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Original Article

Behavioral and pharmacological intervention in autism spectrum disorder: CARS score changes across cognitive levels

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Abstract

Objectives: This study aimed to investigate the core symptom of autism in Indonesian children using Childhood Autism Rating Scale (CARS) scores and their relationship with cognitive profiles while evaluating the effectiveness of aripiprazole and behavioral intervention across different cognitive levels. **Materials and Methods:** A multicenter, randomized, double-blind, placebo-controlled trial was conducted in Bandung City, Indonesia, from February 2023 to January 2024. Participants aged 6–10 years with autism spectrum disorder (ASD) were assessed using CARS and Stanford-Binet Intelligence Scales Form L-M. They were randomized to receive either aripiprazole with behavioral therapy (BT) or placebo with BT for 12 weeks. CARS scores and cognitive levels were evaluated at baseline and after treatment. **Results:** The study enrolled 51 participants (29 placebo and 22 aripiprazole). Both groups showed significant improvements in CARS and cognitive scores over 12 weeks. The aripiprazole group demonstrated greater reductions in CARS scores (5.17 points for higher-cognitive level [HC-ASD]; 4.88 points for lower-cognitive level [LC-ASD] compared to the placebo group. Significant improvements were observed in visual response, taste/smell/touch response, and fear/nervousness CARS subcategories ($P < 0.05$). Receiver operating characteristic analysis revealed that CARS scores at end-of-treatment (EoT) were strong predictors of cognitive improvement, with an optimal cutoff of 36.25 achieving high sensitivity and specificity (AUC 0.776, $P < 0.05$). **Conclusion:** Early identification, accurate differentiation between LC-ASD and HC-ASD, and targeted interventions combining pharmacological treatment with BT are essential for improving outcomes in children with ASD. These approaches can reduce symptom complexity while fostering long-term functional skills development.

Keywords: *Aripiprazole, Autism spectrum disorder, Behavioral therapy, Childhood autism rating scale, Cognitive level*

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by challenges in social communication and interaction, as well as restricted or repetitive patterns of behavior, interests, or activities [1,2]. The prevalence of ASD in Southeast Asian countries is estimated at six cases per 1000 persons, with a higher occurrence in males [3]. However, significant disparities exist in ASD diagnosis among different demographic groups, and approximately 27% of children with ASD remain undiagnosed by the age of eight, highlighting the need for improved diagnostic processes and awareness [4].

The diagnostic landscape for ASD has evolved significantly in recent years. In 2013, the American Psychiatric Association released the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), which significantly revised the diagnostic criteria for ASD. It consolidated previously separate categories from DSM-IV (autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS) into a single ASD diagnosis [1]. This

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change acknowledges the considerable variability within the spectrum but has raised concerns about potentially overlooking cases with better intelligence potential, such as those previously diagnosed with Asperger's Syndrome or PDD-NOS [5]. The heterogeneous nature of ASD presentations poses significant challenges in assessment and diagnosis, necessitating comprehensive evaluation approaches.

To address the complexities of ASD diagnosis and assessment, standardized tools like the Childhood Autism Rating Scale (CARS) and intelligence tests such as the Stanford–Binet Intelligence Scales play crucial roles. In Indonesia, the Stanford–Binet Intelligence Scale Form L-M (SB-LM) [6], adapted for use since 1970, remains a primary tool for assessing cognitive function in children with ASD. The relationship between ASD severity and cognitive function is a key area of investigation, with Intelligence quotient (IQ) scores associated with social functioning and predicting cognitive outcomes later in life [2]. Research indicates that IQ remains relatively stable across the lifespan for children with IQs ≥70 [7], highlighting the importance of understanding this relationship for developing effective, individualized interventions and educational plans.

Treatment approaches for ASD have evolved significantly, integrating behavioral interventions and pharmacological management to address a wide range of deficits and symptoms. Applied Behavior Analysis (ABA), which originated from the Lovaas model and UCLA Young Autism Project, had expanded into diverse treatment models and focused intervention practices [8]. One of these methods, Discrete Trial Training (DTT), is a structured ABA technique that systematically breaks down complex skills into small, "discrete" components. This approach allows therapists to teach skills one by one, using a highly structured, fast-paced format of instruction typically conducted in a one-to-one situation with minimal distractions. DTT is designed to improve cognitive, linguistic, social, and daily living skills across all ASD functioning levels [9]. While no medications target ASD's core deficits, atypical antipsychotics such as aripiprazole are Food and Drug Administration-approved for managing associated irritability in pediatric patients aged 6–17 years [10-13]. This comprehensive approach aims to enhance communication, social relationships, and overall quality of life for individuals with ASD.

