale).¹⁶ The Global Improvement subscale requires the clinician to rate how much the patient's illness has improved or worsened relative to a baseline state. Although it is a 7-point scale, in the literature, the results are typically dichotomized into "improved" versus "not improved" in reporting success with therapy. In Children's Hospital Boston clinic notes, although the Clinical Global Impressions Scale was not recorded, the clinician's impression of improvement in a patient's symptomatology was consistently recorded. Therefore, these 2 variables together provided the most robust marker of success for this retrospective review.

Data Analysis

The primary outcome measure, as described above, was the binary variable of treatment success versus nonsuccess that was defined by the investigators. To more objectively explore predictors of length of treatment duration, we ran a secondary analysis using treatment duration (in months) as a continuous outcome measure.

For the binary response variables, logistic regression models were fit. For the continuous duration outcome, we fit a generalized linear model with gamma error distribution and a log link. Generalized linear models are similar to ordinary least squares regression models except that we assume a non-normal error distribution. Such models are often useful in time-to-event data, which are typically right-skewed. The response in the model was duration of treatment. The goal of this analysis was to find a model that best describes the variability in the treatment duration without the inclusion of unnecessary terms that would increase model variability. Candidate predictors were age, gender, epilepsy, comorbidities, previous history of failed medications, absence of clinical improvement, reason for initiation, reason for discontinuation, absence of side effects, baseline weight, and weight gain. Model selection was based on likelihood ratio tests and Akaike's information criterion.

Results

Descriptive. Eighty patients were initiated on risperidone over the 8-year period being analyzed. These patients were divided into 2 groups, which were defined as "treatment success" or "treatment failure." There were no significant

Table 1. Characteristics of the Study Population

Variable	Treatment success (n = 53)	Treatment failure (n = 27)
Age, y		
Mean	7.7	7.3
Range	3–13	3–14
Gender, n		
Male	38	23
Female	15	4
Reason for n		
Aggression	39	14
Impulsivity	5	6
Stereotypies	2	1
Failed medications, n		
Yes	28	19
No	25	8
Side effects, n		
Weight gain	24	5
Somnolence	1	6
Other	1	8

differences in age (7.7 vs 7.3 years), gender (28.3% vs 14.8% girls), or treatment indication between groups. Treatment indications included aggression, impulsivity, and stereotypies. There were no significant differences in the rate of comorbid epilepsy, attention deficit hyperactivity disorder, obsessive compulsive disorder, or anxiety disorders between groups. Fifty-three percent of the patients in the success group had a history of failed medications, as compared to 70% in the non-success group. The most common indications for treatment included aggression (66%), impulsivity (14%), and stereotypies (4%). Sixty-six percent of patients met criteria for success at 6 months and 53% at 1 year (Table 1).

Sixty-seven percent of the nonsuccess group reported side effects, compared to 47% of the success group. Weight gain was the most common side effect in both groups, followed by somnolence, aggression, and abnormal movements. Forty-five percent of children in the success group experienced weight gain, as compared to 18.5% in the nonsuccess group. Although percentage weight gain was not recorded for all subjects, the mean percentage weight gain in the success group (n = 26) was 1.67% per month.

Thirteen of the children started on risperidone pharmacotherapy were younger than 5 years (Table 2). Of those, 69% (9/13) met criteria for success. The youngest child initiated on risperidone was 3 years old. Only 30% of young children initiated on risperidone had a history of failed medications, suggesting that risperidone is frequently being used as first-line treatment. Failed medications included clonidine, guanfacine, and valproic acid. Thirty-three percent of those in the success group experienced side effects, as compared to 75% in the failure group. The most common side effect was weight gain (n = 5), followed by somnolence (n = 1). No children experienced atypical side effects, such as

Table 2. Characteristics of Young Patients (Age < 5 Years)

Variable	Treatment success (n = 9)	Treatment failure (n = 4)
Age, y		
Mean	3.78	3.50
Range	3–4	3–4
Gender, n		
Male	8	3
Female	1	1
Language ability		
Verbal	6	3
Nonverbal	3	1
Presence of stereotypies		
Present	5	3
Absent	4	1
Reason for initiation, n		
Aggression	5	1
Impulsivity	1	1
Stereotypies	2	0
Failed medications, n		
Yes	3	1
No	6	3
Side effects, n		
Weight gain	3	2
Somnolence	0	1
Other	0	0

Table 3. Coefficient Estimates From Logistic Regression Model Fit

	Coefficient estimate	SE	z value	P
Intercept	1.2629	0.7621	1.667	.0975
Presence of side effects	−1.0050	0.5177	−1.941	.0522

Response = success at 12 months (yes/no).

exacerbation of aggressive behaviors or dystonic reactions. Thirty-three percent of children in the success group were nonverbal, as compared to 25% in the failure group.

Correlation Analyses

Dichotomized variable (success vs nonsuccess). Because this was a binary response, logistic regression was used. In this case, there was only 1 predictor that was mildly significant, the presence of side effects (Table 3).

We broke down presence of side effects into 3 categories: weight gain, somnolence, and other less common side effects. We fit a model with success (yes/no) as the response and the presence of each of the side effects as predictors. A single subject may have more than 1 side effect; however, there were too few subjects to consider interactions between side effects (Table 4). There appears to be some relationship between somnolence and success; however, this effect is not very strong.

Table 4. Coefficient Estimates From Logistic Regression Model Fit

	Coefficient estimate	SE	z value	P
Intercept	0.6082	0.3770	1.613	.1067
Weight gain	0.1325	0.5685	0.233	.8157
Somnolence	-2.0487	1.15	-1.773	.0762

Response = success at 12 months (yes/no).

