META-ANALYSIS

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Efficacy and Safety of Risperidone Interventions in Children and Adolescents with Autism Spectrum Disorder

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ABSTRACT

Background: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition that severely impairs children's health. Current data suggest that behavioral therapies are successful. Risperidone has been approved by the US Food and Drug Administration (FDA) to moderate impulsive behavior in people with ASD. This study aimed to evaluate the efficacy and safety of risperidone in children and adolescents with ASD.

Methods: This study involved searching electronic databases for relevant articles, screening them based on inclusion and exclusion criteria, and performing a combined data analysis of the selected articles using Review Manager software.

Results: This meta-analysis comprised 7 articles. The pooled analysis indicated that: (1) Risperidone intervention decreased scores on the Aberrant Behavior Checklist (ABC) scale in children and adolescents with ASD, as well as reduced scores related to stereotypy, social withdrawal, hyperactivity, inappropriate speech, and irritability on the ABC scale; (2) The use of risperidone raised the risk of weight gain, tremors, upper respiratory tract infection, and increased appetite. Other adverse responses, however, did not differ significantly from the placebo group.

Conclusion: Risperidone demonstrated effectiveness and safety in managing behavioral issues and decreased ABC scores in children and adolescents with ASD. However, further research is needed, and the associated risks still need to be considered.

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INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by difficulties with social interaction and communication, as well as repetitive behaviors[1] that can impact various aspects of a child's development, including behavioral, problem-solving, self-care, social communication, language, and executive functioning skills.[2] In the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic system, the diagnostic criteria for autism continue to evolve from DSM-IV (4th edition, text) to DSM-5. In the past, the 3 different diagnoses—unspecified pervasive developmental disorders, autism, and Asperger's syndrome—were merged into one: ASD.[1] The DSM-5 defines ASD impairment in 2 main areas: social communication and interaction challenges; and restricted, repetitive, and instantaneous behavior patterns.[2] Worldwide, ASD affects 1% of children, with a reported disability-adjusted life year of 4.31 million.[3] The incidence of ASD has increased throughout Asia in recent years and is 4 to 5 times more prevalent in boys than in girls.[4] Studies have shown that the genetic risk of ASD overlaps with various developmental and neurological diseases,[5] and several genes have been associated with ASD development,[6,7] which may contribute to the diagnosis and treatment of ASD.[8] Depending on their symptoms, ASD can be diagnosed as early as 14 months.[9] There is currently no effective treatment, and prognostic outcomes are better with early diagnosis and treatment.[1,4,10,11] The current affirmative care of children with ASD predominantly depends on behavioral therapies to mitigate fundamental symptoms.[1,2] Drugs are primarily used to address the comorbidities associated with ASD, as no treatment can treat the basic symptoms.[11,12] Currently, melatonin, alpha-2-adrenergic agonists, atypical antipsychotics, serotonergic drugs, N-acetylcysteine, and serotonergic medications are the main treatments used to treat symptoms associated with ASD.[2] Relevant studies suggest that aripiprazole and risperidone can effectively improve behavior problems.[3,5,11]

Risperidone's chemical name is 3-12 - [4 - (6 - fluoro - 1, 2 - benzo different oxazole - 3 - base) - 1 - pyridyl) ethyl - 6,7,8,9-4-2 - methyl - 4 h - hydrogen pyridine [1, 2 - a] pyrimidine - 4-1. It is a class of 5-hydroxytryptamine (5-HT)-2 receptor and dopamine D2 receptor antagonist,[13,14]

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which is an effective and well-tolerated alternative drug for the treatment of chronic schizophrenia. It is characterized by reduced evoked potentials, antipsychotic action, and positive effects on anxiety and depression with neuralgia.[15] Risperidone is being utilized extensively for the treatment of schizophrenia and is both safe and effective. In 2006, the United States Food and Drug Administration (FDA) authorized risperidone for the management of impulsive behavior among individuals with ASD,[16] but still not for the fundamental characteristics of ASD.[17] For children and adolescents with autism, risperidone should be used before the age of 5 years old.[18] To provide further details for therapeutic decision-making, this study attempted to thoroughly examine the safety and effectiveness of risperidone intervention in children and adolescents with ASD using published data.

MATERIALS AND METHODS

Search Strategy

Relevant published publications were retrieved from electronic databases (PubMed, FMRS, CNKI, Sinomed, Wanfang, and Cochrane) from the databases' inception until December 2023. This study employed the search term (Risperidone) AND ("Autism" OR "autistic disorder" OR "Autism Spectrum Disorder" OR "ASD" OR "Asperger" OR "Pervasive" OR "Kanner's syndrome" OR "Asperger's" OR "unspecified pervasive developmental disorders").

