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ORIGINAL CONTRIBUTION

Baclofen as an adjuvant therapy for autism: a randomized, double-blind, placebo-controlled trial

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Abstract

Increasing evidence suggests that the function of the GABAergic system is abnormally low in autism spectrum disorder (ASD). Baclofen, which functions as a selective agonist for $GABA_B$ receptors, does appear promising for the treatment of ASD. We conducted a 10-week randomized-controlled study aimed at evaluating the potential of baclofen as an adjuvant therapy to enhance the effect of risperidone in children with ASD. Sixty-four children (3–12 years) with moderate-to-severe irritability symptoms of ASD were included. We used the Aberrant Behavior Checklist-Community Edition (ABC-C) for the outcome measures on each of the follow-up visits (weeks 0, 5, and 10). Analysis of the combined data revealed significant improvement for all the ABC subscales (irritability: $F=51.644$, $df=1.66$, $p<0.001$, lethargy: $F=39.734$, $df=1.38$, $p<0.001$, stereotypic behavior: $F=25.495$, $df=1.56$, $p<0.001$, hyperactivity: $F=54.135$, $df=1.35$, $p<0.001$, and inappropriate speech: $F=19.277$, $df=1.47$, $p=0.004$). Combined treatment with baclofen and risperidone exerted a greater effect on improvement of hyperactivity symptoms at both midpoint [Cohen's d, 95% confidence interval (CI) = −3.14, −5.56 to −0.72] and endpoint (d, 95% CI = −4.45, −8.74 to −0.16) when compared with treatment with placebo plus risperidone. The two treatments achieved comparable results for other outcome measures. Our data support safety and efficacy of baclofen as an adjuvant to risperidone for improvement of hyperactivity symptoms in children with ASD.

Keywords Baclofen · Autism · GABA · GABAergic inhibition · Hyperactivity · Randomized-controlled trial

Introduction

Autism spectrum disorders (ASD) are defined by DSM-V as comprising persistent deficits in social communication and social interaction and restricted, repetitive patterns of behavior, interests, or activities. Both the children and their parents may need social support to cope with challenges and stressors associated with ASD, and to accomplish this, the governments face high costs [1]. Nevertheless, the exact causes of ASD remain obscure to us. Aberration in both the serotonin system and the dopamine system [2] has been recognized as possible pathways involved in ASD. Risperidone, as a serotonin 5-HT (2A) receptor antagonist that can attenuate dopamine release as well [3], is approved by the Food and Drug Administration (FDA) for the treatment of irritability in children with ASD. In recent years, research correlates risperidone use with significant weight gain [4] and with high rate of relapse after discontinuation of the medication in children with ASD [5]. Despite this, due to lack of insight into the exact pathogenesis of ASD, no new medication could be approved as an adjuvant or standalone treatment for patients with ASD.

Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter that can bind to two pharmacologically distinct receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors are pentameric ligand-gated chloride-ion channels (pLGIC) located on post-synaptic membrane. They are specifically required to mediate fast synaptic inhibition. $GABA_B$ receptors are heterodimeric G protein-coupled

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receptors located on presynaptic, synaptic, and on extrasynaptic membranes. With this broad availability, $GABA_B$ receptors can play a role as an important source of neuromodulation in different brain functions [6]. As a result, dysfunction of $GABA_B$ receptors is implicated in major psychiatric disorders notably depression and anxiety [7].

Increasing evidence suggests abnormalities of the GABAergic system in ASD. Both $GABA_A$ and $GABA_B$ are expressed at lower levels in brain of patients with ASD [8–12]. In vivo studies using the Proton magnetic resonance (1H-MRS) spectroscopy and spectral editing techniques confirm downregulation of GABA in auditory and motor areas including the superior and medial frontal cortex in children with ASD [13, 14]. Moreover, analysis of brain tissue has revealed lower mRNA levels of rate-limiting GABA synthesizing enzymes, such as glutamic acid decarboxylase (GAD) type 65 and 67, in a specific population of neurons within the cerebellar dentate nuclei in ASD [15, 16], while plasma levels of the neurotransmitter GABA are high in these patients [17].

