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RESEARCH ARTICLE

Autism Spectrum Disorder: a Two-center Evaluation of Pharmacological Intervention and Behavioral Therapies on Core Symptoms

Purboyo Solek,[1] Uni Gamayani,[2] Kusnandi Rusmil,[1] Irvan Afriandi,[3] Taufan Prasetya,[1] Anggia Farrah Rizqiamuti,[1] Eka Nurfitri,[1] Burhan Burhan,[1] Indra Sahril,[1] Kevin Gunawan[4]

[1]Department of Child Health, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, [2]Department of Neurology, Faculty of Medicine, Universitas Padjadjaran/ Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, [3]Department of Public Health, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, [4]Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia

Abstract

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by chronic deficits in social communication and interaction, with sensory processing abnormalities affecting over 90% of individuals across different sensory areas. This study investigated the combined effects of aripiprazole and behavioral therapy (BT) on core symptoms of ASD in children aged 6–10. Utilizing the considerable neuroplasticity still present at this age, we hypothesized that this combined approach might yield superior outcomes compared to BT alone. The 12-week randomized, double-blind, placebo-controlled trial was conducted from February 2023 to January 2024 at two sites of Child Development Centers in Bandung city, involving 51 participants (22 intervention, 29 placebo). The intervention group received aripiprazole and BT, while the placebo group received saccharum lactis and BT. Both groups underwent BT comprising applied behavioral analysis (ABA) and discrete trial training (DTT). The Childhood Autism Rating Scale (CARS) assessed treatment effects. The independent 2-sample t-tests and Mann-Whitney tests showed no significant differences in overall CARS scores between groups. However, the analysis revealed significant improvements in three subcategories: VII (visual response, p=0.021), IX (taste-smell-touch response, p=0.035), and X (fear or nervousness, p=0.043). These findings suggest that the combined approach may enhance sensory processing and emotional regulation in children with ASD. The study highlights the potential benefits of a multimodal approach to ASD treatment, combining targeted pharmacological intervention with behavioral therapies. However, limitations such as study duration and sample size warrant further research to optimize treatment strategies for individuals across the autism spectrum.

Keywords: Aripiprazole, autism spectrum disorder, behavioral therapy, Childhood Autism Rating Scale, sensory processing

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent impairments in social communication and interaction, along with restricted and repetitive patterns of behaviors, interests, or activities.[1] The global prevalence of ASD is estimated at 6 cases per 1,000 individuals in Southeast Asian countries, with a significant male predominance.[2] Children with ASD often experience additional challenges, including aggressive behaviors, self-injurious behaviors, tantrums, and irritability.[3]

Diagnosis of ASD involves a multifaceted approach, incorporating behavioral observation, parental interviews, and standardized assessment tools, with updated criteria provided by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[1] However, the heterogeneous presentation in ASD poses significant challenges in assessment and diagnosis. The Childhood Autism Rating Scale (CARS) is a widely utilized instrument for differentiating between mild-to-moderate and severe ASD in children aged two and above.[4]

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Correspondence: Purboyo Solek, dr., Sp.A(K). Department of Child Health, Faculty of Medicine, Universitas Padjajaran/Dr. Hasan Sadikin General Hospital. Jln. Pasteur No. 38, Bandung 40161, West Java, Indonesia. E-mail: purboyosolek@yahoo.com

Sensory processing abnormalities are a core feature of ASD, affecting over 90% of individuals across multiple sensory modalities (visual, auditory, tactile, gustatory, and olfactory).[5] These atypical sensory responses manifest as hypo-responsiveness, hyper-responsiveness, and sensory-seeking behaviors, with some researchers proposing an additional pattern of enhanced perception. These abnormalities can significantly impact daily functioning, academic performance, and social interactions. Studies using tools like the Sensory Processing Measure, Second Edition (SPM-2) have shown that children with ASD exhibit higher scores across all subscales, indicating worse sensory processing, praxis, and social participation in daily activities than typically developing peers.[6,7]

While behavioral interventions for ASD symptoms like hyperactivity and irritability exist, effective treatments for sensory abnormalities remain limited.[8,9] Recent research has focused on aripiprazole, a novel antipsychotic with a unique pharmacodynamic profile.[9] Aripiprazole acts as a partial agonist at dopamine D2 and serotonin 5-HT1A receptors and an antagonist at 5-HT2A receptors. FDA-approved for treating ASD-associated irritability in children aged 6–17, ongoing studies are evaluating its efficacy in managing sensory processing abnormalities in ASD.[9] This research may provide new therapeutic options for addressing the complex sensory issues inherent to ASD.

