

Variation in Response to Pharmacological Intervention with Risperidone and the Role of Adjuvant Medications in the Treatment of Autism Spectrum Disorders: A Systematic Review and Meta-analysis

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Abstract

Non-genetic traits as predictors of variation in response to pharmacological interventions in ASD need to be identified for better management. This review aims to identify these non-genetic traits and the role of adjuvant medications in ASD. An electronic database search in PUBMED and Cochrane library was conducted using MeSH search terms “Autism” and “Risperidone.” Randomized or cross-over trials comparing the efficacy of ‘risperidone plus placebo’ vs. ‘risperidone plus adjuvant medications’ using Aberrant Behavior Checklist- Community Version (ABC-CV) scores in ASD patients of any age group were included in the analysis. The quantity of reduced irritability (ABC-I) sub-score was the primary outcome measure analyzed. The reduction in remaining ABC-CV sub-scores at the end of 10 weeks was the secondary outcome measure analyzed. All the outcome measures were estimated by calculating the Mean Difference (MD) values and their 95% Confidence Intervals (CI) by both fixed and random effect models using Revman 5.4.1 software. A total of 13 trials were found to be eligible and included in the quantitative synthesis of efficacy. A small but significant decrease in the ABC irritability sub-score was evident in the ‘risperidone plus adjuvants’ group (MD: -3.19, 95% CI:-3.82, -2.56, N=658). The meta-analysis results attributed the highest decrease in ABC-irritability sub-score to adjuvant topiramate. There is a possibility of bias and minimal impact of adjuvants in alleviating irritability symptoms of ASD. Baseline severity of irritability symptoms and the dose/medication regimen appear to be possible non-genetic traits responsible for variation in response to pharmacological intervention.

Keywords: Autism, Autism spectrum disorder, Risperidone, Adjuvant

Introduction

Autism spectrum disorders (ASD) consist of a spectrum of neurological and developmental disorders, which includes autistic disorder, Asperger's syndrome, pervasive developmental disorder-not otherwise specified (PDD-NOS), Rett's disorder, and disintegrative disorder. As per DSM-V criteria, it is diagnosed primarily by the presence of impaired social interaction, social communication, and stereotypical behaviors.¹⁻³

There has been a steady increase in the incidence of ASD, perhaps owing to increased screening and changing diagnostic criteria.¹⁻³ The etiology of ASD is still unknown, with multiple genetic, epigenetic, and environmental factors being major contributors.^{1,2} Involvement of hundreds of genes and numerous genetic deficits in patients with ASD supports a strong genetic basis for its etiopathogenesis.¹ The fact that it is more common in twins and men, that its clinical manifestations vary, and that it coexists with other genetic disorders further strengthens the genetic basis of its etiopathogenesis.

The core strategy of ASD management includes early diagnosis and intervention, either non-pharmacological or pharmacological. Among non-pharmacological interventions, behavioral therapy is considered the treatment of choice.^{3,4} Expensiveness and the need for extensive time and resources discourage the adoption of behavioral therapy as a universal treatment strategy.³⁻⁵ pharmacological agents, risperidone and aripiprazole, are the only drugs approved by the FDA to treat irritability and disruptive symptoms of ASD. Both are equally efficacious and have their own advantages and drawbacks concerning their spectrum of adverse drug reactions (ADRs), which guide the selection between them.^{2,4,6} Selective efficacy only on disruptive symptoms, minimal efficacy on core symptoms of ASD, and a high

incidence of ADRs are the major drawbacks of pharmacological interventions.³⁻⁵

With increased knowledge about ASD, its heterogeneity in etiopathogenesis, and clinical manifestation, the coincidence of other co-morbidities has been understood to a greater extent. These features have become the hallmark of ASD.^{2,3} Inter-individual variations in response and thus, inconsistency in the efficacy of non-pharmacological and pharmacological interventions has been attributed to this heterogeneity in ASD.³⁻⁵ Perhaps the same is the major challenge in generalizing the treatment efficacy of pharmacological and non-pharmacological interventions used for ASD.^{2,3} Hence, there is a need to select and individualize the type of intervention based on the genetic and phenotypic traits of the patients.⁴

This approach must be adopted to get maximum benefits from non-pharmacological and pharmaceutical interventions.⁴ As an essential strategy to enhance the efficacy of risperidone, various adjuvant medications were added to risperidone and have been found to alleviate irritability symptoms further.⁷⁻²⁸ However, an expected wide variation in efficacy in 'risperidone alone' treated groups is also quite evident in these trials. Since not only genetic factors influence the response to pharmacological interventions, other non-genetic traits which are predictors of response to pharmacological interventions need to be identified and understood. This may help in the selective treatment of patients who may benefit.

Hence, the present systematic review was conducted to determine the non-genetic traits responsible for variation in response to pharmacological intervention with risperidone as the reference drug. The meta-analysis was conducted with the aim to quantify benefits

of adjuvants with risperidone and identify which adjuvant is better for each sub-score of the ABC-CV scale.

Methods

Inclusion and Exclusion Criteria

Randomized or cross-over trials comparing the efficacy of ‘risperidone plus placebo’ vs. ‘risperidone plus adjuvant medications’ using Aberrant Behavior Checklist-Community Version (ABC-CV) scores in ASD patients of any age group were included in the analysis. Diagnosis of having autism or ASD using either DSM IV/IV-TR/V criteria was considered for eligibility. There were no restrictions on patient age, risperidone dose, phase, or sample size used in the trials. No restrictions on language or year of publication were imposed. Trials publishing incomplete data required for statistical analysis or those published as abstracts were considered for exclusion.

Information Source and Literature Search

Electronic database searches in PUBMED and Cochrane library were conducted using MeSH search terms “Autism” and “Risperidone.” Limits applied for the examination in PUBMED were “randomized controlled trial” and “humans,” while the limit applied in the Cochrane library search was “in trials.” The search was restricted to articles published or available online until October 20th, 2020, with no language restrictions. A manual search of relevant articles was also conducted to identify any missed trials by reviewing their references. Two authors independently conducted electronic database searches and manual searches.