Baclofen functions as a selective agonist for $GABA_B$ receptors. Studies in mice show the potential of R-Baclofen to reduce the core deficits of ASD notably social deficits and repetitive behaviors [18] and, as well, to improve cognitive performance [19]. Recently, an open-label trial [20] and a randomized, controlled, phase 2 trial [21] has confirmed effectiveness of arbaclofen in treatment of ASD. The present randomized, double-blind, placebo-controlled study aimed at evaluating the potential of Baclofen as an adjuvant therapy to enhance the effect of risperidone in children with ASD.

Materials and methods

Trial design and setting

The protocol of the present trial was delineated consistent with ethical principles developed by the Declaration of Helsinki [22]. The protocol was approved by the institutional review board/ethics committee (IRB/IEC) of Tehran University of Medical Sciences (Code No. IR.TUMS.VCR.REC.1395.1255). The trial was commenced on April, 2016. It was planned as a 10-week randomized, parallel group, double-blind placebo-controlled trial. The trial was carried out among patients attending Children's Outpatient Clinic at a tertiary hospital (Roozbeh Hospitals) in Iran. Prior to enrollment in the study, written informed consent was obtained from the parents or legal guardians of children. The trial was completely closed in August, 2018. This trial is registered with the Iranian Registry of Clinical Trials (IRCT; http://www.irct.ir) number IRCT201701131556N95.

Participants

Subjects were children 4–12 years old meeting the DSM-V (Diagnostic and Statistical Manual of Mental Disorders, fifth edition) criteria [23] for diagnosis of an autism spectrum disorder (ASD). In addition, children selected must have had irritability symptoms of at least moderate severity, defined as scores greater than or equal to 12 on the Aberrant Behavior Checklist-Community (ABC-C) Irritability subscale [24]. Diagnosis was initially confirmed by two expert child psychiatrists based on behavioral observations of the child and semi-structured interviews with the parents (Autism Diagnostic Interview-Revised) [25]. Before commencing the trial, parents or legal guardians of children were informed about the study, scheduled visits, and their right to withdraw from the study at any time.

Children in whom the symptoms at enrollment were not pronounced enough to be considered for treatment with risperidone were ineligible for the trial. Also children were excluded if they had (a) concomitant prominent psychiatric disorders, (b) preexisting medical or disease conditions (particularly epileptic disorders and febrile seizures), (c) severe intellectual disability, (d) history of alcohol/drug abuse, (e) tardive dyskinesia, or (f) history of antipsychotic medication or behavior therapy within the past 6 months before enrollment to this trial. To adhere to the ethical guidelines and avoid asking patients to stop taking any medication prior to entry, only children who were drug-free for at least 6 weeks before beginning of the study due to other reasons (discontinuation of drugs by their parents) were included in the present trial. In addition, to complete clinical examination, liver and kidney parameters were assessed for each eligible child.

Randomization, allocation, concealment, and blinding

Randomization was performed by a randomization operator who was not otherwise involved in this trial. Randomization codes were kept secure until data curation was completed. Among the 64 children enrolled in the study, 32 were randomly assigned to a combination of risperidone and baclofen (first arm or arm A) and 32 subjects were randomized to the risperidone plus placebo group (second arm or arm B). Participants and their parents were blinded to group allocations.

Interventions

Participants in both groups received risperidone (Risperdal; Janssen Pharmaceuticals, Beerse, Belgium) in a similar fashion. It was started with an initial dose of 0.5 mg and stepwise 0.5-mg weekly increases for the first 3 weeks were

implemented. Maximum dose of risperidone was 1 mg/d for children weighing less than 20 kg and 2 mg/d for those with a body weight equal to or greater than 20 kg. In addition, individuals allocated into arm A (first arm) were administered 0.6 mg Kg^{-1} baclofen three times a day. The placebo pills were similar in appearance (shape, size, and color) and taste to baclofen. During the trial period, participants were instructed to avoid any other kind of intervention (medications and cognitive behavioral interventions). Drug adherence was evaluated on the basis of parental reports and by pill counts at each visit.

Study assessment

Study outcomes were measured using the Aberrant Behavior Checklist-Community Edition (ABC-C) [24]. The ABC scale was originally developed in 1985 [26] to assess the efficacy of different therapeutic protocols on behavioral outcomes in mentally retarded subjects. It is a 58-item scale that includes five subscales: irritability (15 items), lethargy (16 items), stereotypy (7 items), hyperactivity (16 items), and inappropriate speech (4 items). The primary outcome of interest to the present trial was change in score on the ABC-irritability subscale. The secondary outcomes were change in scores on the other ABC subscales. Study visits were scheduled at baseline (day 1), midpoint (week 5), and completion (week 10).