Inclusion Criteria and Exclusion Criteria

The inclusion criteria were as follows: (1) patients diagnosed with ASD, including autism, Asperger's syndrome, and unspecified pervasive developmental disorders, according to DSM requirements; (2) participants were under 18 years of age; (3) the intervention involved oral administration of risperidone; (4) the control involved either placebo oral treatment or no treatment; (5) outcome indicators were unrestricted; (6) Study design: randomized controlled trial (RCT).

The exclusion criteria were established as follows: (1) Non-RCTs, (2) full text unavailable, (3) participants aged 18 years or older, (4) animal studies, (5) article categories included reviews and systematic reviews, (6) interventions did not involve risperidone or risperidone in conjunction with other drugs, (7) the included population had additional mental or physical disorders.

MAIN POINTS

- Autism Spectrum Disorder (ASD) is a neurodevelopmental condition. At present, the most effective treatment is behavioral intervention.
- The United States Food and Drug Administration approved risperidone to control impulsive behavior in patients with ASD.
- Risperidone can degrade the total score and each item score on the Aberrant Behavior Checklist scale in children and adolescents with ASD.
- Increased appetite, upper respiratory tract infections, tremors, and weight gain should be considered when risperidone is used in children and adolescents with ASD.

Study Selection

The search articles were selected by 2 evaluators using the inclusion and exclusion criteria. Discussions between the 2 evaluators were used to settle any disputes. Three researchers reached an agreement after a third assessor debated disagreements. A fourth pertinent individual was consulted if the 3 investigators could not agree.

Assessment Quality

After screening, article data were extracted. The article quality was evaluated using the Review Manager software.

Article quality evaluation table of RevMan: (1) Random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data; (6) selective reporting; (7) other biases. The bias can be divided into low risk of bias, high risk of bias, and unclear risk of bias.

Outcome

The Aberrant Behavior Checklist (ABC) scale evaluated ASD in children and adolescents. The ABC comprises 57 items related to autism behavior. The 5 dimensions encompass stereotypy, social withdrawal, hyperactivity, inappropriate speech, and irritability. This scale is primarily utilized to evaluate behavioral issues and the efficacy of interventions in ASD; elevated scores signify more severe behavioral problems.[19] Secondary indicators of the effectiveness and safety of risperidone include its side effects.

Evidence Analysis

The Review Manager program (RevMan 5.3) assessed the included RCTs. The aggregated outcomes are presented through a forest plot. The 95% CI was calculated for the outcome measures of each study, and heterogeneity among the studies was assessed. A random effects model was employed in cases with significant heterogeneity ($P < .10$, $I^2 > 50\%$). On the other hand, this study employed a fixed-effects model ($P > .10$, $I^2 \leq 50\%$). Statistical significance was established at $P < .05$.

RESULTS

Articles Search Results

A total of 1488 publications were retrieved (PubMed, n = 570; FMRS, n = 156; Cochrane, n = 194; CNKI, n = 59; Sinomed, n = 485; and WanFang, n = 24). Of these, 1346 papers were rejected for being non-RCTs. Titles and abstracts were

reviewed, resulting in the exclusion of 110 articles. The full text of the remaining articles was read according to the inclusion and exclusion criteria; 25 articles were excluded because they did not meet the inclusion criteria, and 7 articles were included in the analysis, as shown in Figure 1.

Quality of Articles

The quality of the included articles was analyzed using RevMan software. The quality analysis encompassed selection, performance, detection, attrition, reporting, and other biases, as shown in Figures 2 and 3.

Characteristics of the Article

Seven articles were included in this study, and the total number of participants was 330. The age of the participants was less than 18 years, and the age range was 2.5-17 years old. This study included participants diagnosed with ASD according to the DSM-IV criteria. The experimental group received risperidone for ASD, while the control group was administered a placebo. The main techniques used to evaluate the results were the ABC, adverse reactions, and drug reaction rates. Table 1 provides a summary of the characteristics of the included studies.

Meta-analysis

Efficacy Outcome: Seven articles used the ABC scale score as their primary outcome evaluation; Figure 4 demonstrates a substantial difference between the 2 groups. The risperidone intervention decreased the ABC score in comparison to a placebo.

Significant differences were found between the 2 groups regarding stereotypy, social disengagement, hyperactivity, improper speech, and irritability when the ABC scale scores for each dimension were analyzed. Risperidone decreased the ABC stereotypy, ABC social withdrawal, ABC hyperactivity, ABC-inappropriate speech, and ABC irritability scores as compared to a placebo (Table 2).

