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ORIGINAL ARTICLE

MANAGEMENT OF AUTISM SPECTRUM DISORDER: A PILOT STUDY IN SAUDI PAEDIATRICS

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Summary

The aim of the current pilot study is to depict the pattern of management of autism spectrum disorder (ASD) in Saudi Arabia, focusing on the efficacy of risperidone in reducing the target symptoms of ASD compared to only behavioral therapy. A cross-sectional study was conducted at two main centers for 10 months. On a convenience basis, prospective visits were scheduled for children, who had received regular behavioral therapy and/or antipsychotics¬ (mainly risperidone), and their parents to assess the efficacy and side-effects of the treatment. The improvement of symptoms of ASD was assessed using the Aberrant Behavior Checklist-Community Version (ABC-CV) including five subdomains: Irritability, Lethargy, Stereotypic behavior, Hyperactivity, and Inappropriate speech. Twenty-nine children (26 boys and 3 girls) with a mean age of 8.96 years (range: 5–15 years) were included in this study. The distribution of management strategy was: risperidone (11, 37.9%), behavioral therapy only (9, 31.0%), risperidone and behavioral therapy (9, 31.0%). The use of a combination of antipsychotics and psychostimulants (17.24%) was less common than in a previous American study (38%). Surprisingly, scores for all ABC subdomains were higher than those of previous studies, indicating less efficacy of risperidone in this group. Additionally, for the Lethargy subdomain, the score was 74.3±24.3. Interestingly, children who received behavioral therapy only, had lower scores compared to their counterparts who received risperidone only in all ABC subdomains and the total score. Consistent with other reports, this study highlighted the efficacy of risperidone alongside behavioral therapy on reducing hyperactivity symptoms and total ABC score. Despite the published data regarding the efficacy and safety of risperidone, supporting that it may have an important role in the management of ASD in children, further prospective design studies in Saudi Arabia are warranted to confirm the findings or encourage its continuous employment as long-term maintenance therapy.

Key words: Autism spectrum disorder; Risperidone; Behavioral therapy; efficacy

Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by challenges with social skills, repetitive behaviors (1), and speech and nonverbal communication (2), which are core symptoms of ASD.

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In addition, children with a diagnosis of ASD often have a variety of co-occurring physical and mental health conditions, such as, anxiety, attention deficit hyperactivity disorder (ADHD) - a mental health disorder characterized by a persistent pattern of instability and hypersensitivity-impulses (3), obsessive-compulsive disorder (OCD), depression, seizures, and sleep problems, with additional aggression and self-injurious comportment in some children. Therefore, children with a diagnosis of ASD may present a broad spectrum of variable symptoms and conditions (1-3). Co-occurring physical and mental health conditions may worsen autism symptoms and, in some instances, can delay the diagnosis of autism (4).

Several tools were identified to aid in the differential diagnosis and assessment of ASD (5-7). Among the scales that are widely used to diagnose ASD are: the Diagnostic and Statistical Manual of Mental Disorders (DSM-V), Aberrant Behavior Checklist (ABC), Autism Diagnostic Observation Schedule (ADOS), and the Childhood Autism Rating Scale (CARS) (8).

The prevalence of ASD has been increasing worldwide due to the broadening of diagnostic criteria and wider public awareness. It ranges from about 25 to 110/10,000 children (9). The ratio of ASD was found to be higher in male children, and symptoms can sometimes be detected in children around 18 months. By age 2, it can be diagnosed by an experienced doctor (10).

However, in the Middle East, the prevalence is still unknown. According to ASD statistics in Saudi Arabia, about 42,500 children were diagnosed with ASD in 2002. A recent study in 2013 disclosed that the prevalence was higher in male participants than in their female counterparts. However, the definite prevalence has not been ascertained yet, largely due to the lack of diagnoses or acceptance from parents (9).

A genetic factor is said to be one of the causes of ASD, having a fragile X syndrome - a genetic disorder characterized by mild-to-moderate intellectual disability (11). Additionally, environmental factors, such as mothers' taking selective serotonin reuptake inhibitors (SSRIs) during pregnancy, can increase the risk of ASD; the results showed a 50% increase in the risk of autism in their children (12).