This study aims to investigate the cognitive profiles of Indonesian children with ASD, their relationship to CARS scores, and the efficacy of aripiprazole combined with behavioral intervention across cognitive ranges. It is anticipated that aripiprazole may offer benefits in managing complex ASD symptomatology, particularly among children presenting with more severe manifestations and lower cognitive levels. Aripiprazole is expected to support improvements in ASD symptoms beyond irritability, potentially enhancing engagement in behavioral interventions and contributing to more favorable outcomes when used alongside behavioral therapy (BT) [14]. By examining the efficacy of aripiprazole and behavioral intervention across cognitive levels, and identifying prognostic CARS cutoff points, the research seeks to provide clinicians with valuable tools for treatment planning and outcome prediction. These findings will aid clinicians in treatment determination and provide therapists with valuable insights to support children with ASD.

Materials and methods

Study design

A multicenter, randomized, double-blind, fixed-dose, placebo-controlled trial was conducted at two clinical research facilities in Bandung City, West Java, Indonesia (Melinda 2 Child Developmental Center and Indigrow-Child Development Center), between February 2023 and January 2024. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was formally reviewed and approved by the Research Ethics Committee of Padjadjaran University (Letter number 988/UN6/KEP/EC/2022, registration number 2201050016). This approval ensured that the trial adhered to established ethical and regulatory standards. The informed consent was obtained from the patients.

Throughout the investigation, strict adherence to Good Clinical Practice guidelines was maintained. These included randomization of participants, double-blinding procedures to minimize bias, standardized fixed-dose regimens, and the use of placebo controls. Particular emphasis was placed on participant safety, data integrity, and ethical conduct. This rigorous approach ensured that the study met international standards for clinical research while safeguarding the well-being of all participants involved [Figure 1].

Participants

Inclusion and exclusion criteria

The study focused on a group of outpatients between the ages of 6-–10, who had been diagnosed with autistic disorder as their primary condition according to DSM-5 criteria [1] and had not previously undergone any pharmacological treatment. The study excluded participants who had been diagnosed with Asperger Syndrome, Pervasive Developmental Disorder-Not Otherwise Specified, Rett Syndrome, Childhood Disintegrative Disorder, or Intellectual Disability [16].

Assessment

The CARS, widely used for differentiating mild-to-moderate from severe ASD in children aged 2 and above, was employed in its Indonesian version (sensitivity 85.2%, accuracy 85.7%, and internal consistency 0.819) for diagnosis and assessment of autism severity [17]. Experienced pediatric neurologists administered the CARS, which comprises 15 questions rated on a scale of 1–4 (normal to severely abnormal), based on caregiver interviews and direct child observation. Total scores range from 15 to 60, with <30 indicating nonautism, 30–36.5 suggesting mild to moderate autism, and 37–60 signifying severe autism [18].

Cognitive function assessment was conducted through comprehensive psychological evaluations, including the Stanford–Binet Intelligence Scales Form L-M (SB-LM), administered by a team of qualified psychologists [6,19,20]. This widely-used instrument evaluates seven dimensions of intelligence across 142 age-scaled items, yielding mental age, chronological age, and IQ scores. Participants were classified