Safety Outcome: There was a significant difference in weight increase between the 2 groups (Figure 5). Risperidone, compared to placebo, elevated the risk of enhanced appetite, upper respiratory tract infections, and tremors. However, no disparities were observed in constipation, exhaustion, nausea or vomiting, headache, xerostomia, diarrhea or loose stools, anorexia, appetite loss, stomach discomfort, or sleep disturbances between the 2 groups (Table 3).

DISCUSSION

As of now, no prescription drug has demonstrated a direct enhancement of the primary symptoms of ASD.[16] A better prognosis has been associated with early intervention. Since destructive conduct is frequently associated with ASD, first- and second-generation antipsychotics

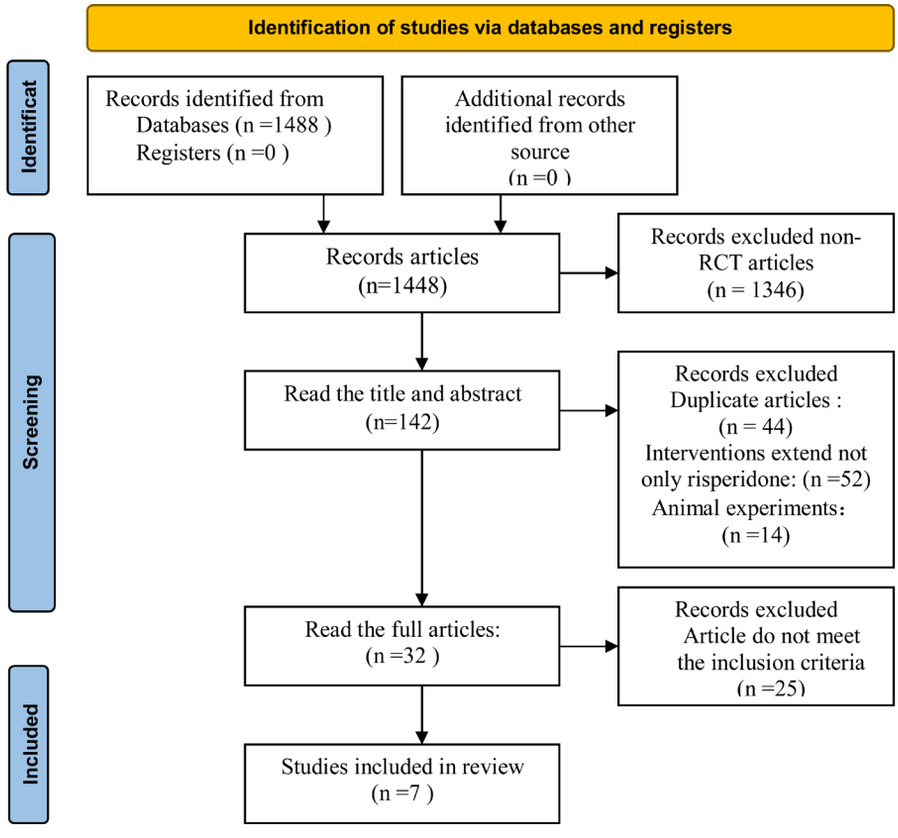

Figure 1. Flow chart of articles screening.