Due to the seriousness of ASD and its negative impact on the parents of children with ASD having other mental health conditions, such as anxiety, depression, and ADHD, primary non-medication treatment strategies such as behavioral and speech therapies, may reduce the difficulties faced by children and decrease their families' responsibility. Therefore, these interventions have been approached by many ADS centers worldwide to alleviate the emotional and behavioral challenges (1).

For example, Applied Behavior Analysis and Cognitive Therapy are routinely approached as the first line of treatment options. Both strategies teach children to alter their beliefs or behaviors to avoid negative emotions (1, 2). Specifically, as explained in some of research analyses, ABA has been established to be effective for moderating difficult behaviors and training several skills and practices (13).

The learning centers in Saudi Arabia follow the Treatment and Education of Autistic and Related Communication Handicapped Children (TEACCH) for educational programs. Since no two individuals with autism are alike and everyone has different abilities, the program may differ from one student to another. We have to work with the children in a delicate way and work on their communication ability to improve their social interaction and relationships through behavioral therapy. Some individuals with autism have sensory sensitivity to certain stimulation, such as touch, sound, smell, lights, and noises, which may make school painful or frightening for them. In order to create a supportive climate for autistic students, it is very important to differentiate the environment and curriculum for them by using the program TEACCH (14).

However, the evidence for other non-medication interventions is deemed insufficient, mainly due to limitations of research methodology and design associated with current publications (2). Therefore, children with ASD who are also experiencing symptoms related to comorbid conditions, such as sleep problems, aggression, and self-injurious behavior, would be candidates for medication therapy, which are indicated to partially relieve these manifestations, depending on their frequency and intensity (15). Medications are usually employed to target these associated illnesses, that are distinguished as emotional and behavioral challenges, rather than to cure the core symptoms

of ASD, since no medication has proven obvious impact on social withdrawal or constricted, repetitive behaviors (1, 2). A study in 2013 estimated that approximately two out of three youths with ASD had been prescribed a psychoactive medication during the three-year study period, and one in seven had required management with three or more medications concurrently (16).

A recent population-based study in the UK revealed that 33.4% of patients with ASD received at least one psychotropic prescription, of which 92.7% were off-label uses. Moreover, one-third of those who were prescribed antipsychotic drugs were on continuous antipsychotic therapy for more than one year (17). The rate of prescribing psychotropic drugs was even higher in the US compared to the UK (approximately two-thirds of the US cohort had at least one psychotropic drug prescription compared to one-third of the UK cohort) (18). In several cases, it has been reported that successful drug therapy could augment the improvements patients with ASD gained from former non-medication therapies (19).

The United States Food and Drug Administration (FDA) approved only two drugs for the management of irritability, displayed mostly as physical assault and serious tantrum behavior (15, 20), in children and adolescents with ASD: risperidone (21) and aripiprazole (22). However, their indication is as a second line option. Both are atypical antipsychotics that work on the D2 receptor in the neurotransmitter of the brain (23). In addition, there are abundant off-label therapies that doctors may often consider in treating complications associated with ASD, grounded on existing studies. Though when research is incomplete, the usage may be grounded on evidence from reports on children or adults without ASD and physicians' clinical judgment (1,2).

Existing literature revealed a lack of published studies concerning descriptive data on the management strategies of drug and/or non-drug therapies in Saudi children with ASD.

The primary aim of the study is to describe the pattern of management used in ASD among a cross-sectional sample of Saudi children with autism.

The specific objectives are:

- To estimate the prevalence of prescription and duration of use of psychotropic medications, such as antipsychotics, antidepressants, antiepileptic drugs and stimulants, that have been employed for children with ASD and associated psychiatric comorbidities.

- To examine the efficacy of risperidone and other psychoactive medications in reducing the target symptoms of ASD, as compared to only behavioral therapy.

This study is significant due to the lack of comprehensive data regarding ASD medication prescribing in the Middle East region and the higher incidence of ASD in Saudi Arabia compared to international records.

Materials and methods

Study Design and Participants

A cross-sectional study was piloted at two centers: King Abdullah Bin Abdulaziz University Hospital (KAAUH) and King Fahad Medical City (KFMC) for 10 months. Initially, all the electronic records of children with ASD who were receiving treatment in the clinics of the Child and Adolescent Development Centers, were reviewed retrospectively to identify the candidate population. The inclusion criteria were:

- diagnosed with ASD using one of the most reliable instruments (CARS, ABC, etc.)
- undergone at least one ASD intervention (of any type, i.e., non-drug or drug therapy)
- either under supervision of healthcare providers in the center or in other centers prior to enrolment
- used medication therapy (antipsychotics or others) for a minimum of 8 weeks. The non-drug intervention subgroup was included to act as a control group.