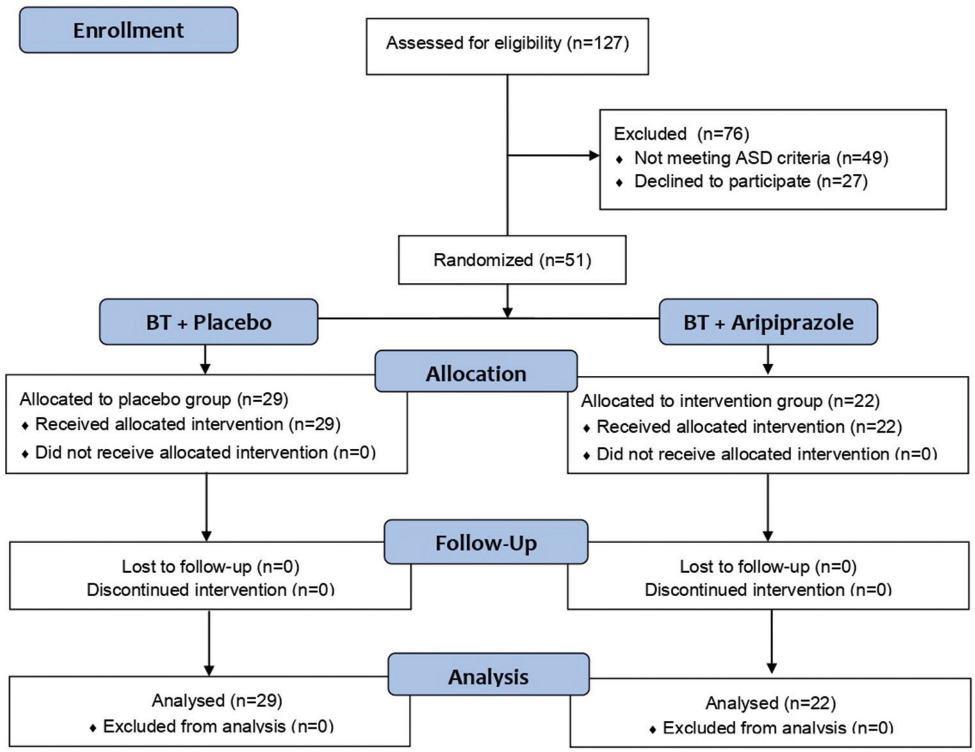

Figure 1: Consort diagram of study [15]

as having lower cognitive (LC-ASD) or higher cognitive (HC-ASD) levels based on a holistic assessment of clinical manifestations, symptom complexity (as measured by CARS), IQ scores, and observed changes in both cognitive and CARS scores over time.

For LC-ASD individuals, where the SB-LM's lower limit of IQ 30 posed interpretative challenges, mental age (in years) was used as the primary metric. This approach allowed for a more nuanced understanding of cognitive abilities in severely impaired individuals. HC-ASD individuals were assessed using standard IQ scores. Despite its age, the SB-LM remains the primary cognitive assessment tool for children with ASD in Indonesia, offering valuable insights into the diverse cognitive profiles within this population [6,21].

Cognitive evaluations were conducted concurrently with CARS assessments at baseline and after a 12-week intervention period. IQ scores were calculated by comparing chronological and mental ages using standardized norms.

Randomization and blinding

Randomization of eligible participants was performed using GraphPad software (Dotmatics). The results were converted into Sealed sealed-numbered opaque Sequential Envelope and further randomized by an independent research assistant. Subjects were allocated to either the aripiprazole group (aripiprazole + BT) or the placebo group (Saccharum lactis + BT). The aripiprazole group received ABILIFY DISCMELT Orally Disintegrating Tablets (10 mg, Otsuka Indonesia) [22], while the placebo group received Saccharum lactis powder (DFE Pharma GmbH and Co. Kg, Germany) [23].

Interventions

Pharmacological intervention and placebo were administered in powder form. The aripiprazole dosage regimen was: 2 mg/day (Week 1), 5 mg/day (Weeks 2–5), and 10 mg/day (Weeks 6–12). Concurrent BT was implemented, consisting of ABA with DTT over 12 weeks (5 sessions/week, 60 total, minimum 75% attendance required). Each session comprised 50 min of therapy and 10 min of parental counseling, conducted by certified therapists with >10-year experience. Following the initial assessment, therapists maintained daily progress notes, monitored medication adherence, and facilitated parental logbook maintenance for outcome evaluation.

Outcome measures

Our research primarily focused on the efficacy of aripiprazole and behavioral interventions across cognitive levels, utilizing CARS scores as the primary endpoint. Secondary outcomes encompass the analysis of cognitive-based treatment outcomes and CARS score changes from baseline to 12-week follow-up. In addition, the study examined the relationship between baseline cognitive levels and CARS score changes over the treatment period. Furthermore, we aim to establish CARS cutoff points with prognostic value, facilitating easier assessment and providing predictive insights into potential symptom improvement in children with ASD.

Statistical analysis

Statistical analysis was conducted using Statistical Analysis Software Package for Windows (SPSS) Version 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Descriptive statistics were calculated for all variables, with continuous data presented as mean ± standard deviation and discrete data as frequency (percentage of frequency). The Kolmogorov–Smirnov test was employed to assess the normality of data distribution.

For analytical statistics, Chi-square tests were used for discrete clinical demographic characteristics. Continuous data were analyzed using independent sample *t*-tests for normally distributed variables and Mann–Whitney *U* tests for nonnormally distributed variables. One-way ANOVA with Tukey *post-hoc* tests was applied for multiple group comparisons. For all statistical analyses, a significance level of $P < 0.05$ was adopted.

Results

The study enrolled 51 participants divided between placebo (n = 29) and aripiprazole (n = 22) groups [Table 1], with comparable mean ages (placebo: 6.60 ± 0.37 years; aripiprazole: 6.82 ± 0.39 years). Both groups exhibited improvements over the 12 weeks, with lower-cognitive individuals showing increases in mental age (placebo: 2.004 to 2.115; aripiprazole: 1.968 to 2.365) and higher-cognitive individuals demonstrating IQ score improvements ((placebo: 40.13 to 41.80; aripiprazole: 40.89 to 44.00). CARS scores also improved across both groups (placebo: 42.16 to 37.62; aripiprazole: 40.00 to 35.00). Notably, significant enhancements ($P < 0.05$) were observed in three specific CARS sub-categories: Visual response (VII), taste/smell/touch response (IX), and fear/nervousness (X), suggesting targeted impacts on core autism symptoms [Table 2 and Supplementary Figure 1].