As our understanding of sensory processing in ASD continues to evolve, it is crucial to develop targeted interventions and support strategies to enhance the overall functioning and quality of life for children with ASD. This study may provide insights into the efficacy of aripiprazole and behavioral therapy (BT) in managing the complex core symptoms associated with ASD.

Methods

This randomized, double-blind, fixed-dose, placebo-controlled study was conducted at two sites (Melinda 2 Child Developmental Center & Indigrow-Child Development Center) in Bandung city, Indonesia, between February 2023 and January 2024. The ethics committee approved the study from the Research Ethics Committee of Universitas Padjadjaran with letter number 988/UN6/KEP/EC/2022.

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-V 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.[3]

An experienced pediatric neurologist validated the diagnosis using the CARS Indonesian version (sensitivity of 85.2%, accuracy of 85.7%, and internal consistency of 0.819).[10] CARS scores range from 15 to 60, with a 30 or above indicating autism.[4] Following 12 weeks of medication and behavioral therapy, subjects underwent a repeat CARS assessment to evaluate treatment effects.

Eligible participants were randomly assigned using GraphPad randomizer software by Dotmatics, with results converted into sequentially numbered opaque sealed envelope (SNOSE) and further randomized by a third-party research assistant. Participants were divided into an intervention group (aripiprazole+BT) and a placebo group (saccharum lactis+BT). The intervention group received Abilify Discmelt® orally disintegrating tablets (10 mg, Otsuka Indonesia),[11] while the placebo group received saccharum lactis powder (DFE Pharma GmbH & Co. KG, Germany).[12] Both treatments were given in powder form, and the intervention dosage schedule was 10 mg/day (week 1), 5 mg/day (weeks 2–5), and 10 mg/day (weeks 6–12).

Alongside pharmacotherapy, participants underwent intensive BT comprising applied behavioral analysis (ABA) and discrete trial training (DTT) for 12 weeks (5 sessions/week, 60 total, 75% minimum attendance).[13] Each session comprised 50 minutes of therapy and 10 minutes of parent counseling conducted by certified therapists (>10 years experience). Following the initial assessment, therapists documented daily progress notes, monitored medication adherence, and facilitated parental logbook maintenance for outcome evaluation.

The data collected were analyzed using the Statistical Package for Social Sciences (SPSS) version 22 for Windows. Independent 2-sample t-tests were applied when the data followed a normal distribution, while the Mann-Whitney U test was used for non-normally distributed data.

