Efficacy and Safety of Aripiprazole in Children and Adolescents With Autism Spectrum Disorder

A Meta-Analysis

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Aim: Aripiprazole is one of the few pharmacological agents approved for managing irritability in children and adolescents with autism spectrum disorder (ASD).

Methods: Randomized controlled trials comparing oral aripiprazole with placebo or active drugs in participants under 18 years were systematically searched in major databases through September 2025 (last search: September 15, 2025). The primary outcome was change in Aberrant Behavior Checklist–Irritability (ABC-I) scores; data were synthesized using random-effects models.

Results: Eleven trials (N = 1,135) were included. Aripiprazole significantly reduced irritability (mean difference = −5.18; 95% CI = −6.72 to −3.64; I^2 = 0%) and improved global ratings versus placebo. Common adverse effects were weight gain, sedation, and extrapyramidal symptoms, though discontinuation rates were comparable to placebo.

Conclusions: Aripiprazole effectively and safely reduces irritability in pediatric ASD. Although adverse effects are frequent, they are generally manageable, supporting individualized dosing and long-term monitoring.

Key Words: Autism spectrum disorder, aripiprazole, irritability, meta-analysis, adverse events

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Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by persistent deficits in social communication and interaction, along with restricted, repetitive patterns of behavior and interests. These symptoms usually appear in early childhood and persist throughout life, significantly impairing social, academic, and functional development (Lord et al., 2020; McCabe et al., 2023). According to recent global estimates, ASD affects approximately 1%–2% of children, with a prevalence that continues to rise worldwide (Salari et al., 2022; Zeidan et al., 2022). Males are diagnosed more frequently than females, with a ratio of nearly 4:1 (Loomes et al., 2017). The etiology of ASD is multifactorial, involving genetic, neurobiological, and environmental contributions (Aishworiya et al., 2022; Kilincel & Baki, 2021; Manoli & State, 2021; Willsey et al., 2022).

Despite the increasing prevalence and disease burden, no pharmacological therapy has demonstrated efficacy in improving the core symptoms of ASD. Current management, therefore, relies heavily on behavioral and educational interventions as first-line strategies (Aishworiya et al., 2022; McCabe et al., 2023). Nevertheless, many children and adolescents with ASD also present with disruptive behaviors such as irritability, aggression, self-injury, and severe temper outbursts, which pose considerable challenges for families and caregivers and often require pharmacological management (Hirota & King, 2023; Iffland et al., 2023).

Second-generation antipsychotics (SGAs) have emerged as the main pharmacological option for addressing these behavioral symptoms. Risperidone was approved in 2006, while aripiprazole followed in 2009 (Bartram et al., 2019; Siafis et al., 2022). Both agents have demonstrated short-term efficacy in reducing irritability and aggression; however, their pharmacological profiles and adverse event spectra differ substantially. Risperidone acts primarily as a dopamine D2 and serotonin 5-HT2 receptor antagonist, and its use is often limited by metabolic side effects, weight gain, and hyperprolactinemia (Keks & Culhane, 1999; Sepulveda-Lizcano et al., 2023). In contrast, aripiprazole is a partial agonist at dopamine D2 and serotonin 5-HT1A receptors and an antagonist at serotonin 5-HT2A receptors, conferring a distinct mechanism of action with potentially lower risk of prolactin elevation and some metabolic advantages (Casey & Canal, 2017; Tadori et al., 2011).

Several randomized controlled trials (RCTs) conducted over the past two decades have investigated the efficacy and safety of aripiprazole in children and adolescents with ASD. These studies consistently demonstrate improvements in Aberrant Behavior Checklist–Irritability (ABC-I) scores and Clinical Global Impression (CGI) ratings compared with placebo (17–20). Moreover, aripiprazole has shown effectiveness across different dosing regimens and durations of treatment. However, adverse events such as sedation, weight gain, extrapyramidal symptoms, and gastrointestinal disturbances remain important clinical considerations (Findling et al., 2014; Ichikawa et al., 2017; Marcus et al., 2009; Owen et al., 2009). A small number of head-to-head studies comparing aripiprazole with risperidone suggest similar efficacy, but potentially different tolerability profiles (Correll et al., 2011). Despite these encouraging findings, the overall body of evidence remains fragmented, and questions remain regarding the consistency of therapeutic benefits, the risk–benefit balance, and the long-term safety of aripiprazole in pediatric ASD populations.