On a convenience basis, prospective visits were scheduled for children who had received regular behavioral therapy and/or antipsychotics (mainly risperidone) and their parents for the assessment of efficacy (therapeutic response) and side-effects.

Sample size

The expected sample size for the pilot study was approximately 30 children who were more than 3 years old with ASD diagnosed by DSM-V; 50% of them should have been treated with antipsychotics (risperidone or others) for at least 2 months after being prescribed by their doctors (could potentially benefit from antipsychotics) as the exact clinical picture is determined individually for each group of children".

Data collection protocol

Demographic and clinical information, including age, sex, weight, height, body mass index (BMI), medical history, concurrent medication use, and risperidone (or other psychoactive medications) treatment duration and dosage (daily dose), were collected from the medical records of the participants.

Data regarding the psychiatric diagnoses of the participants were also collected and recorded in the REDCAp application for further analysis. These data included scores identified on the following instruments, which were routinely used in both centers: DSM-5, CARS, Stanford-Binet Intelligence Scales-5th edition, and the Vineland Adaptive Behavior Scales (VABS).

Measurements

Efficacy

According to the aim of the study, the efficacy marker will be the resolution or improvement of the core symptoms of ASD or behavioral disorders measured using the Aberrant Behavior Checklist-Community Version (ABC-CV) (parent-rated under the guidance of the investigators) (24). The Arabic version of ABC-CV was used in this study after obtaining the permission of the original authors and receiving professional training in applying this tool.

The ABC-CV contains 58-items which are rated on a scale of 0 ("not at all a problem") to 3 ("problem is severe in degree"). Items contribute to one of five subscales (Irritability, Lethargy (Social Withdrawal), Stereotypic behavior, Hyperactivity, Inappropriate speech) and an overall score. In previous clinical trials of ASD, the ABC-CV has been sensitive to drug effects (5, 8). The impact on each subscale of ABC has been examined separately (24). This was rated by the participants' direct clinicians or parents (on a scheduled clinic visit).

Safety and side effects

Information about adverse drug reactions was collected by electronic record appraisal and physical examination, concentrating on two frequent manifestations: weight gain and neurological abnormalities, including, dystonia, akathisia, and extrapyramidal symptoms. Furthermore, the parents or caretakers were asked about their observations of weight gain and neurological ADRs. Other relevant data, comprising lipid profiles and prolactin levels, were collected by chart review of laboratory surveillance, which was performed every 3 months. Previously mentioned demographic and medical data were collected from electronic records of patients' files in KAAUH and KFMC. Additional information was considered by conducting a telephonic interview with the children's parents regarding obstacles and difficulties in adhering to medication during the drug-treatment period.

Statistical Analysis

Version 23 of SPSS software was used to conduct the statistical analysis. All study variables were endangered to descriptive statistics calculations. The Kolmogorov-Smirnov test was used to verify that the variables within each group were normal. Analysis of variance (ANOVA) was used to examine mean score differences in patients' responses with respect to their treatment groups. Statistical significance was set at a value of $p \leq 0.05$.

Results

Study Sample

A total of 29 children with a mean age of 8.96 years (range: 5-15 years) were included in this study: KAAUH (14, 48.3%) and KFMC (15, 51.7%). The gender distribution was higher for male children: female (3, 10.3%), male (26, 89.7%). Children were either affiliated to residential institutions (9, 36.0%) or community setting (16, 64.0%). The education mode of children was either regular school (2, 7.1%), special education (24, 85.7%), or other (2, 7.1%). Their mean BMI was 18.12 kg/m^2 (range: 13-32.2).

Pattern of ASD Management

The distribution of management strategy was as follows: risperidone therapy (11, 37.9%), behavioral therapy only (9, 31.0%), risperidone and behavioral therapy (9, 31.0%).

The distribution of antipsychotic therapy was as follows: risperidone (16, 100.0%), aripiprazole (0, 0.0%), haloperidol (0, 0.0%), olanzapine (1, 6.3%), chlorpromazine (1, 6.3%), and quetiapine (1, 6.3%). The mean daily dose of risperidone administered during the treatment period (mean 50.7 months), which included a minimum of a 1-week titration period, was 1.34 ± 1.5 mg (range: 0.25-6 mg).