Duration of treatment. Out of the candidate predictors, 2 were significantly associated with duration of treatment: clinical improvement and side effects. A summary of the fit is described in Table 5, which shows the coefficient estimates (on the natural log-scale), their SEs, and the *P* value for the test that these coefficients are equal to zero. Because the log-link function was required, the coefficients are reported on the log-scale.

Discussion

In summary, we found that risperidone is prescribed commonly to children of many ages, with aggression being the most common indication for treatment. In our clinic-referred sample of children with an autism spectrum disorder, the short-term success rate of risperidone therapy was 66% at 6 months and 53% at 1 year. Although weight gain was common, somnolence and atypical side effects seemed to more significantly influence treatment discontinuation.

Risperidone was prescribed over a wide range of ages. The most common reasons for initiation were aggression and impulsivity. In the success group, more than 50% of the patients had a history of failed medications. This result suggests that many children who were refractory to other interventions benefitted from risperidone. A wide spectrum of medications were used prior to risperidone pharmacotherapy, including aripiprazole, sertraline, paroxetine, fluoxetine, venlafaxine, citalopram, clonidine, methylphenidate valproic acid, and guanfacine.

Side effects were common in both groups. Weight gain was the most common side effect reported. However, although weight gain was common, it was not a predictor of treatment discontinuation. This result suggests that clinicians generally tolerate weight gain in the setting of behavioral improvement. We report a mean weight gain of 1.67% per month in these children. Although this figure may be inflated secondary to selection bias, it is clear that weight gain in this population is significant.

Although somnolence was less commonly seen, it was a more robust predictor of treatment discontinuation. This novel finding suggests that prescribers and/or parents are less tolerant of somnolence, even in the setting of an improvement in target symptoms. It could also be inferred that somnolence typically manifests early in the course of treatment, whereas weight gain continues over time. Given that somnolence is likely a dose-related side effect, more detailed information regarding dosing, frequency, and titration is needed to fully understand this finding. A prospective study with standardized titration

Table 5. Coefficient Estimates From Generalized Linear Model Fit (Gamma Family With Log Link)

	Coefficient estimate	SE	z value	P
Intercept	4.1323	0.432	9.64	<.001
No improvement	-1.7367	0.224	-7.77	<.001
No side effects	0.4960	0.204	2.429	.018

Response = duration of treatment.

of risperidone based on patient weight and age would elucidate the etiology of this side effect.

Our results also suggest that for children with a history of failed medications, the odds of successful treatment decrease with time. This result should be interpreted with caution, however, given that our clinic-referred sample may be biased to older, more refractory patients. To fully understand this finding, more detailed phenotype information is needed.

Finally, in our subgroup analysis of this clinic-referred population, we found that several young children (younger than 5 years) were initiated on risperidone pharmacotherapy. It is particularly interesting that success rates were comparable to the group as a whole, suggesting that there may be utility in using risperidone in young children. Although we are limited by a small sample size, the side effect profile did not differ significantly from that seen in the larger population. Risperidone was initiated as first-line therapy in the majority of these children. Our results suggest that risperidone is used commonly in young children, often as first-line treatment. Despite this frequent off-label use, there is no literature to date that clearly justifies the use of risperidone as first-line therapy in this age group. Prospective studies are needed to define efficacy and potential toxicities of risperidone in young populations.

An important limitation to this study is its retrospective design. Phenotype information was significantly limited by the varied styles of physician documentation. Future studies should examine more detailed patient-associated variables such as baseline symptom severity, cognitive profiles, presence of stereotypies, abnormalities on motor examination, and medication-associated variables such as dose, frequency, and titration. Importantly, due to the retrospective nature of the study and reliance on clinical charts, we lacked a standardized scale to document improvement in target symptoms. Our primary outcome measure was a proxy to more gold-standard outcome measures in clinical trials. We partially addressed this by also analyzing treatment duration as an outcome measure. Finally, our sample represents our experience at a major tertiary referral center and therefore may not reflect practices and outcomes in primary and community health care settings.

Despite the limitations discussed above, this study is novel in its attempt to investigate phenotypes associated with treatment outcome, with the ultimate goal of using treatment response to gain insight into endophenotypes within the heterogeneous autism spectrum. Future treatment studies need to better define the clinical and neurobiological characteristics

of children with an autism spectrum disorder to be able to define in more detail the characteristics associated with treatment response. By doing so, we will begin to identify and understand specific neural circuits that may be aberrant in subgroups of children with an autism spectrum disorder. For instance, one could ask whether children with more prominent stereotypies or with specific motor impairments respond more robustly to risperidone, which would suggest that these clinical findings are rooted in aberrant striatal circuitry.

This study is also the first to describe the off-label use of risperidone in young children with an autism spectrum disorder and suggests that young children may benefit from this pharmacotherapy. However, prospective studies need to focus on the administration (dose, frequency, and titration) and side effect profile of this medication in young children. Studies also need to better define phenotypes of the young children who benefit from this medication, particularly in the characterization of symptom severity. Along with behavioral therapies, risperidone could serve as an effective adjunctive therapy for young children with an autism spectrum disorder.

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Author Contributions

MEL was the primary investigator and wrote the first draft of this manuscript. MG performed all statistical analyses and helped with writing of this manuscript. SSJ was the senior investigator and helped with writing of this manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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Ethical Approval

This work was reviewed and approved by the Children's Hospital Boston Institutional Review Board.

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