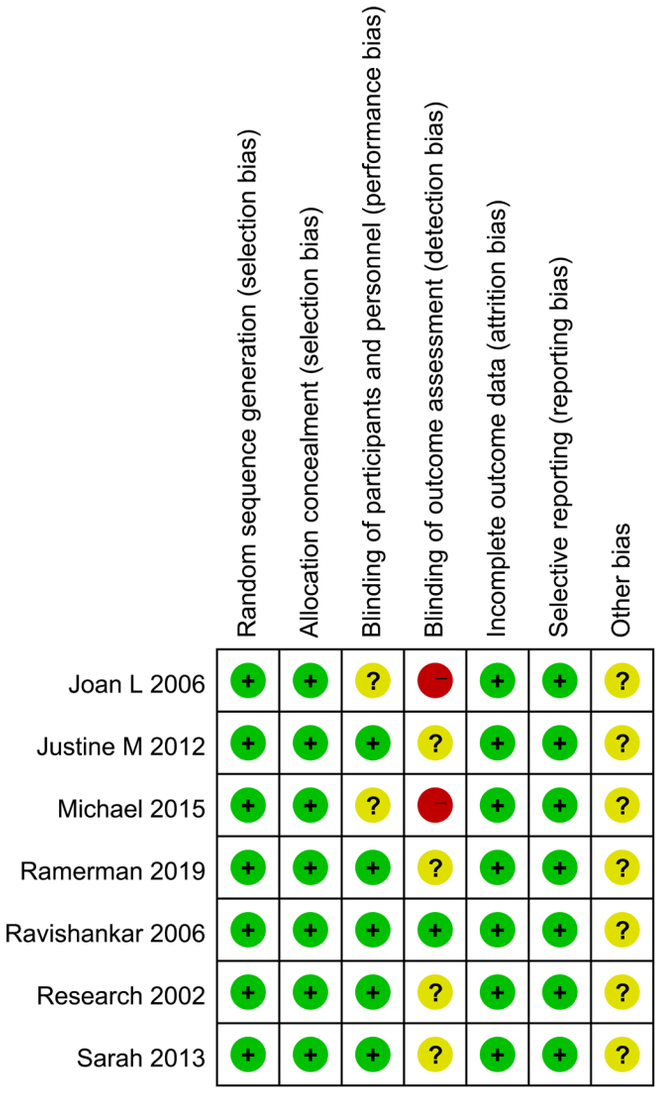

Figure 2. Risk of bias for each included study.

should be taken into consideration. Extrapyramidal side effects (EPS) and drug issues with movement are more common in first-generation antipsychotic drugs.[16] Second-generation antipsychotics are commonly used, and the widely used first-line second-generation antipsychotics include risperidone and aripiprazole.[16] Short-term evidence indicates that risperidone and aripiprazole may be helpful in the treatment of the core symptoms of ASD,[13] and their safety and efficacy are significant.[27] According to the current study, risperidone may help children and adolescents with ASD with behavioral issues such as irritability, social disengagement, hyperactivity, stereotypy, and inappropriate speaking.

Furthermore, Hutchinson et al[28] showed that risperidone does not result in cognitive deficits and can help patients with autism with both core and non-core symptoms. However, the genes that people with ASD possess may have an impact on how they react to risperidone. Related research has demonstrated that DRD3 rs167771 carriers showed significant enhancement in ABC and drowsiness/social withdrawal scores, as well as DRD1 rs1875964 homozygous and DRD2 rs1079598 wild-type in stereotyped behavior, following risperidone administration.[29]

Alongside its therapeutic effects, the side effects of risperidone frequently attract scrutiny. Parents exhibit increased concern for adverse drug reactions in children and adolescents, often demonstrating decreased acceptance. As a second-generation antipsychotic drug, risperidone has common adverse effects such as weight gain, diabetes, and deterioration of blood lipids.[30] Prolactin increases.[31] And the risk of drug-related metabolic problems is also high.[18] Weight gain and increased appetite are the most common problems.[28]

Previous studies have shown that risperidone can lead to weight gain,[28,32,33] increased waist circumference,[32] sleepiness, fatigue, and anxiety.[33] This study found that risperidone also increases the risk of tremors and upper respiratory tract infections. The treatment of children and adolescents with low concentration ranges is different from the adult risperidone therapy window.[17] In children and adolescents, low-dose risperidone is associated with a lower risk of adverse reactions,[34] and low-dose risperidone-associated adverse effects are acceptable.[35] Kloosterboer et al[36] have shown that monitoring risperidone blood levels can help predict body mass index. The total dose of risperidone within the target range of 3.5-7.0

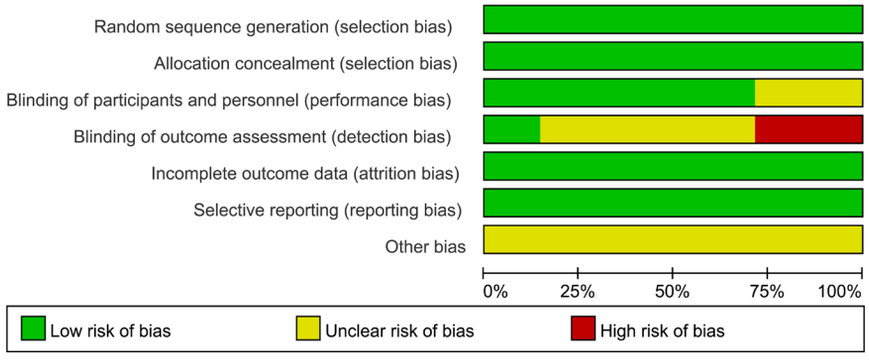

Figure 3. Overview of the risk of bias of the included studies.