In addition, the frequencies of prescribing other psychotropic medications were as follows:

- Mood stabilizers (2, 8.3%): divalproex/valproate (0, 0.0%); carbamazepine (2, 100.0%); oxcarbazepine (0, 0.0%); gabapentin (0, 0.0%)
- Alpha 2 adrenergic agonists (2, 8.3%): clonidine (2, 100.0%), guanfacine (0, 0.0%)
- Psychostimulants (7, 29.2%): methylphenidate (7, 100.0%), dextroamphetamine (0, 0.0%)
- Antidepressants: (0, 0.0%)
- Other common non-psychotropic medications: buspirone (0, 0.0%), diphenhydramine (0, 0.0%), melatonin (0, 0.0%), and atomoxetine (2, 100.0%)

Study outcomes

Efficacy

Table 1 displays the average ABC-CV scores in the five subdomains and the total score.

Table 1. ABC-CV mean scores in the study population.

Domain	Minimum	Maximum	Mean	SD
Irritability	5.00	41.00	15.54	8.25
Lethargy	19.00	117.00	58.96	22.5
Stereotypic behavior	1.00	20.00	7.35	4.99
Hyperactivity	2.00	40.00	20.58	9.51
Inappropriate Speech	0.00	10.00	3.58	3.24
ABC-CV total score	19.00	117.00	58.96	22.5

SD, standard deviation.

Comparison of efficacy by the ABC-CV tool

Table 2 displays the distribution of average ABC-CV scores in the five subdomains and the total score by management type. One-way analysis of variance (ANOVA) was employed for multiple comparisons between different treatment groups. As shown in Table 2, the score for the Irritability (including irritability, agitation, and crying) domain was significantly lower in the group receiving behavioral therapy only (P=0.022). There were no significant differences between treatment groups in other ABC subdomains and the total score (P>0.05).

Table 2. ABC-CV scores in the five subdomains and the total score, by management type.

ABC domain	Management	Mean	SD	ANOVA-P value
Irritability	Behavioral therapy only	11.8	3.93	0.022*
	Risperidone therapy only	21.9	10.22	
	Risperidone plus behavioral therapy	13.7	6.8	
	Total	15.5	8.3	
Lethargy	Behavioral therapy only	54.8	14.5	0.058
	Risperidone therapy only	74.3	24.3	
	Risperidone plus behavioral therapy	49.7	22.6	
	Total	58.96	22.5	
Stereotypic behavior	Behavioral therapy only	6.3	3.4	0.339
	Risperidone therapy only	9.38	7.2	
	Risperidone plus behavioral therapy	6.6	3.8	
	Total	7.4	4.99	
Hyperactivity	Behavioral therapy only	20.4	7.5	0.11
	Risperidone therapy only	25.8	10.3	
	Risperidone plus behavioral therapy	16.1	9.2	
	Total	20.58	9.5	
Inappropriate Speech	Behavioral therapy only	3.3	2.7	0.947
	Risperidone therapy only	3.88	3.8	
	Risperidone plus behavioral therapy	3.56	3.6	
	Total	3.58	3.2	
ABC-CV total score	Behavioral therapy only	54.78	14.5	0.058
	Risperidone therapy only	74.1	24.3	
	Risperidone plus behavioral therapy	49.67	22.6	
	Total	58.96	22.5	

* P-value < 0.05, statistically significant; SD, standard deviation.

Safety

1. Body weight changes during therapy

The body weight and BMI were measured before and after risperidone therapy for 5 children. Table 3 displays the mean difference (-5.166 ± 4.4496). However, the paired sample t-test was statistically nonsignificant.

Table 3. Body weight changes during therapy.

	Mean	N	Std. Deviation	Std. Error	Sig. (2-tailed)
BW1	39.8640	5	14.98184	6.70008	0.06
BW2	45.0300	5	18.13290	8.10928	

BW, body weight.

2. Prolactin level

Prolactin levels were measured and categorized in 15 patients receiving risperidone therapy, as shown in Table 4. The mean prolactin level was 77 ± 117.8 ng/mL. The normal values for prolactin are usually rated as follows: men: less than 20 ng/mL (20 µg/L); non-pregnant women: less than 25 ng/mL (25 µg/L); and pregnant women: 80 to 400 ng/mL (80 to 400 µg/L). Prolactin levels between 30 and 200 ng/mL are considered moderately high. Based on this, the prolactin levels were considered very high in two patients (13.3%).