Safety

At each baseline and follow-up visit, adverse effects were monitored by the responsible child psychiatrist using a checklist. After the first open-ended question about any adverse event, clinical parameters (weight and height) and symptoms (headache, vomiting, nausea, weakness, sweating, increased appetite, and sedation) were carefully assessed at weeks 0, 5, and 10. In the meantime, occurrence of side effects was recorded by a phone call to the parents 1 week after beginning treatment regimens. In addition, participants were provided with a phone number to the 24-h medical help line for medical advice about side effects.

Sample size

The initial sample size of 46 was calculated considering a number of assumptions: (a) mean difference of 4 between the two groups on the ABC-C irritability subscale with a standard deviation (SD) of 4, (b) power of 90%, and (c) two-sided significance level of 5%. Given an attrition rate of 30%, the final sample size was increased to 60. The number of participants required in each arm was 30 considering the 1:1 ratio of sample size (first arm:second arm).

Statistical analysis

Continuous data (age, weight, overall scale score, and score on subscales) were presented as mean ± SD and compared between groups using an independent *t* test with Levene's test for equality of variance. The categorical data (gender and response rate) were translated into numeric values (as percentage values) and compared between groups using Freeman–Halton extension of Fisher's exact test. The overall response rate was the sum of participants with partial and complete responses which were defined as ≥ 25% and ≥ 50% reductions in the ABC-irritability subscale score, respectively. To test for any difference between two treatment arms, the mean difference in change score (between baseline and each point of follow-up evaluation) and respective confidence intervals (95% CI) were calculated. The Cohen's d (95% CI) measure was used to determine the effect size of mean difference. The repeated-measures ANOVA (with the Greenhouse–Geisser correction for nonsphericity) was executed to investigate the therapeutic efficacy over time and also possible interaction between time and treatment (time × treatment). All statistical tests were carried out using the IBM SPSS Statistics 24.0.0 (IBM Corporations) in a two-tailed approach with significance level of 0.05.

Results

Participant baseline characteristics

A total of 104 potential children 4–12 years of age with a diagnosis of autism were initially screened for study eligibility of which 26 did not meet the inclusion criteria, eight met the exclusion criteria, and six refused to participate. Sixty-four subjects (62.5%) were eventually enrolled in the study and were randomized into two treatment groups with an equal allocation ratio of 1:1: A) risperidone plus baclofen and B) risperidone plus placebo. The mean age was 8.04 (SD = 2.33) years in arm A and was 7.9 (SD = 2.0) years in arm B. As noted in Table 1, participants in the two study arms did not differ in demographic and baseline clinical characteristics (age, sex, weight, ESRS score, ABC-irritability, lethargy, stereotypy, hyperactivity, and inappropriate speech subscales). The mean dose of risperidone in arm A and B at end of treatment was 1.55 (SD = 0.48) and 1.58 (SD = 0.51), respectively. Overall, six patients (three from each treatment arm) withdrew from the treatment trial early before the first follow-up visit (week 5). Figure 1 shows the number of patients who were screened, enrolled, and completed the trial.

Table 1 Baseline characteristics of study participants: Risperidone plus Baclofen vs risperidone plus placebo

	Risperidone plus baclofen ($n=29$)	Risperidone plus placebo ($n=29$)	Test of differences
Age in years: mean (SD)	8.04 (2.33)	7.9 (2.0)	$P=0.809$, $df=56$, $t=0.243$
Male no. (%)	23 (79.3)	23 (79.3)	$P=1.000$
Weight in kg: mean (SD)	24.93 (6.40)	25.59 (8.6)	$P=0.744$, $df=56$, $t=-0.329$
ESRS score: mean (SD)	0.17 (0.38)	0.17 (0.38)	$P=1.000$, $df=56$, $t=0.000$
ABC-C subscales scores: mean (SD)			
Irritability	22.76 (8.56)	22.62 (9.24)	$P=0.953$, $df=56$, $t=0.059$
Lethargy/social withdrawal	20.28 (5.62)	20.97 (8.87)	$P=0.725$, $df=47.339$, $t=-0.354$
Stereotypic behavior	8.79 (4.8)	9.0 95.390	$P=0.878$, $df=56$, $t=-0.154$
Hyperactivity/noncompliance	30.41 (6.94)	29.9 (11.2)	$P=0.833$, $df=46.730$, $t=0.211$
Inappropriate speech	6.35 (3.71)	6.83 (3.32)	$P=0.603$, $df=56$, $t=-0.523$