Study Selection and data collection Process

Two authors were independently involved in this process. Article selection and collection of all required data were made in a standard procedure and on a previously designed data extraction sheet. The screening process for

eligible articles were conducted by going through the titles and abstracts of all articles retrieved from the literature search. Potential articles selected by this method were then screened in their full-text form for the availability of required data on population, intervention, comparator, and outcome (PICO) along with trial design and other parameters to assess their eligibility for inclusion as per preset eligibility criteria.

Trials meeting all eligibility criteria were selected. Data on baseline demographic and clinical data, study characteristic data, intervention data, and data required for the estimation of outcome measures were collected by both authors individually. To compare the efficacy, the authors collected data on mean reductions in all ABC-CV sub-scores (irritability, hyperactivity, lethargy, stereotypical behavior, and inappropriate speech). The authors did not seek the data from unpublished trials. Those trials which did not report mean change in ABC-CV sub-scores along with standard deviation (SD) values were excluded from quantitative analysis. However, we used a mathematical formula to calculate SD values from baseline and final mean values and used them in qualitative research.

The following formula was used to calculate the mean change SD value: square root of $(\text{baseline-SD}^2 + \text{final-SD}^2 + 2 \times 0.6 \times \text{baseline-SD} \times \text{final-SD})$.²⁹ Differences in opinions between the authors on the trial selection and data extraction/calculation were resolved after achieving consensus, and the final data extraction sheet was prepared.

Risk of Bias Assessment

Assessment of the risk of bias within the individual trials was independently done by two authors using the Cochrane Collaboration tool.³⁰ Discrepancies in allocating the level of bias in individual trials were resolved after the

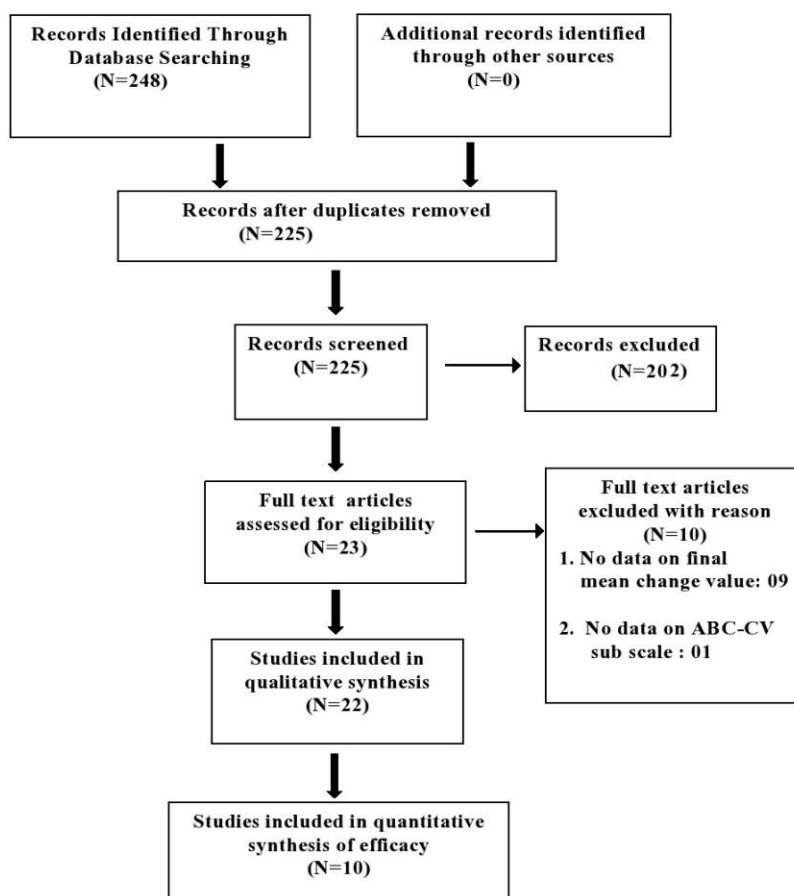


Figure 1. Literature Search Results and Study Attrition Diagram

authors reached a consensus. Publication bias was analyzed by the funnel plot method.

Summary Measurement

Quantity of change in irritability (ABC-I) sub-score was the primary outcome measure analyzed. The changes in the remaining ABC-CV scores at the end of 10 weeks were the secondary outcome measures analyzed.

Subgroup Analysis

Subgroup analysis excluding trials with significant variation in baseline demographic or clinical features was planned. Comprehensive analysis, including the excluded trials that did not publish SD of the mean change values of ABC sub-scores, was done for qualitative

synthesis and to analyze preferred adjuvant added to risperidone.

Synthesis of Results and Statistical Analysis

All the outcome measures were estimated by calculating the Mean Difference (MD) values and their 95% Confidence Intervals (CI) by both fixed and random effect models using Revman 5.4.1 software. The sensitivity of the results was analyzed by assessing the results of the subgroup analyses and also by comparing the results of the fixed effect model and random effects model. Heterogeneity between the studies was analyzed using the Cochrane Q test for heterogeneity and I^2 test. A chi-square test with a P value <0.10 and an I^2 test of $>50\%$ was considered an indicator of significant heterogeneity.

Table 1. Baseline Demographic Features of Included Patients and Risk of Bias Analysis (1)

Groups (No. of patients)	Age (Yrs)	Male (%)	Weight (kg)	Risk of Bias Assessment of Trials				
				RSG	AC	BPP	BOA	IOD
Risperidone + placebo (24)	6.69 ±2.02	75	28.79 ±10.20	LR	LR	LR	UR	LR
Risperidone + Propentofylline (24)	7.45 ±2.24	75	26.20 ±07.86	LR	LR	LR	UR	LR
Risperidone + placebo (33)	7.61 ±2.33	85	26.79 ±9.60	LR	LR	LR	UR	LR
Risperidone + Simvastatin (33)	7.06 ±2.33	76	24.79 ±10.18	LR	LR	LR	UR	LR
Risperidone + placebo (20)	7.10 ±2.02	85	27.30 ±13.9	LR	LR	LR	LR	LR
Risperidone + Amantadine (20)	6.40 ±2.02	80	23.30 ±09.6	LR	LR	LR	UR	LR
Risperidone + placebo (31)	7.42 ±2.02	81	26.00 ±8.24	LR	UR	UR	UR	LR
Risperidone + PEA (31)	6.84 ±2.10	71	23.71 ±9.0	LR	LR	LR	LR	LR
Risperidone + placebo (20)	6.20 ±1.32	85	25.90 ±13.53	LR	UR	UR	UR	LR
Risperidone + Pioglitazone (20)	6.95 ±2.40	75	24.45 ±08.61	LR	LR	LR	LR	LR