Given the clinical importance of managing irritability in ASD and the need for evidence-based pharmacological

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strategies, a comprehensive synthesis of the available data on aripiprazole is warranted. Therefore, the present study aims to conduct a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy and safety of aripiprazole in children and adolescents with ASD. This work seeks to provide updated, quantitative evidence to guide clinicians and inform clinical practice.

METHODS

The performance of meta-analysis adhered to the guidelines in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Page et al., 2021). The PRISMA checklist is presented in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/JNMD/A209).

Eligibility Criteria

This study included only randomized controlled trials (RCTs), either parallel or crossover in design, that evaluated the efficacy and safety of oral aripiprazole in children and adolescents diagnosed with autism spectrum disorder (ASD) according to standardized criteria such as DSM-IV, DSM-5, or ICD-10. For crossover trials, only data from the first treatment period were included in the analyses to avoid potential carryover effects. Eligible participants must be under 18 years of age at the time of enrollment. Interventions of interest were aripiprazole administered at any oral dose or treatment duration, with comparators consisting of either placebo or active pharmacological agents, including risperidone. The primary efficacy outcome was the change in Aberrant Behavior Checklist–Irritability (ABC-I) scores from baseline to endpoint, while secondary efficacy outcomes included changes in the total ABC score, other subscales (stereotypy, hyperactivity, social withdrawal, inappropriate speech), and Clinical Global Impression (CGI) ratings. Safety outcomes encompassed the incidence of treatment-emergent adverse events (TEAEs), discontinuation due to adverse events, and specific side effects such as weight gain, increased appetite, sedation, extrapyramidal symptoms, prolactin alterations, gastrointestinal events, and upper respiratory infections. Studies reporting outcomes with at least a four-week follow-up period were considered eligible, and no restrictions were applied regarding language or publication year.

Search Strategy

A comprehensive literature search was conducted to identify all relevant studies from the inception of each database to the date of the final search. The electronic databases searched included PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, Scopus, and Web of Science. To minimize publication bias and capture ongoing or unpublished trials, grey literature sources such as ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), ProQuest Dissertations and Theses, and major conference abstract databases were also screened. The search strategy combined controlled vocabulary (MeSH and Emtree terms) with free-text keywords related to "aripiprazole," "autism spectrum disorder," and "children or adolescents," together with terms associated with randomized trial design such as "randomized," "randomized," "placebo," and "trial." No language restrictions were applied, and translations were sought if necessary. The complete search strategies tailored to each database were provided as supplementary material (Supplemental Digital Content 1, http://links.lww.com/JNMD/A209) in the final publication.

Study Selection

All records retrieved from the electronic databases and grey literature sources were first imported into a reference management software, and duplicate entries were removed. Two reviewers independently screened the titles and abstracts of all identified citations to determine potential eligibility. Full-text versions of potentially relevant articles were subsequently obtained and assessed against the predefined inclusion and exclusion criteria. Any disagreements regarding study eligibility were resolved through discussion, and, if necessary, a third reviewer was consulted to achieve consensus. The overall process of study selection, including the number of records identified, screened, excluded, and finally included, along with reasons for exclusion at the full-text stage, was documented in detail and illustrated using a PRISMA flow diagram in the final report.

Data Extraction

Data from the included studies were extracted independently by two reviewers using a standardized data collection form specifically developed for this review. Extracted information included study characteristics (first author, year of publication, country, and funding source), participant details (sample size, mean age, sex distribution, and diagnostic criteria), intervention characteristics (aripiprazole dose, titration method, and treatment duration), and comparator details (placebo or active drug). Outcome measures encompassed efficacy endpoints, such as changes in Aberrant Behavior Checklist (ABC) scores and Clinical Global Impression (CGI) ratings, as well as safety outcomes, including treatment-emergent adverse events, treatment discontinuation rates, and specific adverse effects like weight gain, sedation, extrapyramidal symptoms, prolactin alterations, and gastrointestinal events. Any discrepancies in the extracted data were resolved through discussion or consultation with a third reviewer. Where necessary, corresponding authors of the included studies were contacted to obtain missing or clarifying information.

Risk of Bias in Individual Studies

The methodological quality of all included randomized controlled trials was assessed independently by two reviewers using the Cochrane Risk of Bias 2.0 tool. This tool evaluated potential bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of the reported results. Each domain, as well as the overall risk of bias for each study, was judged as "low risk," "some concerns," or "high risk." Any disagreements between reviewers were resolved through discussion, with arbitration by a third reviewer if consensus could not be reached. The results of the risk of bias assessment were presented in both tabular and graphical formats to provide a clear overview of study quality.