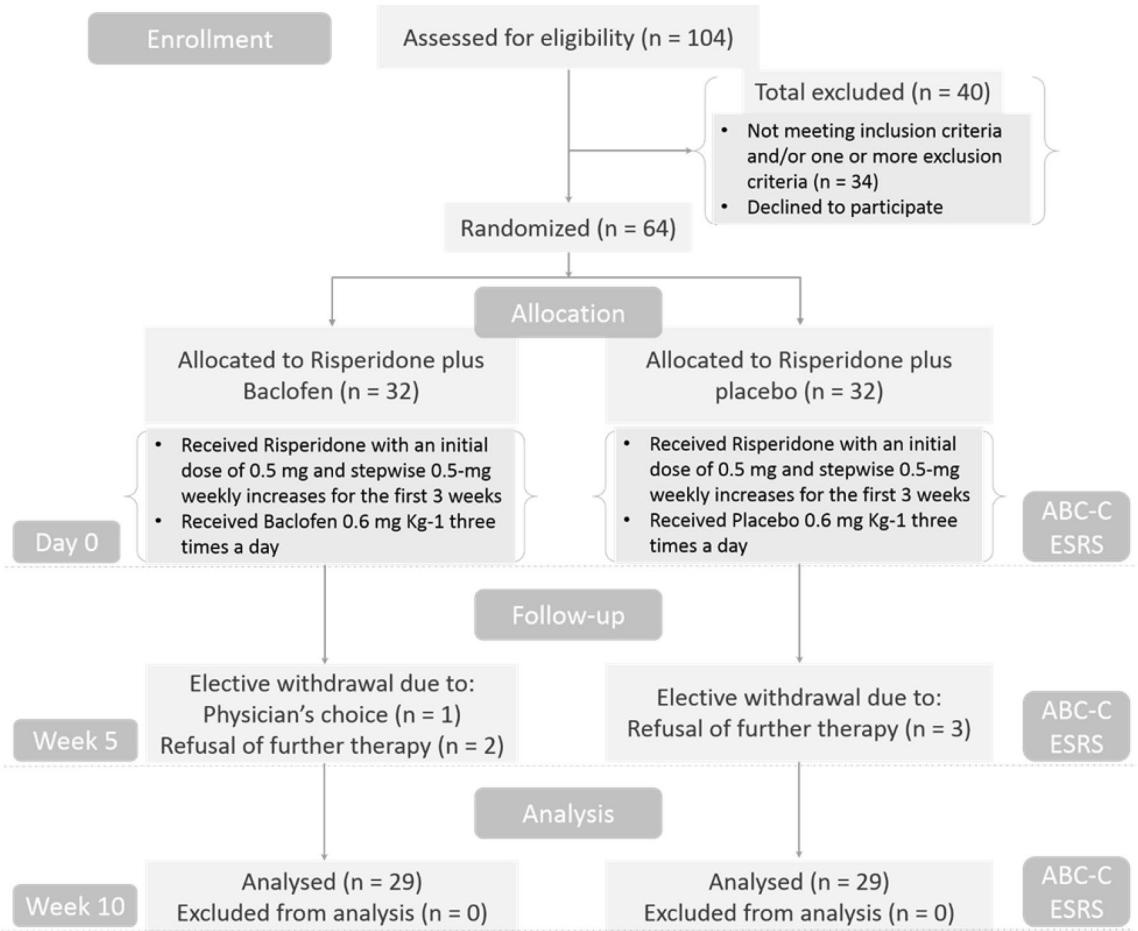

Fig. 1 CONSORT flow diagram

Clinical outcomes

Table 2 summarizes the mean scores on each of the follow-up visits for ABC subscales by treatment group, and presents the results of analyses of within-subjects and of between-subjects.