RSG: Random Sequence Generation, AC: Allocation Concealment, BPP: Blinding of Participants and Personnel, BOA: Blinding of Outcome Assessment, IOD: Incomplete Outcome Data, SR: Selective Reporting, UR: Unclear Risk, HR: High Risk, LR: Low Risk, N/A: Not Available, PEA: Palmitoylethanolamide, NAC: N-Acetyl Cysteine, Values are in mean± SD

Table 1. Baseline Demographic Features of Included Patients and Risk of Bias Analysis (2)

Groups (No. of patients)	Age (Yrs)	Male (%)	Weight (kg)	Risk of Bias Assessment of Trials				
				RSG	AC	BPP	BOA	IOD
Risperidone + placebo (31)	8.1 ±1.9	81	25.10 ±07.7	LR	LR	LR	LR	LR
Risperidone +Resveratrol (31)	7.8 ±2.1	81	25.70 ±7.80	LR	LR	LR	LR	LR
Risperidone + placebo (21)	7.90 ±1.89	86	NA	LR	LR	LR	LR	LR
Risperidone + l-carnosinel (21)	8.24 ±2.22	81	NA	LR	LR	LR	LR	LR
Risperidone + placebo (20)	7.60 ±2.60	85	28.00 ±11.04	LR	LR	LR	LR	LR
Risperidone + NAC- 1 (20)	7.50 ±2.63	80	26.45 ±10.21	LR	LR	LR	LR	LR
Risperidone + placebo (29)	7.9 ±2	79	25.59 ±8.6	LR	LR	LR	UR	LR
Risperidone + Baclofen (29)	8.04 ±2.33	79	24.93 ±6.40	LR	LR	LR	LR	LR
Risperidone + placebo (23)	7.78 ±2.59	78	28.65 ±11.2	LR	LR	LR	LR	LR
Risperidone + Minocycline (23)	7.39 ±2.48	74	25.70 ±9.78	LR	LR	LR	LR	LR

RSG: Random Sequence Generation, AC: Allocation Concealment, BPP: Blinding of Participants and Personnel, BOA: Blinding of Outcome Assessment, IOD: Incomplete Outcome Data, SR: Selective Reporting, UR: Unclear Risk, HR: High Risk, LR: Low Risk, N/A: Not Available, PEA: Palmitoylethanolamide, NAC: N-Acetyl Cysteine, Values are in mean± SD

Table 1. Baseline Demographic Features of Included Patients and Risk of Bias Analysis (3)

Groups (No. of Patients)	Age (Yrs)	Male (%)	Weight (kg)	Risk of Bias Assessment of Trials				
				RSG	AC	BPP	BOA	IOD
Risperidone + placebo (30)	7.67 ±2.35	70	26.13 ±8.13	LR	LR	LR	LR	LR
Risperidone + Sulforaphane (30)	6.87 ±2.06	63	23.40 ±8.45	LR	LR	LR	LR	LR
Risperidone + placebo (20)	7.5 ±1.5	65	24.30 ±9.30	LR	LR	LR	LR	LR
Risperidone + Celecoxib (20)	7.6 ±1.7	60	24.70 ±9.20	LR	LR	LR	LR	LR
Risperidone + placebo (27)	7.52 ±1.84	70	32.89 ±9.50	LR	LR	LR	LR	LR
Risperidone + folic acid (28)	8.36 ±1.81	57	36.71 ±9.08	LR	LR	LR	LR	LR

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Results and Discussion

Literature Search Results and Trials Selected

A total of 13 trials were found to be eligible and included in the quantitative synthesis of efficacy.⁷⁻¹⁹ Nine trials did not publish standard deviation (SD) values of the mean change values in ABC-CV sub-scores.²⁰⁻²⁸ We calculated their SD values and included them in qualitative synthesis to analyze which adjuvant is better for each ABC-CV sub-score. The data search results and the attrition diagram with the number of articles excluded and the reasons for their exclusion is shown in Figure 1.

Characteristics of Included Trials

The baseline demographic and clinical features of patients included in the analysis, along with the risk of bias assessment of included trials and treatment regimens of adjuvant medications are shown in Tables 1 and 2. There was no significant difference between the trials and patients included in the analysis. Risperidone dose and regimen were identical to FDA-approved guidelines for patients with irritability symptoms.³¹ Except for minor variations in the celecoxib trial, the risperidone dosage regimen followed in all trials was similar.¹⁷

Risperidone was started at a dose of 0.5 mg and increased to 0.5 mg per week for the first three weeks till a maximum amount of 1 mg/day for patients below 20 kg and 2 mg/day for patients > 20 kg was reached.

The only variation in the celecoxib trial was the weekly increment dose, which was 3 mg/day but only for children weighing over 40 kg. All the trials originated from a single country (Iran) and were randomized, double-blind, placebo-controlled parallel group studies with a follow-up period of 10 weeks duration. All trials included patients with autistic disorder only, and no patients with other diseases in the spectrum of ASD were included. In addition, patients with other co-morbidities were excluded. All trials included patients with a baseline ABC-irritability sub-score of 12, and the same was the primary outcome measure analyzed.

There were minor variations between the trials regarding demographic features. The age range of patients included was between 6 and 8 years of age. Except in three trials (celecoxib, sulforaphane, and folinic acid), all trials included > 75% of male patients. Except for the folinic acid trial, including slightly heavier patients, all the trials had patients with a mean body weight of between 25–30 kg.

The Forest plot in Figure 2 shows the efficacy of “adjuvants plus risperidone” vs. “risperidone plus placebo” on the ABC-irritability sub-score. Table 3 shows the results of secondary outcome measures, subgroup analysis, and analysis used for qualitative synthesis. A small but significant decrease in the ABC irritability sub-score was evident in the ‘risperidone plus adjuvants’ group (MD: -3.19, 95% CI: -3.82, -2.56, N=658).