Certainty of Evidence

The overall quality and certainty of the evidence for each primary and secondary outcome were evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach. This framework considered five key domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. For each outcome, the certainty of evidence was rated as high, moderate, low, or very low, depending on the extent of potential limitations in these domains. Evidence originating from randomized controlled trials was initially considered high quality but could be downgraded based on methodological weaknesses or variability across studies. Conversely, if there was strong consistency of results, large effect sizes, or evidence of a dose–response gradient, the quality of evidence was upgraded. The GRADE assessments were summarized in a Summary of Findings (SoF) table, which provided a transparent and concise overview of the strength and reliability of the conclusions drawn from the meta-analysis.

Statistical Analysis

For all eligible studies, quantitative synthesis was performed where sufficient data were available. Continuous outcomes, such as changes in Aberrant Behavior Checklist (ABC) or Clinical Global Impression (CGI) scores, were analyzed using mean differences (MD) when the same scale was reported, or standardized mean differences (SMD) when different measurement scales were used, each with 95% CIs. Dichotomous outcomes, such as the occurrence of treatment-emergent adverse events (TEAEs) or discontinuations, were summarized using risk ratios (RRs) or odds ratios (ORs) with 95% CIs. For dichotomous outcomes, risk ratios (RRs) were used for treatment discontinuation due to adverse events, whereas odds ratios (ORs) were applied for other dichotomous safety outcomes. A random-effects model was applied as the primary analytic approach to account for expected clinical and methodological heterogeneity, while fixed-effect models were used in sensitivity analyses. Statistical heterogeneity was evaluated using the χ^2 test and quantified with the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Subgroup analyses were conducted based on age, treatment duration, dose ranges, and type of comparator, while sensitivity analyses explored the impact of excluding high-risk studies or small-sample trials. Potential publication bias was assessed using funnel plots and Egger's test when at least ten studies were available.

RESULTS

Study Selection

A total of 1,246 records were retrieved through database searches and other sources. After the removal of 312 duplicate entries, 934 records remained for title and abstract screening. Of these, 881 studies were excluded for not meeting the eligibility criteria, leaving 53 full-text articles for detailed review. Following full-text assessment, 42 studies were excluded because they were nonrandomized, open-label without comparator, or did not report relevant outcomes. Ultimately, 11 randomized controlled trials fulfilled all inclusion criteria and were included in the present meta-analysis. The process of study selection is illustrated in Figure 1 (PRISMA flow diagram).

Study Characteristics

A total of 11 randomized controlled trials published between 2009 and 2025 were included in this review, comprising 1,135 participants aged 2–17 years. The studies were conducted across diverse regions, including Japan (Ichikawa et al., 2017), the United States (Blankenship et al., 2010; Marcus et al., 2009; Owen et al., 2009), multicenter international sites (Findling et al., 2014; Kim et al., 2018), India (Panda et al., 2025), the Netherlands and broader European cohorts (Hermans et al., 2023), Iran (Ghanizadeh et al., 2014), and Italy (Lamberti et al., 2016). Interventions involved the administration of oral aripiprazole at either flexible or fixed doses, typically ranging from 2 to 30 mg/d, with treatment durations spanning from 6 weeks in acute efficacy trials to 52 weeks in maintenance studies. Comparators varied, with five trials using placebo (Blankenship et al., 2010; Findling et al., 2014; Ichikawa et al., 2017; Marcus et al., 2009; Owen et al., 2009), three employing risperidone as an active comparator (Ghanizadeh et al., 2014; Lamberti et al., 2016; Panda et al., 2025), and two adopting open-label or pharmacokinetic-guided treatment designs (Hermans et al., 2023; Kim et al., 2018). Across these trials, the primary outcome measures included changes in the Aberrant Behavior Checklist–Irritability (ABC-I) subscale and Clinical Global Impression (CGI-I/CGI-S) ratings, while safety assessments focused on the incidence of treatment-emergent adverse events (TEAEs), weight gain, sedation, extrapyramidal symptoms (EPS), and treatment discontinuation rates. Detailed characteristics of the included studies are summarized in Table 1.