Table 1. The Characteristics of the Included Articles

Included Trail	Country	Diagnosis	Age	Interventions		Outcome
				Experimental Group	Control Group	
Joan[20] 2006	America	DSM-IV/ASD	2.5-6	Risperidone (n=12) 0.5-1.5 mg/d	Placebo (n=12)	1,4,5,7,11
Justine[21] 2013	America	DSM-IV/ASD	5-17	Risperidone (n=31) 0.125-1.25 mg/d	Placebo (n=35)	2,5,6,3,8,10
Michael[22] 2015	America	DSM-IV/ASD	5-17	Risperidone (n=57) 2.47±1.29 mg/d	Placebo (n=27)	3,5,6,7,10,11
Ramerman[23] 2019	Netherlands	DSM-IV/ASD	5-17	Risperidone (n=14) 0-6 mg/d	Placebo (n=11)	2,3,7,9
Ravishankar 2006[24]	India	DSM-IV/ASD	5-12	Risperidone (n=19) 0.5-1 mg/d	Placebo (n=20)	2,5
James[25], 2002	America	DSM-IV/ASD	5-17	Risperidone (n=12) 0.25-2.5 mg/d	Placebo (n=12)	1,2,4,5,8
Sarah[26] 2004	Canada	DSM-IV/ASD	5-12	Risperidone (n=40) 0.01-0.06 mg/(d*kg)	Placebo (n=39)	2,3,5

1, Childhood Autism Rating Scale (CARS); 2, Aberrant Behavior Checklist (ABC); 3, Clinical Global Impression (CGI); 4, Childhood Behavior Checklist (CBCL); 5, Adverse reaction; 6, Children's Yale-Brown Obsessive Compulsive Scale-Pervasive Developmental Disorder (CY-BOCS-PDD); 7, Weight; 8, Drug response rate; 9, Extrapyramidal side effects (EPS); 10, Electrocardiogram; 11, Prolactin levels.

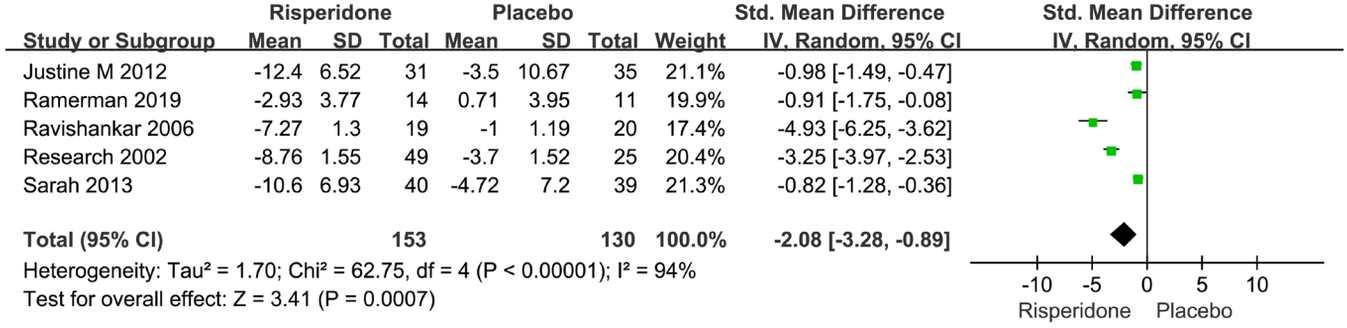

Figure 4. The forest figure of aberrant behavior checklist score.

mcg/L can minimize body mass index.[37] Risperidone can stimulate hunger, resulting in weight gain and metabolic problems. When treating children and adolescents with ASD, monitoring their body weight, lipids, blood glucose, and other metabolic indicators is essential. However, one should also be sufficiently concerned about additional unpleasant effects such as somnolence, rhinitis, upper respiratory tract infection, tremors, excessive saliva, or drooling.

In recent years, research has revealed that additional treatments may be effective for ASD. Physical activity improves the behavior and emotional management of children with ASD.[38,39] Stem cell therapy can also help improve the ASD children rating scale.[40,41] An increasing number of studies have shown that some ASD symptoms are related to the brain-gutmicrobiome axis[42,43] Gut microbes can improve ASD symptoms.[44] Research indicates that ASD is linked to several genes and is anticipated to provide benefits to individuals with ASD via precision gene therapy.[45]

Strengths and Limitations

The present study included thorough RCTs and comprehensively assessed the impact of risperidone on children and adolescents with autism. However, because of the limited research, bias may have developed, and some adverse effects may have been neglected.

In conclusion, risperidone can degrade ABC scale scores in children and adolescents diagnosed with ASD. It may improve behavioral problems in children and adolescents with ASD, including stereotypy, social withdrawal, hyperactivity, improper speech, and irritability.