Two subgroup analyses, one excluding three trials (celecoxib, sulforaphane and folinic

acid) with 75% male patients and the second excluding the folinic acid trial, which included relatively heavier body weight patients, were conducted. Excluding three trials that had 75% male patients didn’t alter the results of the primary outcome measure (MD-3.27, 95% CI: -4.07, -2.48). Excluding a trial which included relatively heavier patients also didn’t change the result of the irritability sub-score (MD-3.27, 95% CI: -3.94, -2.61).

Other Secondary Outcome Measures

There was evidence of an equal and significant decrease in the hyperactivity sub-score (MD-3.48, 95% CI: -4.36, -2.61) as that of the irritability sub-score. However, there was evidence of publication bias in this efficacy measure analyzed. The amount of decrease in stereotypical behaviour sub-score (MD-0.77, 95% CI: -1.29, -0.25) and inappropriate speech sub-score (MD-0.42, 95% CI: -0.63, -0.21) was minimal but significant. The quantity of decrease in lethargy (MD-0.74, 95% CI: -1.62, 0.14) sub-score was both minimal, insignificant and biased with publication bias and inter-trial heterogeneity. We ranked the most preferred adjuvant for combination with risperidone based on their statistically significant MD and 95% CI values.

The results of the meta-analysis revealed that the highest decrease in ABC-irritability, ABC-hyperactivity, and ABC-stereotypical behavior sub-scores was attributed to adjuvant topiramate. While the ABC- lethargy and ABC-inappropriate speech sub-scores, it was attributed to the adjuvant’s prednisolone and pentoxifylline, respectively. The top three rankings in decreasing order of preference for the irritability sub-score are Topiramate (MD-7.55, 95% CI: -11.55, -3.45), Pentoxifylline (MD-5.12, 95% CI: -8.1, -2.14), and Memantine (MD-4.45, 95% CI: -7.38, -1.52).

Table 2. Baseline Clinical Features of Included Patients and Treatment Regimen (1)

Groups	Baseline scores					Treatment regimen of adjuvant medications
	ABC-I	ABC-L	ABC-S	ABC-H	ABC-IS	
Risperidone + placebo	26.29 ±4.70	12.83 ±7.64	10.7 ±4.03	27.29 ±4.00	4.16 ±4.08	Propentofylline: 300 mg/d, increased to 600 mg/d after week 2, or 900 mg/d if body weight >45kg.
Risperidone + Propentofylline	25.79 ±5.39	12.79 ±6.61	11.0 ±5.62	27.87 ±7.99	4.37 ±4.79	
Risperidone + placebo	19.97 ±7.24	19.79 ±8.01	11.21 ±5.49	25.73 ±8.82	4.9 ±3.45	Simvastatin: 20 mg/d for children <10 years of age and 40 mg/d for those ≥10 years of age.
Risperidone + Simvastatin	20.97 ±5.37	20.48 ±6.00	11.67 ±4.14	27.39 ±6.11	5.64 ±2.77	
Risperidone + placebo	20.90 ±6.61	18.15 ±4.80	11.30 ±5.42	28.55 ±8.67	4.55 ±3.48	Amantadine: For patients less than 30 kg, 100 mg/d, and for the rest 150 mg/d twice daily.
Risperidone + Amantadine	20.00 ±5.30	18.55 ±7.13	10.90 ±4.03	28.15 ±6.88	5.70 ±3.1	
Risperidone + placebo	20.97 ±6.80	19.84 ±8.20	11.16 ±5.50	25.87 ±8.98	5.19 ±3.46	PEA: 600 mg twice daily
Risperidone + PEA	21.97 ±5.06	20.71 ±6.18	12.00 ±4.10	27.97 ±5.70	5.81 ±2.93	
Risperidone + placebo	19.00 ±5.70	13.66 ±7.26	9.40 ±5.28	27.86 ±9.85	4.70 ±3.78	Pioglitazone: 15 mg BD
Risperidone + Pioglitazone	18.25 ±3.8	15.05 ±7.56	7.70 ±4.61	25.00 ±10.05	5.70 ±3.60	

ABC-I (Irritability), ABC-L (Lethargy), ABC-S (Stereotypic behaviour), ABC-H (Hyperactivity), ABC-IS (Inappropriate Speech), PEA: Palmitoylethanolamide, NAC: N-Acetyl Cysteine, Values are in mean ± SD

Table 2. Baseline Clinical Features of Included Patients and Treatment Regimen (2)

Groups	Baseline Scores					Treatment regimen of adjuvant medications
	ABC-I	ABC-L	ABC-S	ABC-H	ABC-IS	
Risperidone + placebo	22.80 ±7.7	20.20 ±5.5	8.80 ±10.5	30.20 ±3.3	6.8 ±8.3	Resveratrol: 250 mg BD
Risperidone + Resveratrol	22.20 ±8.80	9.70 ±5.70	8.90 ±4.30	30.60 ±6.90	6.5 ±3.6	
Risperidone + placebo	22.71 ±10.16	18.95 ±7.64	8.52 ±5.97	31.52 ±11.28	6.95 ±3.34	l-carnosine: 400 mg BD
Risperidone + l-carnosinel	22.09 ±9.54	18.29 ±6.00	8.62 ±5.64	31.38 ±6.89	7.09 ±3.81	
Risperidone + placebo	19.70 ±7.61	20.65 ±9.62	10.05 ±5.36	25.10 ±9.44	4.75 ±3.72	NAC: 200 mg thrice daily for children weighing <20 kg and 300 mg thrice daily for >20 kg body weight.
Risperidone + NAC	21.20 ±5.17	21.10 ±6.34	10.55 ±4.22	27.65 ±6.16	5.70 ±2.92	
Risperidone + placebo	22.62 ±9.24	20.97 ±8.87	9.0 ±5.39	29.9 ±11.2	6.83 ±3.32	Baclofen: 0.6 mg/Kg three times a day.
Risperidone + Baclofen	22.76 ±8.56	20.28 ±7.64	8.79 ±4.8	30.41 ±6.94	6.35 ±3.71	
Risperidone + placebo	19.91 ±7.20	20.30 ±9.12	11.09 ±5.77	25.04 ±9.04	5.04 ±3.56	Minocycline: 50 mg twice a day
Risperidone + Minocycline	21.26 ±4.82	21.39 ±6.05	10.96 ±4.09	28.22 ±5.97	6.17 ±3.01	
Risperidone + placebo	21.3 ±6.13	19.97 ±8.25	11.4 ±5.34	26.67 ±8.22	5.37 ±3.19	Sulforaphane: 50 and 100 µmol/day for patients with a body weight of <45kg and 45-90kg respectively.
Risperidone + Sulforaphane	22.5 ±4.89	20.90 ±6.10	12.1 ±4.26	28.47 ±5.24	6.07 ±2.69	