Table 4. Prolactin changes and elevation categories during therapy.

Category	Frequency	Percent
Normal	8	53.3
High	1	6.7
Moderately high	4	26.7
Very high	2	13.3
Total	15	100.0

Discussion

The study revealed a high prevalence of prescription and use of antipsychotic medication in the 29 Saudi children with ASD. The highest prevalence was for risperidone (68.9%), followed by psychostimulants (29.2%). Our results were comparable to a large-scale American study on children with ASD, which reported that 64% had evidence of at least one psychotropic prescription (16). However, the use of mood stabilizers (8.3%) and alpha-2 adrenergic agonists (8.3%) in combination with antipsychotics was less common in this study than in the American study.

The use of combinations of antipsychotics and psychostimulants (17.24%) in children with ASD was also less common than in the American study (38%) (16). Our results were consistent with a previous international study in 30 countries (25), including Saudi Arabia, on the pattern of prescription of drugs (risperidone 64.7%, carbamazepine 19.2%, piracetam 5.4%). In contrast, our results showed a lower prevalence of psychotropic prescriptions than a recent population-based study in the UK that reported 33.4% of patients with ASD receiving at least one psychotropic prescription (17). The observed variability in prescribing pattern among different countries could be justified in light of the absence of a unified practical guideline for the pharmacological treatment of associated symptoms in children and adolescents with ASD.

Regarding the efficacy of risperidone for children with ASD, a substantial body of evidence, including four large, randomized, double-blind, placebo-controlled studies, demonstrated its additional value in controlling the behavior of children who had undergone behavioral therapy (Table 5) (26-29). In particular, a multisite study was conducted by the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network between June 1999 and April 2001 (27). The primary outcome measures were the score of eight weeks on the Irritability (tantrums, aggression, and self-injurious behavior) subscale of the ABC tool, based on the parents' rating. The other outcomes were scores on the other subscales of the same checklist (Social withdrawal, Stereotypic behavior, Hyperactivity, and Inappropriate speech), based on ratings by the parents or primary caretakers. This large-scale study revealed that risperidone in short-term duration (eight weeks) improved behavior primarily in Irritability, as well as in Stereotypic behavior and Hyperactivity subscales, as compared to placebo. However, the results suggested that scores for Social withdrawal and Inappropriate speech domains did not differ significantly between the risperidone and placebo groups, suggesting no impact of risperidone on the Social withdrawal subscale, which rated social isolation and interest in communicating with others. These results were further supported by Pandina *et al*. (28) who studied a group of children with autism, treated with risperidone or placebo for two months. The short-term data supported the efficacy of risperidone for the treatment of irritability, lethargy/social withdrawal, and hyperactive behavior of children with ASD, compared with placebo (28). In contrast with the RUPP study, no significant improvement was noted in the stereotypical behavior of children in Pandina *et al*'s study.

Additionally, the findings of the two studies regarding Irritability and Hyperactivity subscales are comparable with the results of the short-term randomized, double-blind, placebo-controlled trial conducted by Shea *et al*. (26). However, Shea *et al*.'s study demonstrated that patients treated with risperidone also exhibited significantly greater decreases on all the other subscales of the ABC. Interestingly, the largest difference was observed for the Hyperactivity/Noncompliance subscale in Shea *et al*.'s study.

Possible explanations for these discrepancies in efficacy of risperidone on various ABC subscales are the differences in severity of autism between the three studies; small sample sizes; and short duration of observation in all three studies.

Another study assessed the long-term maintenance of response in children who continued to use risperidone for 6 months (29). This global study revealed a continuous favorable impact of risperidone on the Irritability domain only. However, less significant effects were noted on other ABC subscales compared to the placebo group.