Table 1: Clinical characteristics of participants

Characteristics	Placebo group (*n*=29)	Aripiprazole group (*n*=22)
Age (years) mean±SD	6.60±0.37	6.82±0.39
Gender		
Boys	18 (62.1)	18 (81.8)
Girls	11 (37.9)	4 (18.2)
Cognitive levels		
Mental ages (years)		
Lower cognitive (LC-ASD)	21 (72.4)	13 (59.1)
Baseline*	2.004±0.449	1.968±0.389
End of treatment (week 12)	2.115±0.353	2.365±0.586
IQ levels		
Higher cognitive (HC-ASD)	8 (27.6)	9 (40.9)
Baseline	40.13±8.36	40.89±11.08
End of treatment (week 12)	41.80±9.05	44.00±11.39
Total score CARS		
Baseline	42.16±0.97	40.00±1.21
End of treatment (Week 12)	37.62±0.88	35.00±1.32

*Two subjects (9.5%) in the placebo group and one (7.7%) in the aripiprazole group could not be accurately assessed due to testing instrument limitations and performance constraints, highlighting challenges in cognitive evaluation for ASD cases. CARS: Childhood Autism Rating Scale, HC-ASD: Higher cognitive Autism spectrum disorder, LC-ASD: Lower cognitive Autism spectrum disorder, SD: Standard deviation

The analysis of treatment efficacy highlighted distinct patterns based on cognitive levels and treatment groups in individuals with ASD. At baseline, the lower-cognitive level (LC-ASD) groups exhibited higher CARS scores, with the placebo group (LP) at 43.74 ± 5.00 (n = 21) and the aripiprazole group (LA) at 42.88 ± 5.19 (n = 13). Conversely, the higher-cognitive level (HC-ASD) groups showed lower initial CARS scores, with the placebo group (HP) at 38.00 ± 3.25 (n = 8) and the aripiprazole group (HA) at 35.83 ± 3.39 (n = 9). After 12 weeks of treatment, all groups demonstrated improvements in CARS scores. The LC-ASD groups experienced reductions of 4.09 ± 0.76 (LP) and 4.88 ± 0.96 (LA), while the HC-ASD groups showed more pronounced decreases of 5.12 ± 1.23 (HP) and 5.17 ± 1.16 (HA) [Table 3 and Supplementary Figure 2].

ANOVA analysis demonstrated significant between-group differences (P = 0.0005) in CARS total scores. Notable baseline differences were observed between LP versus HA (7.90, 95% confidence interval [CI]: 2.87–12.94), LP versus HP (5.74, 95% CI: 0.49–10.99), and HA versus LA (−7.05, 95% CI: −12.53–-1.57). At the endpoint, the largest difference was between LP versus HA (8.81, 95% CI: 4.04–13.58), suggesting cognitive level and treatment type

Table 2: The profile of Childhood Autism Rating Scale (CARS) sub-category at End of the treatment (Week 12)

Sub-category CARS (mean±SD)	Placebo group (*n*=29)	Aripiprazole group (*n*=22)	*P*
CARS I (relationship with people)	2.58±0.116	2.29±0.121	0.137
CARS II (imitation)	2.53±0.124	2.38±0.135	0.582
CARS III (emotional response)	2.46±0.092	2.25±0.108	0.182
CARS IV (body use)	2.39±0.091	2.34±0.129	0.574
CARS V (object use)	2.43±0.101	2.23±0.138	0.196
CARS VI (adaptation to change)	2.39±0.10	2.34±0.124	0.720
CARS VII (visual response)	2.43±0.90	2.07±0.10	0.021*
CARS VIII (auditory response)	2.17±0.090	2.07±0.10	0.520
CARS IX (taste, smell, and touch response)	2.24±0.128	1.91±0.153	0.035*
CARS X (fear or nervousness)	2.39±0.094	2.14±0.10	0.043*
CARS XI (verbal communication)	2.89±0.134	2.86±0.128	0.745
CARS XII (nonverbal communication)	2.60±0.109	2.43±0.120	0.487
CARS XIII (activity level)	2.45±0.071	2.32±0.101	0.386
CARS XIV (intellectual inconsistency)	2.72±0.130	2.70±0.149	0.853
CARS XV (general impression)	2.89±0.112	2.66±0.120	0.174

*P<0.05. Mann–Whitney *U*-test. SD: Standard deviation, CARS: Childhood Autism Rating Scale

Table 3: Cognitive-based treatment outcomes and Childhood Autism Rating Scale (CARS) score changes: Baseline to 12-week follow-up