ABC-I (Irritability), ABC-L(Lethargy), ABC-S(Stereotypic behaviour), A
BC-H(Hyperactivity), ABC-IS(Inappropriate Speech), PEA: Palmitoylethanolamide,
NAC: N-Acetyl Cysteine, Values are in mean± SD

Table 2. Baseline Clinical Features of Included Patients and Treatment Regimen (3)

Groups	Baseline Scores					Treatment regimen of adjuvant medications
	ABC-I	ABC-L	ABC-S	ABC-H	ABC-IS	
Risperidone + placebo	17.60 ±2.40	17.10 ±3.20	9.20 ±2.30	22.60 ±3.00	5.50 ±0.9	Celecoxib: 100 mg/day for first week in all patients, then 200 mg/day for <30 kg and 300 mg/day for >30 kg.
Risperidone + Celecoxib	17.30 ±1.60	17.00 ±3.00	9.10 ±2.20	22.00 ±2.90	5.40 ±1.40	
Risperidone + placebo	22.67 ±6.34	20.37 ±8.57	11.30 ±5.45	26.37 ±8.26	6.41 ±2.23	Folinic acid: 2 mg/kg up to 50 mg per day.
Risperidone + folinic acid	22.82 ±4.89	20.57 ±6.08	12.32 ±4.02	28.25 ±5.03	6.5 ±1.69	

ABC-I (Irritability), ABC-L (Lethargy), ABC-S (Stereotypic behaviour), ABC-H (Hyperactivity), ABC-IS (Inappropriate Speech), PEA: Palmitoylethanolamide, NAC: N-Acetyl Cysteine, Values are in mean ± SD

Similarly, for ABC-hyperactivity it is: Topiramate (MD-14.32, 95% CI:-21.75,-6.89), Memantine (MD-6.15, 95% CI:-11.4,-0.9), l-carnosine (MD-5.05, 95% CI:-9.56,-0.54); for ABC-lethargy: Prednisolone (MD 17.26, 95% CI:-26.2,-8.32), Pentoxifylline (MD-5.8, 95% CI:-9.1,-2.5), Celecoxib (MD-2.7, 95% CI:-3.98,-1.42), and for ABC-inappropriate speech: Pentoxifylline (MD-2.29, 95% CI:-3.19,-1.39), Folinic acid (MD-0.82, 95% CI:-1.48,-0.02).

Quality of the Studies and Publication Bias

Details of risk of bias assessment as per the Cochrane tool are shown in the Table. 2. There was no evidence of publication bias in the primary outcome measure analysed using the funnel plot method. But there was evidence of it in the ABC-hyperactivity sub-score. Evidence of both inter-trial heterogeneity and publication bias was found in the ABC-lethargy sub-score analysis. All the results appeared to be robust since they remained significant even

when estimated by a fixed effect model. In extended analysis after including other trials which did not publish the SD values, there was a similar amount of decrease in the irritability sub-score but with evidence of publication bias (MD-3.39, 95% CI:-3.97, -2.80, N = 1021).

Results of our meta-analysis support adding adjuvant medications to risperidone for treatment of ASD. An expected observation from the analysed results is the variation in quantity of decrease in mean change values of all ABC-CV sub-score. Still, it is difficult to ascertain whether the results of our study are unbiased for one reason: publication bias. The possibility of publication bias is supported by the results of other trials comparing the effects of “adjuvants alone” with placebo.

Data on three trials (one trial on folinic acid and two trials on N-Acetyl cysteine, NAC) comparing the efficacy of two adjuvants vs. placebo were available and used for

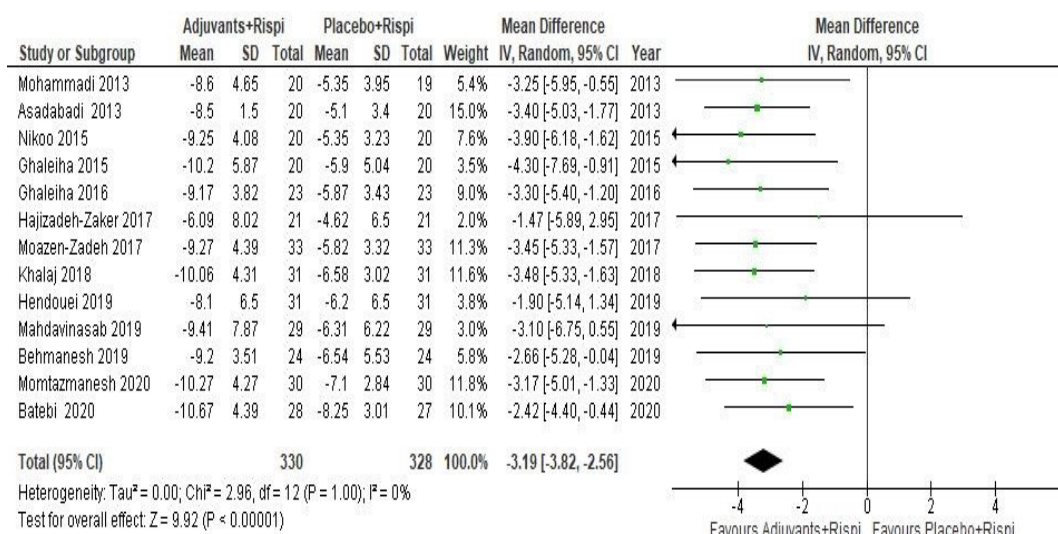


Figure 2. Forest Plot Showing Mean Difference in ABC-Irritability Sub-score

comparison.³²⁻³⁴ We estimated the mean change in irritability sub-score after including these three trials and it was found to be insignificant (MD:-2.84, 95% CI:-8.13, 2.45). For comparison, we estimated the mean change in irritability sub-score of three of our eligible trials of the same adjuvants (one trial on folinic acid and two trials on N-Acetyl cysteine NAC) combined with risperidone.