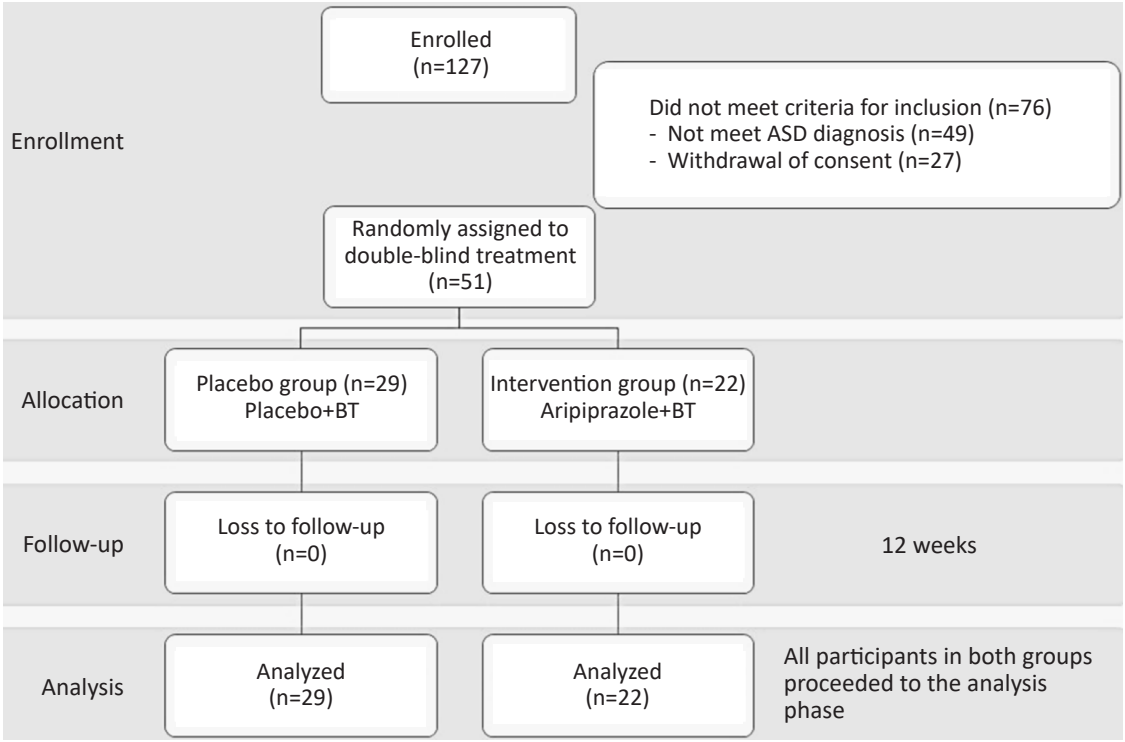

Figure Participant Flow

These tests aimed to assess whether there was a significant improvement of core symptoms in ASD between the placebo and intervention groups, with a significance threshold set at $p<0.05$.

Results

This study included 51 participants (22 intervention, 29 placebo) with similar mean ages (intervention: 6.82±0.39 years, placebo: 6.60±0.37 years). Participants had diverse educational backgrounds and varied gender distribution (intervention: 18M/4F; placebo: 18M/11F) as shown in Table 1.

Table 2 shows that baseline and final total CARS scores showed no significant differences between groups. However, further analysis in Table 3 revealed significant differences ($p<0.05$) in three CARS sub-categories after 12 weeks of treatment: VII (visual response), IX (taste, smell,

Table 1 Contingency of Chi-Square for Social Value Orientation and Pro-environmental Behavior

Characteristics	Placebo Group n=29	Intervention Group n=22
Age (years)		
Mean (SD)	6.60 (±0.37)	6.82 (±0.39)
Gender		
Boys	18	18
Girls	11	4
School placement		
General school	7	13
Special school	6	4
Homeschooling	2	0
Do not attend	14	5

Table 2 Clinical Measure of CARS

Clinical Measure	Placebo Group n=29	Intervention Group n=22	p
Total score CARS (mean±SD)			
Baseline	40.00 (±1.21)	42.16 (±0.97)	0.310
End of treatment	35.00 (±1.32)	37.62 (±0.88)	0.054

Note: t-test independent

Table 3 Profile of CARS Sub-category at the End of Treatment

Sub-Category CARS (Mean±SD)	Placebo Group n=29	Intervention 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)	2.7 (±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 (Non-verbal 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

Note: Mann-Whitney U test, *significance p<0.05

and touch response), and X (fear or nervousness). These findings suggest the treatment significantly impacted specific aspects of autism core symptoms in both groups.

Discussion

This comprehensive study investigates the combined effects of pharmacological treatment (specifically aripiprazole) and behavioral interventions on core symptoms of ASD, utilizing the CARS to assess various aspects of the disorder, including social/communication skills, stereotyped behavior, sensory abnormalities, and emotional regulation.[4,10]

While the overall CARS scores did not show statistically significant differences between groups at the 12-week intervention, a change of at least 4.5 points in CARS score is considered a benchmark for successful intervention. However, the clinical relevance of minimal changes can vary between individuals.[14] A more detailed analysis revealed notable improvements in three specific CARS sub-categories: VII (visual response), IX (taste-smell-touch response), and X (fear or nervousness). These findings suggest potential advancements in sensory processing and emotional regulation, two domains frequently challenging for individuals with ASD.