Repeated-measure ANOVA across three points of time revealed significant improvement for all the ABC subscales (irritability: $F=51.644$, $df=1.66$, $p<0.001$, lethargy: $F=39.734$, $df=1.38$, $p<0.001$, stereotypic behavior: $F=25.495$, $df=1.56$, $p<0.001$, hyperactivity: $F=54.135$, $df=1.35$, $p<0.001$, and inappropriate speech: $F=19.277$,

Table 2 Treatment responses of participants: results of within-subjects and between-subjects analyses

Outcome	Baseline		Week 5		Week 10		Time			Time × treatment interaction			Between subjects		
	Mean	SD	Mean	SD	Mean	SD	*F*	*df*	*P*	*F*	*df*	*P*	*F*	*df*	*P*
Irritability															
Risperidone plus Baclofen	22.76	8.56	17.66	9.34	13.35	5.47	51.644	1.66	< 0.001	2.043	2	0.134	0.509	1	0.478
Risperidone plus placebo	22.62	9.24	19.41	10.29	16.31	9.32									
Lethargy/social withdrawal															
Risperidone plus Baclofen	20.28	5.62	17.86	6.03	16.00	5.50	39.734	1.38	< 0.001	0.078	2	0.925	0.162	1	0.689
Risperidone plus placebo	20.97	8.87	18.86	9.79	16.66	9.09									
Stereotypic behavior															
Risperidone plus Baclofen	8.79	4.80	7.79	4.55	6.76	4.51	25.495	1.56	< 0.001	0.070	2	0.933	0.017	1	0.897
Risperidone plus placebo	9.00	5.40	8.04	5.23	6.79	4.83									
Hyperactivity/noncompliance															
Risperidone plus Baclofen	30.41	6.94	24.52	6.05	19.59	7.79	54.135	1.35	< 0.001	3.821	1.35	**0.042**	0.837	1	0.364
Risperidone plus placebo	29.90	11.20	27.14	10.99	23.52	10.42									
Inappropriate speech															
Risperidone plus Baclofen	6.35	3.71	5.90	3.54	5.31	3.53	19.277	1.47	< 0.001	0.023	2	0.977	0.353	1	0.555
Risperidone plus placebo	6.83	3.32	6.41	3.24	5.86	2.96									

Bold values indicate significant correlations at the level of 0.05

df = 1.47, p = 0.004) within the two groups combined. In addition, the analyses of time-treatment interactions showed a significantly higher effectiveness for combination of risperidone plus baclofen versus combination of risperidone plus placebo over time regarding hyperactivity ($p = 0.042$) subscale. There was no significant variation between subjects in symptom improvement.

Table 3 shows treatment effects on outcome measures over course of the trial. Regarding hyperactivity/noncompliance symptoms, the effect of combination treatment of risperidone and baclofen over risperidone plus placebo was significantly pronounced at both midpoint (MD, 95% CI = − 3.14, − 5.56 to − 0.72) and endpoint (MD, 95% CI = − 4.45, − 8.74 to − 0.16).

Table 3 Treatment effects on outcome measures over the trial course

Outcome	Mean (SD) change in score		Mean difference (95% CI)	*t* (*df*)	*P*	Cohen's d (95% CI)
	Risperidone plus Baclofen ($n = 29$)	Risperidone plus placebo ($n = 29$)				
Irritability						
Week 5	− 5.104 (6.236)	− 3.207 (4.065)	− 1.90 ((− 4.67 to 0.87)	− 1.372 (56)	0.176	0.36 (− 0.16 to 0.88)
Week 10	− 9.414 (7.872)	− 6.310 (6.223)	− 3.10 (− 6.84 to 0.63)	− 1.666 (56)	0.101	0.44 (− 0.09 to 0.96)
Lethargy/social withdrawal						
Week 5	− 2.414 (3.418)	− 2.104 (3.353)	− 0.31 (− 2.09 to 1.47)	− 0.349 (56)	0.7280.978	0.09 (− 0.42 to 0.61)
Week 10	− 4.276 (4.978)	− 4.310 (4.401)	0.035 (− 2.44 to 2.51)	0.028 (56)		0.01 (− 0.30 to 0.31)
Stereotypic behavior						
Week 5	− 1.000 (2.236)	− 0.966 (1.742)	0.04 (− 2.44 to 2.51)	− 0.066 (56)	0.948	0.02 (− 0.50 to 0.53)
Week 10	− 2.035 (3.006)	− 2.207 (2.569)	0.17 (− 1.30 to 1.64)	0.235 (56)	0.815	0.06 (− 0.45 to 0.58)
Hyperactivity/noncompliance						
Week 5	− 5.897 (5.473)	− 2.759 (3.461)	− 3.14 (− 5.56 to − 0.72)	− 2.610 (47.3)	**0.012**	0.69 (0.15 to 1.21)
Week 10	− 10.828 (8.929)	− 6.379 (7.292)	− 4.45 (− 8.74 to − 0.16)	− 2.078 (56)	**0.042**	0.55 (0.02 to 1.07)
Inappropriate speech						
Week 5	− 0.448 (0.985)	− 0.414 (1.018)	− 0.04 (− 0.56 to 0.49)	− 0.131 (56)	0.896	0.03 (− 0.48 to 0.55)
Week 10	− 1.035 (1.401)	− 0.966 (1.701)	− 0.07 (− 0.89 to 0.75)	− 0.169 (56)	0.867	0.04 (− 0.47 to 0.56)