The result of this analysis was found to be significant (MD:-3.02, 95% CI:-4.49,-1.55). The major differences between these two compared groups which could be responsible for this variation in efficacy are: relatively low baseline ABC-irritability score (around 16), inclusion of patients with other co-morbidities, country of origin being USA, duration of study being 12 weeks, and higher dose of NAC use in trials comparing “adjuvants alone” vs placebo. Among them, the first two factors could be the major factors responsible for the observed differences in the mean change values between the two compared groups.

In three trials comparing “adjuvants alone” to placebo, irrespective of treatment or placebo group, those with high baseline ABC-

irritability scores demonstrated high mean change values at the end of the trial. Hence, higher baseline ABC-irritability scores could be the major reason for insignificant effects seen in “adjuvant alone” vs. placebo trials.

However, influence and evidence of baseline severity as a predictor of response in both the comparator groups was absent in the results of three trials of “adjuvants plus risperidone” vs. “risperidone plus placebo”. In fact, it was not evident in all the 13 trials included in our meta-analysis. In all the trials included in our study, the baseline score of ABC-irritability was > 17 , with a score of around 22 in most of the trials. The impact of this baseline severity value is insignificant since a baseline score of > 30 has a strong impact on mean change values.³⁵

In addition, there was no relationship between a proportionate decrease in quantity of ABC-irritability score and a proportionate baseline severity of ABC-irritability score in all these trials. This makes understanding the reasons for the wide variation in response to pharmacological interventions all the more intriguing. These observations provide insight

Table 3. Summary of Comparative Analysis for Qualitative Synthesis of Systematic Review

Drug/Study	ABC-Irritability	ABC-Lethargy	ABC-Hyperactivity	ABC-Inappropriate Speech	ABC-Stereotypic Behavior
Mean change	-3.19	-0.74 ^{p, h}	-3.48 ^p	-0.42	-0.77
	[-3.82, -2.56]	[-1.62, 0.14]	[-4.36, -2.61]	[-0.63, -0.21]	[-1.29, -0.25]
Mean change	-3.39 ^p	-1.27 ^{p, h}	-3.69 ^{p, h}	-0.52 ^p	-1.13 ^{p, h}
(All studies)	[-3.97, -2.80]	[-2.22, -0.33]	[-4.66, -2.73]	[-0.72, -0.31]	[-1.67, -0.6]
Mean change (Risperidone vs Placebo)	-7.41	-3.11	-8.18	-1.06	-1.50
	[-11.21, -3.61]	[-5.50, -0.72]	[-11.26, -5.1]	[-2.12, 0.00]	[-3.94, 0.94]
Mean change (Adjuvants vs Placebo)	-0.31	0.80	-0.50	0.10	0.60
	[-0.62, 0.00]	[0.50, 1.09]	[-0.83, -0.17]	[-0.00, 0.20]	[0.44, 0.75]
Mean change (Adjuvants vs Placebo) *	-4.10	-1.11	-3.36	-1.27	-2.30
	[-9.85, 1.64]	[-7.24, 5.02]	[-11.62, 4.91]	[-3.87, 1.33]	[-6.23, 1.64]
Mean change (Adju.+Risp. vs Risp.)	-3.03 ^p	-0.70	-4.22	-0.55	-0.93
	[-4.40, -1.67]	[-2.09, 0.69]	[-6.01, -2.43]	[-1.02, -0.09]	[-1.90, 0.04]
Mean change (Adju. +Risp. vs Risp.) **	-3.02	-1.06	-4.17	-0.80	-1.55
	[-4.49, -1.55]	[-2.75, 0.63]	[-6.14, -2.19]	[-1.37, -0.23]	[-2.66, -0.45]

into the probable lack of significant effects of adjuvants as such, and actual effects may perhaps be attributed to risperidone added to them.

This opinion of ours is further supported by comparing the actual effects of risperidone alone. The quantity of decrease in irritability sub-score in control groups of our 13 included trials treated with ‘risperidone plus placebo’ ranged from -4.62 to -8.25 (mean: -6.07). This relatively lesser and disproportionate variation in response to risperidone was observed despite the inclusion of patients from a single country of origin, identical baseline ABC-irritability score, and treatment with an identical risperidone dose and regimen.

We compared the efficacy of the ‘risperidone plus placebo’ group from 13 trials included in our meta-analysis with that of the three trials comparing ‘risperidone alone’ with placebo.³⁶⁻³⁸ These three trials conducted in North American countries (USA and Canada) reported a mean change in irritability score which ranged from -12.1 to -14.9 (mean: -13.43) in the risperidone group and -3.5 to -7.5 (mean: 5.86) in the placebo group.

The mean change in irritability score caused by ‘risperidone alone’ is more than double the ‘risperidone plus placebo.’ The highest quantity of decrease in irritability score (-8.25) was reported in the ‘risperidone plus placebo’ group among all the ‘adjuvants

plus risperidone' trials is less than the lowest quantity of decrease (-12.1) reported by 'risperidone alone' in risperidone vs placebo trials. The minimal effect of 'risperidone alone' itself was not observed in any of the 'adjuvants plus risperidone' groups of 13 trials. This further creates doubt about the possible lack of benefits of adjuvants in ASD or biased reporting of risperidone efficacy.

All the 22 trials included in the qualitative synthesis of our review and 13 of these trials which were eligible for quantitative synthesis were conducted in one single country (Iran). The likelihood of genetic or ethnic variations in the patient population is perhaps minimal for this reason. Aside from the country of origin, the dosage regimen of risperidone used and the follow-up period differ from trials in North American continent countries. Among the three trials, two from North America used a more flexible risperidone dose (maximum dose of 0.06mg/kg/day, adjusted and based on body weight) than those from Iran (maximum dose of 2mg/day, regardless of higher body weight). While the third trial allowed a maximum dose of 2.5 mg/day.

In addition, North American country trials titrated the initial weeks' risperidone dose at a relatively rapid pace (3 days) compared to studies from Iran (7 days). Nevertheless, the maximum dose used in all of the trials was within the FDA recommended maximum dose range (0.5-3mg/day).³¹ The probability of a directly proportional relationship between a high dose regimen of risperidone and a higher response rate is unlikely. The duration of follow-up was 8 weeks in North American trials compared to 10 weeks in trials conducted in Iran. It is unclear whether this difference influenced treatment effects.