However, there is a significant risk of increased appetite, weight gain, upper respiratory tract infections, and tremors. Risperidone is effective and safe for treating both core and non-core symptoms in autistic children and

Table 2. Five Dimensions of Aberrant Behavior Checklist Scale Score Analysis

Five Dimensions of Aberrant Behavior Checklist	Number of Included Trials	Number of Participants	95% CI	RR	I^2 (%)	*P*
Stereotypy	3	178	[−6.37, −1.44]	−3.91	90	.002
Social withdrawal	3	178	[−0.85, −0.24]	−0.55	0	.0005
Hyperactivity	3	178	[−12.26, −3.69]	−7.97	86	.0003
Inappropriate speech	3	178	[−3.85, −0.70]	−2.27	90	.005
Irritability	3	178	[−12.40, −0.50]	−6.45	94	.03

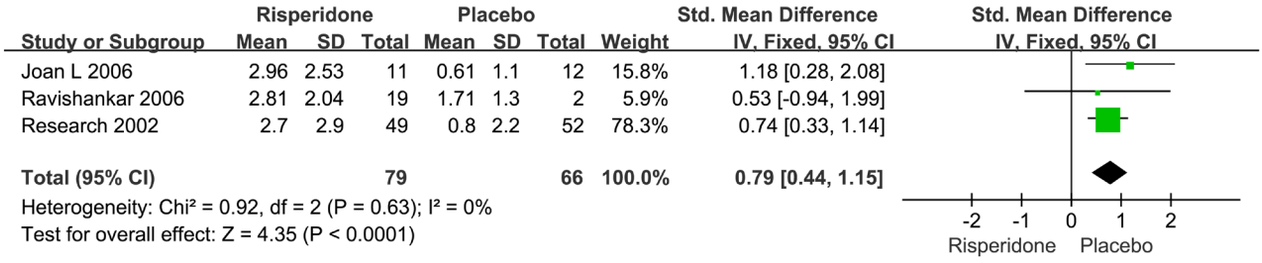

Figure 5. The forest figure of weight increase.

Table 3. Adverse Event Analysis

Adverse Event	Number of Included Trials	Number of Participants	N in Risperidone Group	N in the Placebo Group	RR	95% CI	I^2 (%)	*P*
Increased appetite	3	237	69 of 146	24 of 91	2.45	[1.29,4.65]	41	.006
Upper respiratory tract infection	2	179	20 of 89	8 of 90	3.14	[1.26,7.80]	0	.01
Tremor	2	179	11 of 89	1 of 90	8.22	[1.56,49.82]	0	.01
Rhinitis	2	184	32 of 106	22 of 78	1.64	[0.80,3.35]	0	.17
Constipation	2	163	10 of 97	6 of 66	1.31	[0.10,16.38]	75	.84
Fatigue	3	263	46 of 146	22 of 117	2.18	[0.70,6.85]	61	.18
Nausea or vomiting	3	263	43 of 146	34 of 117	1.33	[0.75,2.35]	0	.33
Headache	2	179	14 of 89	8 of 90	1.95	[0.77,4.93]	0	.16
Dry mouth	2	184	15 of 106	8 of 78	1.31	[0.54,3.15]	33	.55
Diarrhea or loose stools	2	184	18 of 106	12 of 78	1.56	[0.28,8.65]	57	.61
Anorexia or loss of appetite	2	179	7 of 89	5 of 90	1.32	[0.20,8.74]	51	.77
Abdominal pain	2	179	13 of 89	12 of 90	1.20	[0.22,6.57]	71	.83
Sleep problems	2	184	17 of 106	11 of 78	1.38	[0.59,3.22]	0	.45

adolescents. However, considering the small number of included trials, potential medication concerns should be addressed. More correlational investigations are needed in the future.

Data Availability Statement: Research data supporting this publication are available from public electronic databases.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.Z., F.Y.; Design – C.Z.; Supervision – C.Z.; Resources – C.Z.; Materials – F.Y., L.K.; Data Collection and/or Processing – F.Y., L.K.; Analysis and/or Interpretation – F.Y., L.K.; Literature Search – F.Y., L.K.; Writing Manuscript – F.Y.; Critical Review – C.Z.