Aripiprazole, a second-generation (atypical) antipsychotic, has been well-documented for its efficacy in reducing disruptive behaviors in individuals with ASD, leading to its FDA approval for treating irritability.[15,16] A cohort study by Marcus et al.[17] demonstrated that aripiprazole (2–15 mg/day) over one year significantly reduced Aberrant Behavior Checklist-Irritability (ABC-I) scores by −12.9 compared to −5 in the placebo group, with improvements observed as early as the first week at 2 mg/day. A retrospective study by Fung et al.[18] found that aripiprazole improved sensory symptoms in autistic children and

adolescents, particularly inattention, auditory processing, and visual input affecting emotional responses and activity levels.

The study underscores the potential advantages of a multimodal approach to ASD treatment, combining targeted pharmacological interventions with BT. Intensive behavioral intervention (IBI) alone showed substantial decreases in aggressive behavior but was more effective when paired with antipsychotic medication.[19,20] Recent studies in mice have provided a neurobiological basis for these observations, showing that chronic administration of risperidone or aripiprazole improves social interaction deficits and recognition memory impairment, with reductions observed in dendritic spine density in the prefrontal cortex and hippocampus.[21,22]

Strong connections were found between sensory processing and communication abilities in ASD children, with overall sensory scores correlating positively with most communication skills. Interestingly, all patterns of sensory processing showed significant negative correlations with anxiety subsets in ASD children, suggesting that children with more pronounced sensory processing difficulties tended to experience lower levels of anxiety. Social relationship scores in ASD children correlated negatively with all anxiety subsets, implying that improving social relationships may help reduce anxiety and vice versa.[23]

ABA and DTT were identified as two of 27 evidence-based practices for individuals with autism. The study suggests that BT for autism should target core symptoms, address co-occurring issues, be adapted to the individual's cognitive and developmental level, incorporate visual supports and structured teaching, and focus on generalizing skills to natural environments.[24]

The prognosis for individuals with ASD is influenced by several factors, including the child's age when therapy is first given, the intensity of therapy, therapy techniques, parental involvement, and the child's characteristics (such as intelligence level, language capacity, and behavioral problems). Early intervention has significantly improved in several domains, including communication, social-emotional functioning, adaptive behavior, and physical development.[25]

Early IBI is recommended for preschool to early school children with autism, with a minimum of 20–40 hours per week.[8] Behavioral therapy for children with ASD should be tailored to different developmental stages throughout life. In early childhood, interventions focus on language acquisition, play skills, joint attention, and effective communication strategies through intensive behavioral and educational interventions, especially ABA. During childhood and middle adolescence, the focus shifts to continuing skill development, including social skills, peer relationships, and maximizing academic support. For older adolescents and young adults, developing vocational and adaptive life skills becomes crucial to maximize opportunities for independence and support the transition as caregivers age.[26]

Despite its promising findings, the study has several limitations, including suboptimal duration of behavioral therapy, variations in subject compliance and parental involvement, the 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.

Future research should focus on elucidating underlying processes, developing integrated therapies for sensory processing difficulties, communication challenges, and anxiety in ASD, optimizing BT for individuals across the autism spectrum, evaluating long-term outcomes, and combining BT with other evidence-based practices. This comprehensive approach to ASD treatment, combining pharmacological interventions with behavioral therapies, holds promise for addressing both behavioral and sensory symptoms in ASD, potentially leading to more effective and personalized treatment strategies.

Understanding the nuanced relationships between cognitive functioning and sensory processing in ASD is essential for developing targeted and individualized interventions. By considering cognitive abilities and sensory processing when developing support strategies, clinicians can create more effective treatments that address specific sensory challenges based on an individual's cognitive profile.[27] This approach

has the potential to significantly improve the quality of life for those on the autism spectrum across different developmental stages and cognitive levels.

Conclusions

In conclusion, combined pharmacological and behavioral therapy effectively reduced core symptom complexity in children with ASD. Significant improvements in total CARS scores, especially in subcategories VII (visual response), IX (taste, smell, and touch response), and X (fear or nervousness), indicate enhanced sensory processing and emotional regulation. These early positive changes suggest this combined approach is a promising treatment strategy, potentially improving overall functioning and quality of life for children with ASD.

Conflict of Interest

No conflicts of interest occur in this study.

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