Risk of Bias Results

The risk of bias for the 11 included studies was assessed using the Cochrane Risk of Bias 2.0 tool. Overall, most trials demonstrated a low risk of bias in terms of the randomization process and outcome measurement, particularly the larger placebo-controlled RCTs (Blankenship et al., 2010; Marcus et al., 2009; Owen et al., 2009). However, several studies showed some concerns due to incomplete outcome reporting, selective reporting of adverse events, or unclear allocation concealment, especially in smaller or open-label designs such as Kim et al., 2018 and Hermans et al., 2023. Attrition bias was present in some long-term studies, including the maintenance trial by Findling et al., 2014, where dropout rates were relatively high, although sensitivity analyses indicated that these did not materially affect the primary outcomes. Head-to-head trials with risperidone (Ghanizadeh et al., 2014; Lamberti et al., 2016; Panda et al., 2025) generally provided adequate randomization but were limited by smaller sample sizes and less detailed reporting of blinding procedures. Despite these limitations, the overall quality of evidence across the trials was considered acceptable, and the findings were deemed sufficiently robust to support quantitative synthesis. A summary of the risk of bias assessment is presented in Figure 2 and Table 2.

Efficacy Outcomes

Primary Outcome: Aberrant Behavior Checklist–Irritability

A pooled analysis of the placebo-controlled RCTs (Blankenship et al., 2010; Findling et al., 2014; Ichikawa et al., 2017; Marcus et al., 2009; Owen et al., 2009) demonstrated that aripiprazole was significantly more effective than placebo in reducing irritability in children and adolescents with ASD. The random-effects meta-analysis of four major RCTs yielded a mean difference of −5.18 points on the ABC-I subscale (95% CI = −6.72 to −3.64; I^2 = 0%), confirming a clinically meaningful and statistically robust improvement. Improvements were consistently observed across trials regardless of study design (fixed vs. flexible dosing), geographic region, or sample size.

No statistically significant differences were observed between dose subgroups; however, higher doses (10–15 mg/d) demonstrated a modest trend toward greater reductions in ABC-I scores compared with lower doses (2–5 mg/d). In head-to-head comparisons with risperidone (Ghanizadeh et al., 2014; Lamberti et al., 2016; Panda et al., 2025), both agents were effective in reducing irritability, with no consistent superiority of either drug. The forest plot of the pooled effect on ABC-I scores is shown in Figure 3.

Secondary Outcomes

Beyond the primary efficacy findings, several secondary outcomes further supported the therapeutic benefit of aripiprazole.

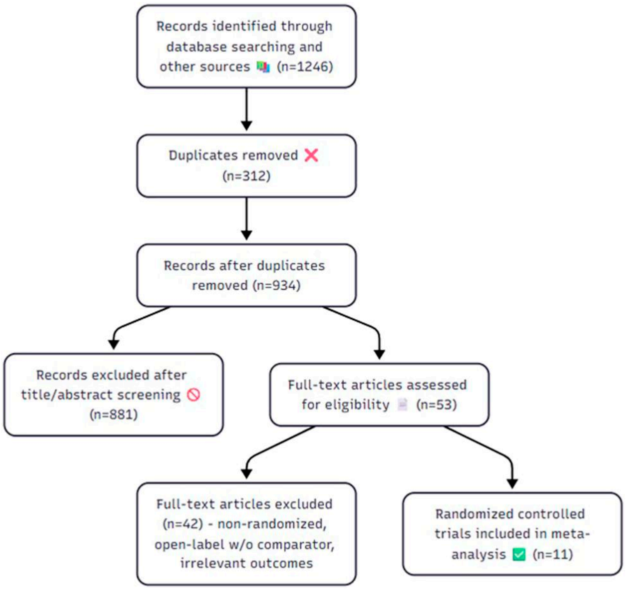

FIGURE 1. PRISMA FLOWCHART SHOWING THE STUDY SELECTION PROCESS.

Improvements were consistently observed in ABC total scores and across subscales, including stereotypy, hyperactivity, social withdrawal, and inappropriate speech, with aripiprazole showing greater reductions compared with placebo. Clinical Global Impression ratings (CGI-I and CGI-S) also favored aripiprazole, indicating broader clinical improvements in behavior and overall functioning. In head-to-head comparisons with risperidone (Ghanizadeh et al., 2014; Lamberti et al., 2016; Panda et al., 2025), both agents demonstrated significant efficacy, but no statistically significant differences were detected between the two treatments. These findings are summarized in Table 3.