Comparison between cognitive levels	ANOVA		
	Mean difference (SE, 95% CI)	*F*	*P*
CARS total baseline		8.132	0.0005
LP versus LA	0.85 (1.62, −3.61–5.31)		
LP versus HP	5.74 (1.91, 0.49–10.99)*		
LP versus HA	7.90 (1.83, 2.87–12.94)*		
HP versus HA	2.17 (2.23, −3.97–8.31)		
HP versus LA	- 4.88 (2.06, -10.56 – 0.79)		
HA versus LA	- 7.05 (1.99, -12.53 - -1.57)*		
CARS total endpoints		11.183	0.0005
LP versus LA	1.47 (1.53, −2.75–5.70)		
LP versus HP	6.73 (1.81, 1.75–11.70)*		
LP versus HA	8.81 (1.73, 4.04–13.58)*		
HP versus HA	2.08 (2.11, −3.73–7.90)		
HP versus LA	−5.25 (1.95, −10.63–0.13)		
HA versus LA	−7.33 (1.88, −12.52–−2.14)*		

*P<0.05. *Post hoc* analysis. LP: Lower-cognitive (placebo); LA: Lower-cognitive (aripiprazole); HP: Higher-cognitive (placebo); HA: Higher-cognitive (aripiprazole); ANOVA: Analysis of variance, CARS: Childhood Autism Rating Scale, SE: Standard error, CI: Confidence interval

influenced outcomes, with higher-cognitive groups showing greater improvement regardless of treatment [Table 3].

The receiver operating characteristic (ROC) analysis results demonstrate the predictive capability of CARS scores for cognitive improvement across two time points: baseline and week 12 (end-of-treatment [EoT]). At baseline, the analysis shows an AUC of 0.645 (95% CI: 0.195–0.825), with an optimal cutoff score of 39.50 demonstrating a sensitivity of 0.674 and specificity of 0.625. The EoT assessment showed improved predictive power with an AUC of 0.776 (P < 0.05, 95% CI: 0.624–0.928), where the optimal cutoff score of 36.25 achieved a sensitivity of 0.605 and specificity of 0.875 [Table 4 and Supplementary Figure 3]. This improvement in AUC from baseline to EoT suggests that CARS scores become more accurate predictors of cognitive improvement over time, with the EoT measurements showing statistically significant predictive value.

Discussion

The study presents a comprehensive analysis of cognitive functioning and treatment outcomes in ASD, revealing important connections between cognitive levels, symptom severity, and treatment response. Initial assessments of 51 subjects (29 placebo and 22 aripiprazole) showed no significant demographic differences between groups, with mean ages of 6.82 and 6.60 years, respectively, including a balanced gender distribution favoring males, aligning with the 4:1 male-to-female autism risk ratio. This gender disparity supports the female protective effect theory, suggesting females require stronger etiological triggers for autism development [24].

When assessing autism severity using CARS measurements, the distribution of LC-ASD was comparable in both groups, with 59.1% in the aripiprazole group and 72.4% in the placebo group. Both groups were classified as having severe autism based on their initial CARS scores, which averaged 40.00 ± 1.21 for the aripiprazole group and 42.16 ± 0.97 for the placebo group, falling within the severe range (37–60) where higher scores indicate greater symptom complexity [25,26]. Cognitive assessments revealed substantial intellectual impairments in both groups. LC-ASD individuals exhibited increases in mental age (placebo: 2.004 to 2.115 years; aripiprazole: 1.968 to 2.365 years), while HC-ASD individuals demonstrated IQ score improvements (placebo: 40.13 to 41.80; aripiprazole: 40.89 to 44.00). These findings are consistent with broader research indicating that approximately 50%–70% of individuals with autism spectrum disorder experience intellectual disabilities (IQ <70) [27].

A comprehensive analysis of CARS scores provides valuable insights for clinicians and therapists in understanding the progression of children with ASD. The rapid response observed in sensory domains, particularly visual processing, can be attributed to the direct and immediate nature of sensory stimuli. Visual, auditory, tactile, gustatory, and olfactory inputs require less cognitive processing compared to complex social or emotional stimuli, making them more responsive to quick intervention effects. This aligns with the neuroplasticity of sensory systems, which can adapt more readily to targeted interventions [28].