The influence of the baseline ABC-irritability score (which was around 20) in these trials

appears to be minimal since these values were identical in all trials. However, the influence of heterogeneity and thus inter-individual variations in response to risperidone cannot be ruled out considering differences in patients' countries of origin.

One opinionated way to minimize heterogeneity and maximize the beneficial effects of interventions in ASD is the individualization of the treatment.⁴ Prior assessment with biomarkers (biochemical and or neurocognitive) and genetic screening may help in the individualization of patients who may benefit from interventions.^{33, 34, 39} Trials assessing the benefits of interventions may need to stratify and select patients based on this strategy to evaluate the actual benefits of both pharmacological and non-pharmacological interventions. An equally significant concept that needs to be addressed while treating cases of ASD is the placebo effect. There is a moderate possibility of a placebo response to both types of interventions used in ASD.^{34,40} Measuring biological measures or biomarkers for response to treatment is a suggested way to nullify bias arising from the placebo effect.⁴⁰

Conclusion

Topiramate appears to be the preferred adjuvant to risperidone to reduce irritability symptoms. However, there is a possibility of bias and minimal impact of adjuvants in alleviating irritability symptoms of ASD. The major strengths of our study are that it helps in enhancing the knowledge and role of various adjuvants in specific symptoms of ASD.

In addition, it highlights that the baseline severity of irritability symptoms and the dose/regimen of medication used appear to be possible non-genetic traits responsible for variation in response to pharmacological intervention. It emphasizes the importance of

analysing the significant influence of placebo effect and co-existing co-morbidities in future studies. Major drawback of our study was the inclusion of trials from one single country, which could negate the generalisation of study results to other ethnic groups.

Moreover, our opinion that adjuvants perhaps lack benefits in relieving irritability symptoms in ASD is based on only two adjuvants and from three trials with a small sample size. This view cannot be extrapolated to other adjuvants as well.

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Conflict of Interest

None declared

References

1. Masini E, Loi E, Vega-Benedetti AF, Carta M, Doneddu G, Fadda R, et al. An overview of the main genetic, epigenetic and environmental factors involved in autism spectrum disorder focusing on synaptic activity. *International journal of molecular sciences*. 2020;21(21):8290.
2. Sharma SR, Gonda X, Tarazi FI. Autism spectrum disorder: classification, diagnosis and therapy. *Pharmacology & therapeutics*. 2018;190:91-104.
3. Masi A, DeMayo MM, Glozier N, Guastella AJ. An overview of autism spectrum disorder, heterogeneity and treatment options. *Neuroscience bulletin*. 2017;33(2):183-193.
4. Eapen V, Crncec R, Walter A. Exploring links between genotypes, phenotypes, and clinical predictors of response to early intensive behavioral intervention in autism spectrum disorder. *Frontiers in Human Neuroscience*. 2013;7:567.
5. Dhanjal DS, Bhardwaj S, Chopra C, Singh R, Patocka J, Plucar B, et al. Millennium Nutrient N, N-Dimethylglycine (DMG) and its Effectiveness in Autism Spectrum Disorders. *Current medicinal chemistry*. 2021 Nov 24.
6. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry & Human Development*. 2014 ;45(2):185-192.
7. Behmanesh H, Moghaddam HS, Mohammadi MR, Akhondzadeh S. Risperidone combination therapy with propentofylline for treatment of irritability in autism spectrum disorders: a randomized, double-blind, placebo-controlled clinical trial. *Clinical neuropharmacology*. 2019 ;42(6):189-196.
8. Moazen-Zadeh E, Shirzad F, Karkhaneh-Yousefi MA, Khezri R, Mohammadi MR, Akhondzadeh S. Simvastatin as an adjunctive therapy to risperidone in treatment of autism: a randomized, double-blind, placebo-controlled clinical trial. *Journal of child and adolescent psychopharmacology*. 2018;28(1):82-89.
9. Mohammadi MR, Yadegari N, Hassanzadeh E, Farokhnia M, Yekehtaz H, Mirshafiee O, et al. Double-blind, placebo-controlled trial of risperidone plus amantadine in children with autism: a 10-week randomized study. *Clinical neuropharmacology*. 2013;36(6):179-184.
10. Khalaj M, Saghazadeh A, Shirazi E, Shalbfan MR, Alavi K, Shooshtari MH, et al. Palmitoylethanolamide as adjunctive therapy for autism: Efficacy and safety results from a randomized controlled trial. *Journal of psychiatric research*. 2018;103:104-111.
11. Ghaleiha A, Rasa SM, Nikoo M, Farokhnia