Surprisingly, in the present cross-sectional observation of the children receiving risperidone, scores for all ABC subdomains were higher than in the previous studies, indicating less efficacy of risperidone in this group. The most peculiar observation was noted in the Lethargy (Social withdrawal) subdomain, which scored 74.3 ± 24.3, highest compared to all other ABC subdomains in this and previous studies. Interestingly, lower scores were noted in the current study for children who received behavioral therapy only, compared to their counterparts who received risperidone only in all ABC subdomains and the total score. The results of direct comparison by ANOVA showed significantly higher scores in the risperidone group compared to the other groups (behavioral or risperidone plus behavioral therapy), as noted in Table 2. These discrepancies could be attributed to the higher severity of autism and/or less responsiveness to the previous behavioral therapy in the group who received risperidone only. In addition, these findings indicated the beneficial impact of adding risperidone management to behavioral therapy in the third arm of this pilot study (n=9), particularly on the Hyperactivity domain.

Table 5. Comparisons of ABC scores in the current study sample to other populations.

Domain	Current Study	Study1 (26) (all improved)	Study2 (27) (no improvement in Social withdrawal and Inappropriate speech)	Study3 (28) (no improvement in Stereotypic behavior and Inappropriate speech)	Study4 (29) (only Irritability improved)
Mean dose (mg/day)	1.813 (1.99)	1.17	1.8 ± 0.7 mg (range, 0.5 to 3.5)	1.37	1.81
Mean Duration (months)	50.7 (21.9)	2	2	2	6
			Risperidone therapy		
	N=11	**N=39**	**N=49**	**N=27**	**N=12**
Irritability	21.9 ± 10.2	6.8 ± 5.8	11.3 ± 7.4	7.2 ± 5.9	12.6 ± 9.8
Lethargy (Social withdrawal)	74.3 ± 24.3	5.1 ± 5.9	8.9 ± 6.4	4.7 ± 4.4	2.8 ± 3.1
Stereotypic behavior	9.38 ± 7.2	3.6 ± 3.8	5.8 ± 4.6	3.9 ± 4.2	3.3 ± 3.5
Hyperactivity	25.8 ± 10.3	12.4 ± 6.7	17.0 ± 9.7	13.3 ± 8.7	18.0 ± 11.8
Inappropriate speech	3.88 ± 3.8	2 ± 2.6	3.0 ± 3.1	1.9 ± 2.2	3.0 ± 2.8
ABC-CV total score	74.1 ± 24.3	NA	NA	NA	NA
			Placebo/Behavioral Therapy		
	N=9	**N=38**	**N=52**	**N=28**	**N=12**
Irritability	11.8 ± 3.9	14.7 ± 8.4	21.9 ± 9.5	14.1 ± 11.3	20.3 ± 10.3
Lethargy	54.8 ± 14.5	8.6 ± 6.9	12.0 ± 8.3	8.2 ± 8.9	4.8 ± 3.5
Stereotypic behavior	6.3 ± 3.4	5.7 ± 4.0	7.3 ± 4.8	6.9 ± 6.9	3.4 ± 4.6
Hyperactivity	20.4 ± 7.5	23.5 ± 7.9	27.6 ± 10.6	26.4 ± 12.8	20.8 ± 12.1
Inappropriate speech	3.3 ± 2.7	3.2 ± 3.0	5.9 ± 3.8	3.1 ± 3.5	3.0 ± 2.3
ABC-CV total score	54.8 ± 14.5	NA	NA	NA	NA

NA, not reported.

Study limitations

This study had several limitations. First, it had a cross-sectional design which did not a include pretreatment baseline measurement of the ABC tool. This could limit the accurate estimation of percentage improvement (% compared to pretreatment baseline) in all ABC subdomains, as well as the total score within each of the three study arms. Additionally, a definite causal relationship could not be established in a cross-sectional design. Also, indirect

comparisons to other populations in previous studies were not reasonable in terms of percentage improvement, duration of follow-up, ethnic differences, or dosing. Second, the small overall sample size and that for each arm in this study could produce type I or type II errors in detecting the significant difference in efficacy of risperidone. Therefore, this could limit the generalizability of the current findings to all children with autism in the Kingdom of Saudi Arabia (KSA). Moreover, univariate analyses of the therapeutic response should be interpreted with caution within this context. Third, the duration of maintenance therapy in this study (50.7, range 23 to 74 months) was longer than that in the previous studies. Therefore, the observed findings could truly and significantly differ with the long-term duration of risperidone therapy compared to previously published short-term therapy studies (2 to 6 months' duration) (26-29). Fourth, the employment of the Arabic version of the ABC tool for assessing improvement in children's behavior by directly interviewing their parents could have produced social desirability bias in this pilot study.