ABA training employs a systematic approach to behavior modification, utilizing positive reinforcement as a primary mechanism for instilling desired behaviors in children with ASD. This methodology involves careful observation and analysis of a child's responses to various environmental stimuli, such as auditory cues or verbal instructions from caregivers or educators. Upon successful demonstration of the target behavior, the child is presented with an individualized reinforcer, which may range from tangible rewards to social reinforcement, tailored to the specific child and the behavior in question [8,9]. Our research indicates that these reinforced behaviors, particularly in the realm of sensory processing, create a crucial foundation for cognitive development. As children enhance their ability to process and integrate sensory information, they develop a better awareness of their environment, facilitating improved engagement with learning materials and activities during BT [29]. While direct cognitive improvements were not the primary focus of the intervention, the success in enhancing sensory processing creates a more receptive state for cognitive learning, potentially leading to broader developmental gains in children with ASD.

The findings underscore the importance of distinguishing between LC-ASD and HC-ASD, as this distinction significantly influences treatment outcomes and long-term prognoses. Key predictors of later success include childhood IQ and early language/communication skills, which are positively correlated with improved adaptive functioning, social skills, and communication abilities [30,31]. The long-term implications of these findings are profound. A systematic review examining adult outcomes revealed that individuals with classic autism experienced significantly poorer long-term outcomes (61.9%) compared to those diagnosed with high-functioning autism

Table 4: ROC analyses for determining Childhood Autism Rating Scale (CARS) cut-off scores to predict cognitive improvement in children With ASD

Cut-off	CARS total (baseline)			Cut-off	CARS total (week 12)		
	Sensitivity	Specificity	AUC (*P*, 95% CI)		Sensitivity	Specificity	AUC (*P*, 95% CI)
30.5	1	0	0.645 (0.195, 0.466 – 0.825)	20.5	1	0	0.776* (0.014, 0.624 – 0.928)
31.75	0.977	0		23.5	1	0.125	
32.75	0.953	0.125		26.75	1	0.25	
33.75	0.93	0.125		28.75	0.977	0.25	
34.25	0.907	0.125		30.0	0.977	0.375	
34.75	0.86	0.125		30.75	0.953	0.375	
35.25	0.837	0.125		31.25	0.93	0.375	
36.25	0.814	0.25		31.75	0.814	0.375	
37.25	0.791	0.25		32.5	0.791	0.5	
37.75	0.744	0.375		33.25	0.767	0.5	
38.25	0.721	0.375		33.75	0.698	0.5	
38.75	0.674	0.5		34.5	0.628	0.625	
39.50	**0.674**	**0.625**		35.25	0.605	0.625	
40.25	0.605	0.625		35.75	0.605	0.75	
40.75	0.581	0.625		**36.25**	**0.605**	**0.875**	
41.25	0.535	0.625		36.75	0.581	0.875	
41.75	0.512	0.75		37.25	0.535	1	
42.25	0.395	0.875		37.75	0.512	1	
43.0	0.372	0.875		38.25	0.465	1	
43.75	0.326	0.875		38.75	0.349	1	
44.25	0.279	0.875		39.5	0.326	1	
45.25	0.233	1		40.5	0.302	1	
46.25	0.186	1		41.25	0.279	1	
47.0	0.163	1		41.75	0.233	1	
48.25	0.14	1		42.25	0.163	1	
49.25	0.116	1		42.75	0.14	1	
49.75	0.093	1		43.25	0.093	1	
50.25	0.07	1		44.75	0.07	1	
51.5	0.047	1		46.75	0.047	1	
54.5	0.023	1		48.5	0.023	1	
57.5	0	1		50.5	0	1	

*$P<0.05$. CARS: Childhood Autism Rating Scale, AUC: Area under curve, CI: Confidence interval

or other forms of autism spectrum disorders (26.4%) [32]. This stark difference highlights the importance of early identification and tailored intervention strategies that align with an individual's cognitive profile.

To differentiate between LC-ASD and HC-ASD effectively, clinicians often utilize observational assessments focused on the complexity of autism symptoms, employing tools like the CARS. According to Chlebowski *et al.*, severe autism is indicated by CARS scores ranging from 37 to 60, where higher scores reflect increased symptom complexity across various domains such as social communication, social interaction, stereotypic behaviors, sensory abnormalities, and emotional regulation [33]. Research indicates that a change in CARS score of at least 4.5 points is considered a benchmark for successful intervention; however, the clinical significance of minor changes can vary among individuals [10]. This variability underscores the necessity for personalized assessment and treatment approaches in managing ASD effectively.

Pharmacological interventions have shown promise in alleviating ASD symptoms [10-12]. Aripiprazole, in particular, has been shown in improving irritability, hyperactivity, and stereotypic behaviors in autistic individuals aged 6–17 years. A cohort study by Marcus *et al.* found that aripiprazole (2–15 mg/day) significantly decreased Aberrant Behavior Checklist-Irritability scores compared to placebo, with improvements noticeable within the 1st week at 2 mg/day [13]. A separate randomized controlled trial with 218 participants confirmed these findings, demonstrating significant reductions in irritability scores across various aripiprazole doses compared to placebo [34]. These findings reinforce the importance of early and targeted interventions based on accurate differentiation between LC-ASD and HC-ASD, while also highlighting the potential advantages of integrating behavioral therapies with pharmacological treatments to manage ASD symptoms effectively and enhance long-term outcomes.