- M, Mohammadi MR, Akhondzadeh S. A pilot double-blind placebo-controlled trial of pioglitazone as adjunctive treatment to risperidone: Effects on aberrant behavior in children with autism. *Psychiatry research*. 2015;229(1-2):181-187.
12. Hendouei F, Sanjari Moghaddam H, Mohammadi MR, Taslimi N, Rezaei F, Akhondzadeh S. Resveratrol as adjunctive therapy in treatment of irritability in children with autism: A double-blind and placebo controlled randomized trial. *Journal of clinical pharmacy and therapeutics*. 2020;45(2):324-334.
 13. Hajizadeh-Zaker R, Ghajar A, Mesgarpour B, Afarideh M, Mohammadi MR, Akhondzadeh S. l-Carnosine as an adjunctive therapy to risperidone in children with autistic disorder: A randomized, double-blind, placebo-controlled trial. *Journal of child and adolescent psychopharmacology*. 2018;28(1):74-81.
 14. Nikoo M, Radnia H, Farokhnia M, Mohammadi MR, Akhondzadeh S. N-acetylcysteine as an adjunctive therapy to risperidone for treatment of irritability in autism: a randomized, double-blind, placebo-controlled clinical trial of efficacy and safety. *Clinical neuropharmacology*. 2015;38(1):11-17.
 15. Mahdavinassab SM, Saghaizadeh A, Motamed-Gorji N, Vaseghi S, Mohammadi MR, Alichani R, et al. Baclofen as an adjuvant therapy for autism: a randomized, double-blind, placebo-controlled trial. *European child & adolescent psychiatry*. 2019 ;28(12):1619-1628.
 16. Ghaleiha A, Alikhani R, Kazemi MR, Mohammadi MR, Mohammadinejad P, Zeinoddini A, et al. Minocycline as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind placebo-controlled trial. *Journal of child and adolescent psychopharmacology*. 2016;26(9):784-791.
 17. Asadabadi M, Mohammadi MR, Ghanizadeh A, Modabbernia A, Ashrafi M, Hassanzadeh E, et al. Celecoxib as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. *Psychopharmacology*. 2013;225(1):51-59.
 18. Momtazmanesh S, Amirimoghaddam Yazdi Z, Moghaddam HS, Mohammadi MR, Akhondzadeh S. Sulforaphane as an adjunctive treatment for irritability in children with autism spectrum disorder: A randomized, double-blind, placebo-controlled clinical trial. *Psychiatry and clinical neurosciences*. 2020;74(7):398-405.
 19. Batebi N, Moghaddam HS, Hasanzadeh A, Fakour Y, Mohammadi MR, Akhondzadeh S. Folinic acid as adjunctive therapy in treatment of inappropriate speech in children with autism: a double-blind and placebo-controlled randomized trial. *Child Psychiatry & Human Development*. 2021;52(5):928-938.
 20. Malek M, Ashraf-Ganjouei A, Moradi K, Bagheri S, Mohammadi MR, Akhondzadeh S. Prednisolone as adjunctive treatment to risperidone in children with regressive type of autism spectrum disorder: a randomized, placebo-controlled trial. *Clinical Neuropharmacology*. 2020 ;43(2):39-45.
 21. Akhondzadeh S, Fallah J, Mohammadi MR, Imani R, Mohammadi M, Salehi B, et al. Double-blind placebo-controlled trial of pentoxifylline added to risperidone: effects on aberrant behavior in children with autism. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2010;34(1):32-36.
 22. Ayatollahi A, Bagheri S, Ashraf-Ganjouei A, Moradi K, Mohammadi MR,

- Akhondzadeh S. Does Pregnenolone Adjunct to Risperidone Ameliorate Irritable Behavior in Adolescents With Autism Spectrum Disorder: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. *Clinical neuropharmacology*. 2020;43(5):139-145.
23. Ghaleiha A, Asadabadi M, Mohammadi MR, Shahei M, Tabrizi M, Hajiaghah R, et al. Memantine as adjunctive treatment to risperidone in children with autistic disorder: a randomized, double-blind, placebo-controlled trial. *International Journal of Neuropsychopharmacology*. 2013;16(4):783-789.
 24. Rezaei V, Mohammadi MR, Ghanizadeh A, Sahraian A, Tabrizi M, Rezazadeh SA, et al. Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2010;34(7):1269-1272.
 25. Hasanzadeh E, Mohammadi MR, Ghanizadeh A, Rezazadeh SA, Tabrizi M, Rezaei F, et al. A double-blind placebo controlled trial of Ginkgo biloba added to risperidone in patients with autistic disorders. *Child Psychiatry & Human Development*. 2012;43(5):674-682.
 26. Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. *BMC psychiatry*. 2013;13(1):1-7.
 27. Ghaleiha A, Mohammadi E, Mohammadi MR, Farokhnia M, Modabbernia A, Yekehtaz H, et al. Riluzole as an adjunctive therapy to risperidone for the treatment of irritability in children with autistic disorder: a double-blind, placebo-controlled, randomized trial. *Pediatric Drugs*. 2013;15(6):505-514.
 28. Ghaleiha A, Ghyasvand M, Mohammadi MR, Farokhnia M, Yadegari N, Tabrizi M, et al. Galantamine efficacy and tolerability as an augmentative therapy in autistic children: A randomized, double-blind, placebo-controlled trial. *Journal of Psychopharmacology*. 2014;28(7):677-685.
 29. Fallah MS, Shaikh MR, Neupane B, Rusiecki D, Bennett TA, Beyene J. Atypical antipsychotics for irritability in pediatric autism: a systematic review and network meta-analysis. *Journal of child and adolescent psychopharmacology*. 2019;29(3):168-180.
 30. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343.
 31. Guzman F. *FDA approval of risperidone and dose regimen in autism*. Psychopharmacology institute. Available at: <https://psychopharmacologyinstitute.com/publication/risperidone-indications-fda-approved-and-off-label-uses-2124> [Accessed on Jan 2022].
 32. Frye RE, Slattery J, Delhey L, Furgerson B, Strickland T, Tippet M, et al. Folinic acid improves verbal communication in children with autism and language impairment: a randomized double-blind placebo-controlled trial. *Molecular psychiatry*. 2018;23(2):247-256.
 33. Hardan AY, Fung LK, Libove RA, Obukhanych TV, Nair S, Herzenberg LA, et al. A randomized controlled pilot trial of oral N-acetylcysteine in children with autism. *Biological psychiatry*. 2012 ;71(11):956-961.
 34. Wink LK, Adams R, Wang Z, Klaunig JE, Plawewski MH, Posey DJ, et al. A randomized placebo-controlled pilot study of N-acetylcysteine in youth with autism spectrum disorder. *Molecular Autism*. 2016 ;7(1):1-9.
 35. Levine SZ, Kodesh A, Goldberg Y,

- Reichenberg A, Furukawa TA, Kolevzon A, et al. Initial severity and efficacy of risperidone in autism: Results from the RUPP trial. *European Psychiatry*. 2016;32:16-20.
36. McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, et al. Risperidone in children with autism and serious behavioral problems. *New England journal of medicine*. 2002;347(5):314-21.
37. Pandina GJ, Bossie CA, Youssef E, Zhu Y, Dunbar F. 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
38. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004 ;114(5):e634-641
39. Nayar K, Gordon PC, Martin GE, Hogan AL, La Valle C, McKinney W, Lee M, Norton ES, Losh M. Links between looking and speaking in autism and first-degree relatives: insights into the expression of genetic liability to autism. *Molecular autism*. 2018; 9(1):1-5.
40. Masi A, Lampit A, Glozier N, Hickie IB, Guastella AJ. Predictors of placebo response in pharmacological and dietary supplement treatment trials in pediatric autism spectrum disorder: a meta-analysis. *Translational psychiatry*. 2015;5(9):e640-e64.