Bold values indicate significant correlations at the level of 0.05

Comparison of response rate between the two treatment groups found difference for none of the ABC subscales (Table 4).

Adverse events

No serious side effects were observed in either treatment groups. Overall, the most common side effects reported were increased appetite (21%) and vomiting (17%). There was no significant difference in the frequency of adverse effects between groups (Table 5).

Table 5 Frequency of adverse effects

Adverse event	No. of patients (%)		Fisher *P* value
	Risperidone plus Baclofen (*n* = 29)	Risperidone plus placebo (*n* = 29)	
Headache	3	4	1.000
Vomiting	4	6	0.730
Nausea	2	3	1.000
Weakness	2	3	1.000
Sweating	1	1	1.000
Increased appetite	7	5	0.747
Sedation	4	3	1.000

Table 4 Comparison of response rate between treatment arms

Outcome Time	Degree of response	No. of patients (%)		Fisher *p* value
		Risperidone plus baclofen (*n* = 29)	Risperidone plus placebo (*n* = 29)	
Irritability week 5	Less than partial	19 (65.5)	21 (72.4)	0.383
	Partial	2 (6.9)	4 (13.8)	
	Complete	8 (27.60)	4 (13.8)	
Irritability week 10	Less than partial	10 (34.5)	15 (51.7)	0.450
	Partial	10 (34.5)	7 (24.1)	
	Complete	9 (31.0)	7 (24.1)	
Lethargy/social withdrawal week 5	Less than partial	23 (79.3)	23 (79.3)	1.000
	Partial	4 (13.8)	4 (13.8)	
	Complete	2 (6.9)	2 (6.9)	
Lethargy/social withdrawal week 10	Less than partial	19 (65.5)	20 (69.0)	0.854
	Partial	6 (20.7)	4 (13.8)	
	Complete	4 (13.8)	5 (17.2)	
Stereotypic behavior week 5	Less than partial	24 (82.8)	24 (82.8)	1.000
	Partial	2 (6.9)	3 (10.3)	
	Complete	3 (10.3)	2 (6.9)	
Stereotypic behavior week 10	Less than partial	19 (65.5)	15 (51.7)	0.517
	Partial	4 (13.8)	7 (24.1)	
	Complete	6 (20.7)	7 (24.1)	
Hyperactivity/ noncompliance week 5	Less than partial	20 (69.0)	24 (82.8)	0.358
	Partial	8 (27.60)	5 (17.2)	
	Complete	1 (3.4)	0 (0)	
Hyperactivity/noncompliance week 10	Less than partial	11 (37.9)	17 (58.6)	0.063
	Partial	9 (31.0)	10 (34.5)	
	Complete	9 (31.0)	2 (6.9)	
Inappropriate speech week 5	Less than partial	27 (93.1)	26 (89.7)	1.000
	Partial	2 (6.9)	2 (6.9)	
	Complete	0 (0)	1 (3.4)	
Inappropriate speech week 10	Less than partial	21 (72.4)	22 (75.9)	0.385
	Partial	4 (13.8)	6 (20.7)	
	Complete	4 (13.8)	1 (3.4)	

Discussion

Our data show that both regimens of risperidone alone or in combination with baclofen can significantly result in improvement of ABC subscales such as irritability, lethargy, stereotypic behaviors, hyperactivity, and inappropriate language in children with ASD. However, addition of baclofen to risperidone monotherapy may exert greater effect on the improvement of hyperactivity symptoms.