BT continues to yield positive effects on both CARS and cognitive levels in children diagnosed with autism, even beyond critical developmental periods. The combination of BT alongside aripiprazole has demonstrated superior results; although total CARS score differences may not be statistically significant, aripiprazole has shown beneficial effects on specific subcategories related to sensory processing and emotional regulation, which are crucial areas for subsequent

BT steps [35] Early intensive behavioral intervention is recommended for preschool to early school children with autism, with a minimum of 25 hours per week [10]. BT for children with ASD should be tailored to different developmental stages throughout life, focusing on language acquisition, play skills, and communication strategies in early childhood, social skills, and peer relationships during childhood and adolescence, and vocational and adaptive life skills for older adolescents and young adults [36].

The dynamic nature of autism as a brain disorder suggests that evidence-based interventions like BT combined with pharmacotherapy can lead to positive changes through neuroplasticity, which is the brain's ability to adapt its structure and function over time [37]. Neuroplasticity encompasses numerous processes such as synapse formation and retraction, axonal regeneration, dendritic growth, and neurogenesis [37,38]. In therapeutic contexts, pharmacotherapy typically operates from a bottom-up approach starting at subcortical regions before influencing higher cortical functions; conversely, BT works top-down by targeting cortical areas first before affecting subcortical regions [39].

While pharmacotherapy can help normalize neuronal abnormalities associated with autism symptoms, core challenges related to social interaction and communication may be less responsive to medication alone. On the other hand, BT has been shown to influence serotonin metabolism positively while also modifying neural structures supporting plasticity within the brain's architecture [40,41]. The environmental reinforcement received during therapy can enhance synaptic reorganization, which is critical for improving social behaviors in children diagnosed with autism [42].

Research indicates that early behavioral interventions can successfully connect synaptic activities within the brains of children aged 18–30 months, leading to enhanced social behavior outcomes. In addition, neuroplasticity associated with therapy has been linked to increased activity within BDNF signaling pathways, further underscoring how meaningful stimuli during therapeutic engagement can leave lasting traces on memory [37,43,44]. Overall, these findings suggest that when implemented correctly [10], behavioral therapies can reduce symptom complexity while fostering permanent functional skills development among children diagnosed with ASD [43].

Given these findings, early intervention becomes crucial in improving outcomes for individuals with ASD. The CARS score serves as a valuable tool in assessing the effectiveness of interventions, with changes in scores potentially indicating shifts in symptom severity. For instance, a change from an initial CARS score of 39.5 (indicating severe autism) to a final score of 36.25 (indicating mild-to-moderate autism) represents a significant improvement. This finding emphasizes the importance of holistic interventions addressing multiple ASD aspects, particularly sensory processing. It suggests that focusing on areas assessed by CARS, especially sensory domains, could be key to enhancing overall cognitive outcomes in children with ASD. Ultimately, EoT CARS scores emerge as a potent tool for predicting long-term cognitive outcomes and guiding ongoing intervention approaches, underscoring the interconnectedness of sensory, behavioral, and cognitive improvements in ASD treatment.

Limitations

Despite promising findings, the study has several limitations, including shorter-than-ideal duration of behavioral therapy, variations in subject compliance and parental involvement, influence of underlying medical conditions on treatment adherence, genetic variations affecting treatment responses, relatively short study duration, potentially limited sample size, and lack of control for concurrent interventions. These limitations highlight the complex nature of ASD treatment and the need for individualized approaches.

Conclusion

This research emphasized the importance of early identification, accurate differentiation between LC-ASD and HC-ASD, and the implementation of targeted interventions combining BT and pharmacological treatment to effectively manage ASD symptoms and improve long-term outcomes. Clinicians should conduct comprehensive assessments using standardized tools (CARS) and develop individualized plans combining behavioral therapies (ABA, DTT) with monitored pharmacological treatments. When implemented correctly, these approaches can reduce symptom complexity while fostering permanent functional skills development among children diagnosed with ASD.

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Data availability statement

All data generated or analyzed in this study are available in this published article.

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Nil

Conflict of interest

There are no conflicts of interest.