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REFERENCES

1. Yu Y, Ozonoff S, Miller M. Assessment of autism spectrum disorder. *Assessment*. 2024;31(1):24-41. [CrossRef]
2. Aishworiya R, Valica T, Hagerman R, Restrepo B. An update on psychopharmacological treatment of autism spectrum disorder. *Neurotherapeutics*. 2022;19(1):248-262. [CrossRef]
3. Shamabadi A, Karimi H, Arabzadeh Bahri R, Motavaselian M, Akhondzadeh S. Emerging drugs for the treatment of irritability associated with autism spectrum disorder. *Expert Opin Emerg Drugs*. 2024;29(1):45-56. [CrossRef]
4. Salari N, Rasoulpoor S, Rasoulpoor S, et al. The global prevalence of autism spectrum disorder: a comprehensive systematic review and meta-analysis. *Ital J Pediatr*. 2022;48(1):112. [CrossRef]
5. Hirota T, King BH. Autism spectrum disorder: a review. *JAMA*. 2023;329(2):157-168. [CrossRef] .
6. Yenkoyan K, Ounanian Z, Mirumyan M, et al. Advances in the treatment of autism spectrum disorder: current and promising strategies. *Curr Med Chem*. 2024;31(12):1485-1511. [CrossRef]
7. Manoli DS, State MW. Autism spectrum disorder genetics and the search for pathological mechanisms. *Am J Psychiatry*. 2021;178(1):30-38. [CrossRef]
8. Kereszturi É. Diversity and classification of genetic variations in autism spectrum disorder. *Int J Mol Sci*. 2023;24(23):16768. [CrossRef]
9. Rojas V, Rivera A, Nilo N. Update in diagnosis and early intervention of autistic Spectrum Disorder. *Rev Chil Pediatr*. 2019;90(5):478-484. [CrossRef]
10. Iles A. Autism spectrum disorders. *Prim Care*. 2021;48(3):461-473. [CrossRef]

11. Lord C, Brugha TS, Charman T, et al. Autism spectrum disorder. *Nat Rev Dis Primers*. 2020;6(1):5. [CrossRef]
12. Safwi SR. Autism spectrum disorder in the US: have we done enough? *Psychiatry Res*. 2023;330:115595. [CrossRef]
13. Leysen JE, Gommeren W, Eens A, de Chaffoy de Courcelles D, Stoof JC, Janssen PA. Biochemical profile of risperidone, a new antipsychotic. *J Pharmacol Exp Ther*. 1988;247(2):661-670. [CrossRef]
14. Bhat AA, Gupta G, Afzal O, et al. Neuropharmacological effect of risperidone: from chemistry to medicine. *Chem Biol Interact*. 2023;369:110296. [CrossRef]
15. Janssen PA, Niemegeers CJ, Awouters F, Schellekens KH, Megens AA, Meert TF. Pharmacology of risperidone (R 64 766), a new antipsychotic with serotonin-S2 and dopamine-D2 antagonistic properties. *J Pharmacol Exp Ther*. 1988;244(2):685-693. [CrossRef]
16. Persico AM, Ricciardello A, Lamberti M, et al. The pediatric psychopharmacology of autism spectrum disorder: a systematic review - Part I: The past and the present. *Prog Neuropsychopharmacol Biol Psychiatry*. 2021;110:110326. [CrossRef]
17. Taurines R, Fekete S, Preuss-Wiedenhoff A, et al. Therapeutic drug monitoring in children and adolescents with schizophrenia and other psychotic disorders using risperidone. *J Neural Transm (Vienna)*. 2022;129(5-6):689-701. [CrossRef]
18. Malone RP, Waheed A. The role of antipsychotics in the management of behavioural symptoms in children and adolescents with autism. *Drugs*. 2009;69(5):535-548. [CrossRef]
19. Aman MG, Singh NN, Stewart AW, Field CJ. The aberrant behavior checklist: a behavior rating scale for the assessment of treatment effects. *Am J Ment Defic*. 1985;89(5):485-491.
20. Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *J Child Adolesc Psychopharmacol*. 2006;16(5):575-587. [CrossRef]
21. Kent JM, Kushner S, Ning X, et al. Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *J Autism Dev Disord*. 2013;43(8):1773-1783. [CrossRef]
22. Aman M, Rettiganti M, Nagaraja HN, et al. Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2015;25(6):482-493. [CrossRef]
23. Ramerman L, de Kuijper G, Scheers T, Vink M, Vrijmoeth P, Hoekstra PJ. Is risperidone effective in reducing challenging behaviours in individuals with intellectual disabilities after 1 year or longer use? A placebo-controlled, randomised, double-blind discontinuation study. *J Intellect Disabil Res*. 2019;63(5):418-428. [CrossRef]
24. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006;21(6):450-455. [CrossRef]
25. McCracken JT, McGough J, Shah B, et al. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002;347(5):314-321. [CrossRef]
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. [CrossRef]
27. Fieiras C, Chen MH, Escobar Liquitay CM, et al. Risperidone and aripiprazole for autism spectrum disorder in children: an overview of systematic reviews. *BMJ Evid Based Med*. 2023;28(1):7-14. [CrossRef]
28. Hutchinson J, Folawemi O, Bittla P, et al. The effects of risperidone on cognition in people with autism spectrum disorder: a systematic review. *Cureus*. 2023;15(9):e45524. [CrossRef]
29. Shilbayeh SAR, Adeen IS, Alhazmi AS, et al. The polymorphisms of candidate pharmacokinetic and pharmacodynamic genes and their pharmacogenetic impacts on the effectiveness of risperidone maintenance therapy among Saudi children with autism. *Eur J Clin Pharmacol*. 2024;80(6):869-890. [CrossRef]
30. Sepúlveda-Lizcano L, Arenas-Villamizar VV, Jaimes-Duarte EB, et al. Metabolic adverse effects of psychotropic drug therapy: a systematic review. *Eur J Investig Health Psychol Educ*. 2023;13(8):1505-1520. [CrossRef]
31. Krøigaard SM, Clemmensen L, Tarp S, Pagsberg AK. A meta-analysis of antipsychotic-induced hypo- and hyperprolactinemia in children and adolescents. *J Child Adolesc Psychopharmacol*. 2022;32(7):374-389. [CrossRef]
32. Mano-Sousa BJ, Pedrosa AM, Alves BC, et al. Effects of risperidone in autistic children and young adults: a systematic review and meta-analysis. *Curr Neuropharmacol*. 2021;19(4):538-552. [CrossRef]
33. Maneeton N, Maneeton B, Putthisri S, Woottiluk P, Narkpongphun A, Srisurapanont M. Risperidone for children and adolescents with autism spectrum disorder: a systematic review. *Neuropsychiatr Dis Treat*. 2018;14:1811-1820. [CrossRef]
34. Tural Hesapcioglu S, Ceylan MF, Kandemir G, Kasak M, Sen CP, Correll CU. Frequency and correlates of acute dystonic reactions after antipsychotic initiation in 441 children and adolescents. *J Child Adolesc Psychopharmacol*. 2020;30(6):366-375. [CrossRef]
35. da Silva JF, Honorato MM, Cremaschi RMC, Coelho FMS. Efficacy and tolerance profile of risperidone use in people with autism spectrum disorder in a clinic in Santarém, Pará, Brazil. A retrospective study. *J Neurosci Rural Pract*. 2023;14(2):308-312. [CrossRef]
36. Kloosterboer SM, de Winter BCM, Reichart CG, et al. Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *Br J Clin Pharmacol*. 2021;87(3):1069-1081. [CrossRef]
37. Hermans RA, Storm AEM, Kloosterboer SM, et al. Therapeutic drug monitoring to optimize risperidone treatment in children with autism spectrum disorder. *Ther Drug Monit*. 2024;46(2):259-264. [CrossRef]
38. Khonsari NM, Badrfam R, Mohammdi MR, et al. Effect of aerobic exercise as adjunct therapy on the improvement of negative symptoms and cognitive impairment in patients with schizophrenia: a randomized, case-control clinical trial. *J Psychosoc Nurs Ment Health Serv*. 2022;60(5):38-43. [CrossRef]
39. Tse ACY. Brief report: impact of a physical exercise intervention on emotion regulation and behavioral functioning in children with autism spectrum disorder. *J Autism Dev Disord*. 2020;50(11):4191-4198. [CrossRef]