Conclusions

While the current literature on the efficacy and safety of risperidone support that it may have an important role in the management of behavioral problems in children with autism, further long-term studies with large samples, including various ethnic groups, are mandatory. Interestingly, the existing short- or long-term studies did not resolve the difference in the impact of risperidone on various ABC subdomains (Irritability, Lethargy (Social withdrawal), Stereotypic behavior, Hyperactivity, Inappropriate speech).

Our initial findings are consistent with other reports in terms of the efficacy of risperidone plus behavioral therapy on reducing hyperactivity symptoms and total ABC score. However, further stringent prospective design studies involving children with ASD in KSA are warranted to confirm the current observations.

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Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Adherence to Ethical Standards

This study was approved by the Institutional Review Board (IRB) of KFMC (IRB Log No: 20-758E) and the IRB of Princess Nourah bint Abdulrahman University (PNU) (IRB Log No: 20-0321). Informed consents were taken from the parents or other legal caretakers of the participants prior to the study. All procedures were performed in accordance with national ethical standards and conducted in accordance with the Declaration of Helsinki (1964).

References

1. Howes O, Rogdaki M, Findon J, et al. Autism spectrum disorder: Consensus guidelines on assessment, treatment and research from the British Association for Psychopharmacology. 2018. Journal of Psychopharmacology (Oxford, England), 32(1):3–29. Available from: https://pubmed.ncbi.nlm.nih.gov/29237331/

2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2018. Available from: https://ajp.psychiatryonline.org/
3. The National Institute of Mental Health (NIMH). Attention-Deficit/Hyperactivity Disorder [Internet]. Nimh.nih.gov. 2019 [cited 10 April 2021]. Available from: https://www.nimh.nih.gov/health/topics/attention-deficit-hyperactivity-disorder-adhd/index.shtml
4. Soke G, Maenner M, Christensen D, et al. Prevalence of Co-occurring Medical and Behavioral Conditions/Symptoms Among 4- and 8-Year-Old Children with Autism Spectrum Disorder in Selected Areas of the United States in 2010. Journal of Autism and Developmental Disorders. 2018;48(8):2663–2676. Available from: https://pubmed.ncbi.nlm.nih.gov/29524016/
5. Volkmar F, Siegel M, Woodbury-Smith M, et al. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Autism Spectrum Disorder. Journal of the American Academy of Child & Adolescent Psychiatry. 2014;53(2):237–257. Available from: https://www.jaacap.org/article/S0890-8567(13)00819-8/pdf
6. Park H, Yi SY, Yoon SA, et al. Comparison of the Autism Diagnostic Observation Schedule and Childhood Autism Rating Scale in the Diagnosis of Autism Spectrum Disorder: A Preliminary Study. Soa--ch'ongsonyon chongsin uihak = Journal of Child & Adolescent Psychiatry. 2018;29(4):172–177. Available from: https://pubmed.ncbi.nlm.nih.gov/32595311/
7. Chlebowski C, Green J, Barton M, et al. Using the childhood autism rating scale to diagnose autism spectrum disorders. Journal of Autism and Developmental Disorders. 2010;40(7):787–799. Available from: https://pubmed.ncbi.nlm.nih.gov/20054630/
8. Sharma S, Gonda X, Tarazi F. Autism Spectrum Disorder: Classification, diagnosis and therapy. Pharmacology & Therapeutics. 2018;190:91–104. Available from: https://pubmed.ncbi.nlm.nih.gov/29763648/
9. Almandil N, Alkuroud D, AbdulAzeez S, et al. Environmental and Genetic Factors in Autism Spectrum Disorders: Special Emphasis on Data from Arabian Studies. 2019. International Journal of Environmental Research and Public Health. 2019;16(4):658. Available from: https://pubmed.ncbi.nlm.nih.gov/30813406/
10. Centers for Disease Control and Prevention [Internet]. 2020. Screening and Diagnosis of Autism Spectrum Disorder. Accessed on 3/3/2021. Available from: https://www.cdc.gov/ncbddd/autism/screening.html
11. MedlinePlus [Internet]. Bethesda (MD): National Library of Medicine (US); Fragile X syndrome: Medlineplus.gov. 2020 Accessed on 3/3/2021. Available from: https://medlineplus.gov/genetics/condition/fragile-x-syndrome/
12. Kobayashi T, Matsuyama T, Takeuchi M, et al. Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis. Reproductive Toxicology (Elmsford, N.Y.). 2016;65:170–178. Available from: https://pubmed.ncbi.nlm.nih.gov/27474253/
13. Weston L, Hodgekins J, Langdon P. Effectiveness of cognitive behavioural therapy with people who have autistic spectrum disorders: A systematic review and meta-analysis. Clinical Psychology Review. 2016;49:41–54. Available from: https://pubmed.ncbi.nlm.nih.gov/27592496/
14. Almasoud, Hanan. "The Education of children with autism in saudi arabia: A teaching guide." Special Education Department: King Saud University (2010). Available from: https://faculty.ksu.edu.sa/sites/default/files/the_education_of_children_with_autism_in_saudi.pdf
15. Posey D, Stigler K, Erickson C, et al. Antipsychotics in the treatment of autism. The Journal of Clinical Investigation. 2008;118(1):6–14. Available from: https://pubmed.ncbi.nlm.nih.gov/18172517/
16. Spencer D, Marshall J, Post B, et al. Psychotropic Medication Use and Polypharmacy in Children With Autism Spectrum Disorders. Pediatrics. 2013;132(5):833–840. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3813388/
17. Alfageh B, Man K, Besag F, et al. Psychotropic Medication Prescribing for Neuropsychiatric Comorbidities in Individuals Diagnosed with Autism Spectrum Disorder (ASD) in the UK. Journal of Autism and Developmental Disorders. 2020;50(2):625–633. Available from: https://pubmed.ncbi.nlm.nih.gov/31724119/
18. Houghton R, Ong R, Bolognani F. Psychiatric comorbidities and use of psychotropic medications in people with autism spectrum disorder in the United States. Autism Research: Official journal of the International Society for Autism Research. 2017;10(12):2037–2047. Available from: https://pubmed.ncbi.nlm.nih.gov/28963809/
19. Frazier T, Youngstrom E, Haycook T, et al. Effectiveness of medication combined with intensive behavioral intervention for reducing aggression in youth with autism spectrum disorder. Journal of Child and Adolescent Psychopharmacology. 2010;20(3):167–177. Available from: https://pubmed.ncbi.nlm.nih.gov/20578929/
20. Blankenship K, Erickson C, Stigler K, et al. Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6-17 years. Pediatric Health. 2010;4(4):375–381. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043611/