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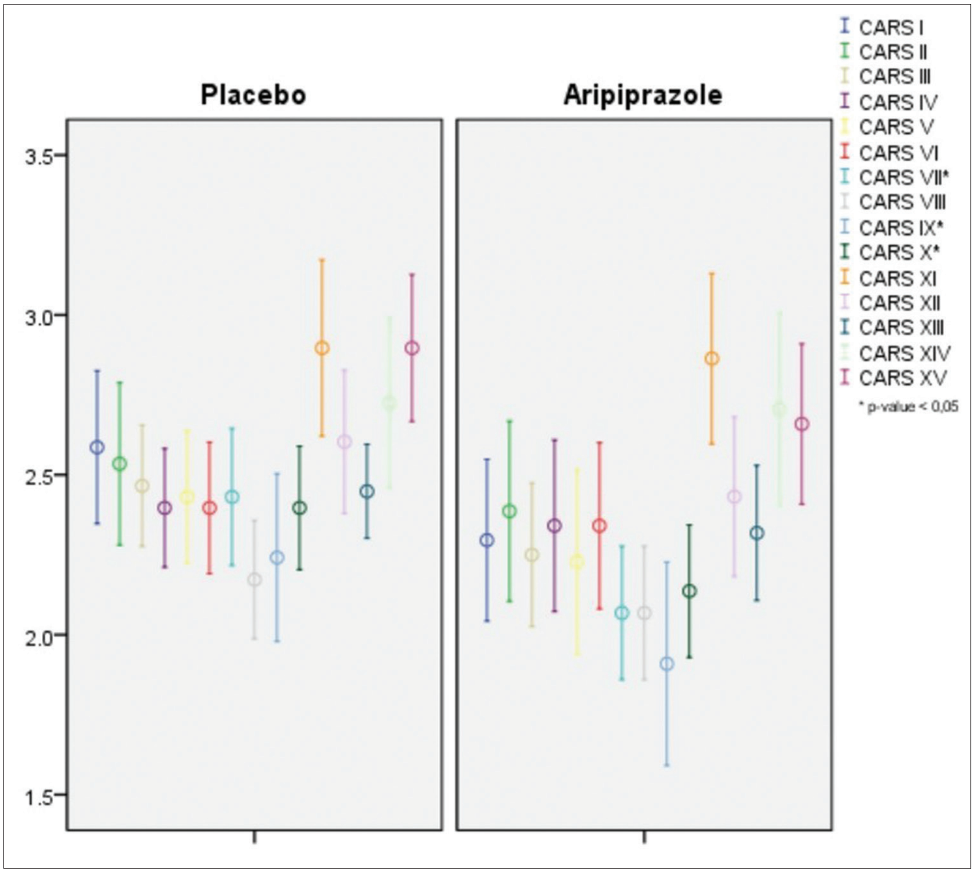
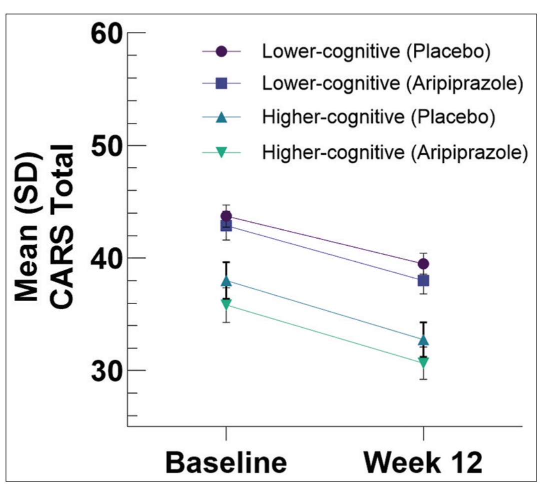
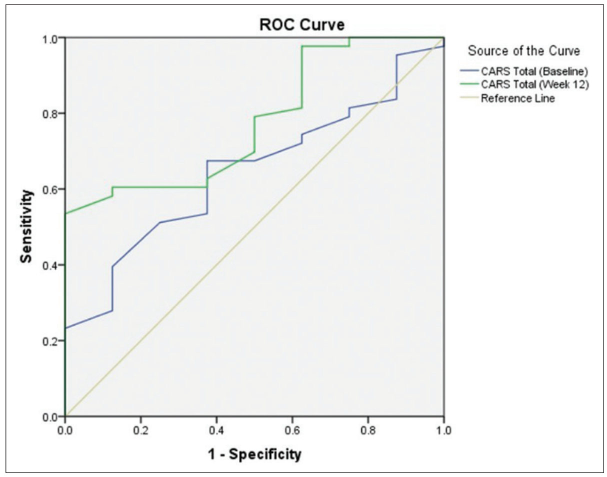
Supplementary material



Supplementary Figure 1: The profile of CARS sub-category at EoT (Week 12). Mann–Whitney *U*-test; *$P < 0.05$



Supplementary Figure 2: Cognitive-based treatment outcomes and CARS score changes: Baseline to 12-week follow-up



Supplementary Figure 3: Receiver operating characteristic analyses for determining CARS cutoff scores to predict cognitive improvement in children with ASD