40. Villarreal-Martínez L, González-Martínez G, Sáenz-Flores M, et al. Stem cell therapy in the treatment of patients with autism spectrum disorder: a systematic review and meta-analysis. *Stem Cell Rev Rep*. 2022;18(1):155-164. [CrossRef]

41. Sun JM, Kurtzberg J. Stem cell therapies in cerebral palsy and autism spectrum disorder. *Dev Med Child Neurol*. 2021;63(5):503-510. [CrossRef]

42. Saurman V, Margolis KG, Luna RA. Autism spectrum disorder as a brain-gut-microbiome axis disorder. *Dig Dis Sci*. 2020;65(3):818-828. [CrossRef]

43. Settanni CR, Bibbò S, Ianiro G, et al. Gastrointestinal involvement of autism spectrum disorder: focus on gut microbiota. *Expert Rev Gastroenterol Hepatol*. 2021;15(6):599-622. [CrossRef]

44. Taniya MA, Chung HJ, Al Mamun A, et al. Role of gut microbiome in autism spectrum disorder and its therapeutic regulation. *Front Cell Infect Microbiol*. 2022;12:915701. [CrossRef]

45. Willsey HR, Willsey AJ, Wang B, State MW. Genomics, convergent neuroscience and progress in understanding autism spectrum disorder. *Nat Rev Neurosci*. 2022;23(6):323-341. [CrossRef]