21. Janssen Pharmaceutica. Risperdal (risperidone) package insert. Titusville, NJ; 2005.. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/020272Orig1s036,s041,020588Orig1s024,s028,s029,21444Orig1s008,s015.pdf
22. Bristol-Myers Squibb and Otsuka America Pharmaceutical. Abilify (aripiprazole) package insert. Princeton, NJ, and Rockville, MD; 2005. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,021866s023lbl.pdf
23. Dodsworth T, Kim D, Procyshyn R. A systematic review of the effects of CYP2D6 phenotypes on risperidone treatment in children and adolescents. Child and Adolescent Psychiatry and Mental Health. 2018;12:37. Available from: https://capmh.biomedcentral.com/articles/10.1186/s13034-018-0243-2
24. Aman M, Singh N, Stewart A, et al. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. American Journal of Mental Deficiency. 1985;89(5):485–491. Available from: https://pubmed.ncbi.nlm.nih.gov/3993694/
25. Wong A, Hsia Y, Chan E, et al. The variation of psychopharmacological prescription rates for people with autism spectrum disorder (ASD) in 30 countries. Autism Research: Official journal of the International Society for Autism Research. 2014;7(5):543–554. Available from: https://pubmed.ncbi.nlm.nih.gov/24895332/
26. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics. 2004;114(5):e634–e641. Available from: https://pubmed.ncbi.nlm.nih.gov/15492353/
27. McCracken J, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. 2002. The New England Journal of Medicine. 2002;347(5):314–321. Available from: https://pubmed.ncbi.nlm.nih.gov/12151468/
28. Pandina G, Bossie C, Youssef E, et al. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. Journal of Autism and Developmental Disorders. 2007;37(2):367–373. Available from: https://pubmed.ncbi.nlm.nih.gov/17019624/
29. Troost P, Lahuis B, Steenhuis M, et al. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. Journal of the American Academy of Child and Adolescent Psychiatry. 2005;44(11):1137–1144. Available from: https://pubmed.ncbi.nlm.nih.gov/16239862/