The combined effect of genetic, epigenetic, and environmental processes may contribute to GABAergic dysfunction in ASD. Population-based genetic association studies and linkage disequilibrium studies have well-documented that single-nucleotide polymorphisms (SNPs) within the $GABA_A$ (especially GABRA4) and $GABA_B$ (especially GABRB3) receptor genes and their interaction might confer susceptibility to ASD [27–32]. Methyl-CpG-binding protein 2 (MeCP2) is required for maintaining neural expression of $GABA_B$ receptors [33]. MECP2 gene mutations are also linked to ASD. This might constitute an epigenetic mechanism for downregulating the expression of $GABA_B$ receptors in the adult autistic brains [11]. In addition, oxytocin acts as a mediator of GABAergic synapses. During delivery, maternal oxytocin has been shown to exert a transient increase in GABAergic inhibition in the fetal brain [34]. Blockage of maternal oxytocin can lead to the development of autistic-like features in the offspring [35]. Bumetanide, which attenuates GABA excitatory activity through reducing intracellular Cl^- accumulation [36], could help to improve the effects of lack of maternal oxytocin [35]. Moreover, clinical studies provide evidence for effect of oxytocin in improving emotion recognition [37] and social cognition [38] and in reducing stereotypic behaviors [39] in patients with ASD. Therefore, the shift to GABAergic excitatory activity in autism might be a possible consequence of defective oxytocin.

Along with its neuromodulatory role, GABA inhibits central inflammation. Glial fibrillary acidic protein (GFAP) is an astrocyte-specific intermediate filament protein that increases in response to inflammatory stimuli. The brain regions associated with lower expression of GABA receptors mainly include the superior frontal cortex, parietal cortex, and cerebellum in patients with ASD [8, 40]. Interestingly, these regions were noted as places where levels of GFAP are significantly high [41]. Therefore, the GABAergic dysfunction might contribute to ASD via aggregation of central inflammation.

Animal models confirm GABAergic dysfunction in autism. Insufficiency of the GABRB3 gene results in social deficits, behavioral impairments, and somatosensory and sensorimotor problems resembling those seen in ASD [42, 43]. Similarly, oxytocin deficiency has been shown to cause autistic-like features such as cognitive impairment, social deficits, and disturbed and aggressive behaviors [44]. Maternal exposure to valproate (VPA) induces autism-like symptoms in the offspring. Therefore, VPA is used an environmental model for ASD. It has been shown to impair GABAergic function at pre- and post-synaptic sites [45] and to induce an asymmetric increase in $GABA_A$ receptor binding in left amygdala in the offspring [46]. In addition, spontaneous reduction of GABAergic function occurs in the BTBR mouse strain, an idiopathic model for autism [47]. PX-RICS-deficient mice, which exhibit autism-like symptoms, have lower concentrations of surface $GABA_A$ receptors [48].

Different pharmacological agents that enhance GABAergic inhibition have been investigated for the treatment of ASD. Benzodiazepines are positive allosteric modulator of $GABA_A$ receptors that boost GABAergic inhibition. Treatment with low-dose L-838,417, which acts as selective positive allosteric modulator for $GABA_A$ receptor α2- and α3-subunits, significantly helped to attenuate behavioral disturbances in the BTBR mouse [47]. In addition, clonazepam (CZP), a benzodiazepine agonist for the $GABA_A$ receptor, could improve social deficits in PX-RICS-deficient mice [48]. In contrast, zolpidem, which acts as selective positive allosteric modulator for GABAA receptor α1-subunit, exerted a worsening effect on social deficits [47].

Imipramine is a GABA-transaminase agonist. It could help to improve social interaction and verbal language while reducing repetitive behaviors in patients with infantile autism [49]. A short-term treatment with imipramine was enough to reduce plasma levels of GABA [49].

A single dose of sodium butyrate could improve social deficits in the BTBR mice [50], whereas DMCM functioning as a GABA reverse agonist worsened social deficits in the BTBR mice treated with sodium butyrate. Therefore, sodium butyrate seems to be a drug for strengthening GABAergic inhibition.

Gaboxadol, which is also known as 4, 5, 6, 7-tetrahydroisoxazolo (5, 4-c) pyridin-3-ol (THIP), acts as an extrasynaptic agonist for $GABA_A$ receptor. Fragile X syndrome (FXS) is a genetic disorder associated with autism-like behavioral abnormalities. In the mice model of FXS, gaboxadol appeared effective in improving behavioral impairments [51]. However, in the VPA model of ASD, gaboxadol could not help to achieve the balance between GABAergic excitation and inhibition [45].

Baclofen is believed to be a selective $GABA_B$ receptor agonist. It has long been used via the intrathecal route to treat spasticity [52]. In addition, clinical studies document efficacy of baclofen in improvement of gastroesophageal reflux (GER) [53] and alcohol withdrawal symptoms [54]. However, in oral use, baclofen is a drug with a narrow absorption window in the upper part of the small intestine

[55]. Arbaclofen or R-Baclofen (STX209) is the R isomer of baclofen. The pharmacological formulation of arbaclofen allows its intestinal absorption by active and passive mechanisms [55]. Arbaclofen was able to rescue behavioral disturbances, abnormal auditory-evoked gamma oscillations, working memory, and synaptic abnormalities that may play key role in FXS [56–58]. Consistently, a phase III trial of children with FXS reported superior efficacy of arbaclofen versus placebo on the ABC-C_{FX} irritability subscale and parenting stress index [59]. However, a trial of adolescents with FXS revealed no benefit of arbaclofen [59]. Of note, arbaclofen could reduce social deficits and repetitive behaviors in the BTBR mouse model of ASD [60]. In addition, it helped to amend abnormal gamma oscillations in the Protocadherin 10 (Pcdh10) gene-deficient mouse model of ASD [61].

Scarce studies investigated the efficacy of arbaclofen for children with ASD. Erickson et al. 2014 [20] conducted an 8-week, open-label trial of 32 patients with ASD. Patients were 6–17 years old at study entry. The authors implemented a protocol with an initial dose of 1 mg BID, with subsequent increases every 3–4 days to a maximum dose of 10 mg BID for patients aged 6–11 years or 10 mg TID for patients aged 12–17 years. Overall, the study demonstrated safety and well tolerability of arbaclofen, and reported agitation, irritability, fatigue, psychomotor hyperactivity, insomnia, and diarrhea as the most common adverse events. The authors noted significant improvement in ABC subscales irritability, lethargy, hyperactivity, and stereotypy, social responsiveness scale (SRS), the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS), ADHD-IV rating scale, and in the Childhood Anxiety Sensitivity Index (CASI).

Recently, Veenstra-VanderWeele et al. 2017 [21] published results of a 12-week randomized, controlled, phase 2 trial. 150 patients with ASD aged 5–21 years completed the trial. The authors implemented a protocol with an initial dose of 5 mg BID, with subsequent increases every 7 days to 10 mg BID, 10 mg TID, and then to 15 mg TID. Compared with placebo, the higher frequency of affect liability, headache, somnolence, vomiting, and nasal congestion was observed with arbaclofen. The authors assessed different primary, secondary, and exploratory efficacy measures. However, outcomes for patients treated with arbaclofen were comparable to those for patients treated with placebo. The only outcome which reached a significant difference between Baclofen and placebo groups was the Clinical Global Impression-Severity scale (CGI-S), suggesting superior efficacy for arbaclofen.

In summary, the present randomized-controlled trial provided clinical evidence of safety and efficacy of baclofen as an adjuvant to risperidone for improvement of hyperactivity symptoms in children with ASD. Here, it is important to be mentioned that patients in both groups were categorized as less than partial responders at week 5 followed by slight improvements at week 10 of therapy for most of outcomes. Given that the study population was made up of patients with moderate-to-severe disease, study findings imply that risperidone, both alone and combined with baclofen, might require additional time to achieve efficacy in these patients. Therefore, having a short follow-up along with implementation of a fixed dose baclofen protocol are important limitations that must be acknowledged. Furthermore, the ABC subscales were used as the only outcome measures in the present study. Thus, it is important for future studies to explore the impact of baclofen on different outcome measures for evaluating autism-related symptoms, especially those other than hyperactivity, e.g., social deficits and repetitive behavior. Finally, future directions for research are determining whether baclofen can be effective (1) as standalone treatment for autism, (2) as alternative for methylphenidate to control autism-related hyperactivity, (3) as an adjuvant to enhance the therapeutic effect of risperidone, and thus, (4) to reduce risperidone dose and related adverse events.

Conclusions

The present randomized-controlled trial provided the first clinical evidence of safety and efficacy of baclofen as an adjuvant to risperidone to improve hyperactivity symptoms in children with ASD.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

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