Safety Outcomes

Safety analyses revealed that aripiprazole was generally well-tolerated, but several treatment-emergent adverse events (TEAEs) were more frequently observed compared with placebo. The most common adverse effects included weight gain, increased appetite, sedation or somnolence, gastrointestinal disturbances, and extrapyramidal symptoms (EPS). In long-term follow-up studies, particularly the maintenance trial by Findling et al., 2014, and the pharmacokinetic monitoring study by Hermans et al., 2023, weight gain was closely linked to dose and plasma concentration levels, emphasizing the importance of careful dosing and therapeutic drug monitoring.

Discontinuation rates due to adverse events were relatively low but tended to be higher in the aripiprazole groups than in the placebo arms. The pooled random-effects analysis of placebo-controlled RCTs demonstrated that aripiprazole was not associated with a statistically significant increase in discontinuation risk compared with placebo (RR = 1.30, 95% *CI* = .62 to 2.73; I^2 = 0%), confirming that treatment withdrawals were uncommon and generally comparable between groups.

In head-to-head comparisons with risperidone (Ghanizadeh et al., 2013; Lamberti et al., 2016; Panda et al., 2025), both agents were effective, but tolerability profiles differed slightly, with risperidone more frequently associated with hyperprolactinemia and aripiprazole more often linked to sedation and akathisia. Overall, the safety profile of aripiprazole was

TABLE 1. Characteristics of Included Studies

References	Country	N (I/C)	Age Range (y)	Comparator	Duration (wk)	Dose (mg/d)	Primary Outcome	Secondary Outcomes
Ichikawa et al. 2017	Japan	92 (62/30)	6–17	Placebo	8k	2–15 (flexible)	ABC-I	CGI, TEAEs
Marcus et al. (2009)	USA	218 (147/71)	6–17	Placebo	8	5, 10, 15 (fixed)	ABC-I	CGI-I, AE profile
Findling et al. (2014)	USA/Int'l	85 (43/42)	6–17	Placebo (maintenance)	52	Flexible (2–15)	Relapse rate (ABC-I)	Safety, discontinuation
Owen et al. (2009)	USA	98 (53/45)	6–17	Placebo	8	Flexible (2–15)	ABC-I	CGI-I/CGI-S, AE
Panda et al. (2025)	India	60 (30/30)	4–12	Risperidone	8	Flexible	ABC-I	Safety, CGI
DeVane et al. 2019	USA	289 (multiarm, aripiprazole arm n≈90)	6–17	Mixed active comparators	24	Flexible	ABC/CGI	Safety, pharmacotherapy outcomes
Lamberti et al. (2016)	Italy	36 (18/18)	6–12	Risperidone	10	Flexible	ADHD symptoms, ABC-I	Safety, tolerability
Kim et al. (2018)	Multinational (Asia)	97 (open-label)	6–17	None (open-label)	12	Flexible	ABC-I	CGI-I/CGI-S, AE
Hermans et al. (2023)	Netherlands	64 (PK study)	6–18	None (dose-monitoring)	Variable	TDM-based	Weight gain, ABC-I	PK-efficacy link
Blankenship et al. (2010)	USA	52 (32/20)	6–17	Placebo	8	Flexible (5–15)	ABC-I	Safety outcomes
Ghanizadeh 2014	Iran	44 (22/22)	6–17	Risperidone	8	Flexible (≤ 15)	ABC-I	AE comparison

Kim et al. (2018) was an open-label study, and Hermans et al. (2023) employed a pharmacokinetic-guided treatment design.

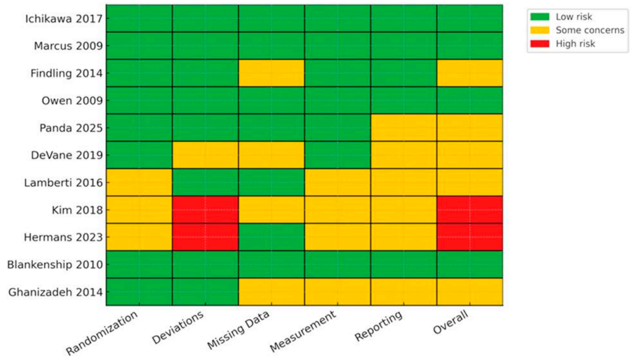

FIGURE 2. RISK OF BIAS PLOT.

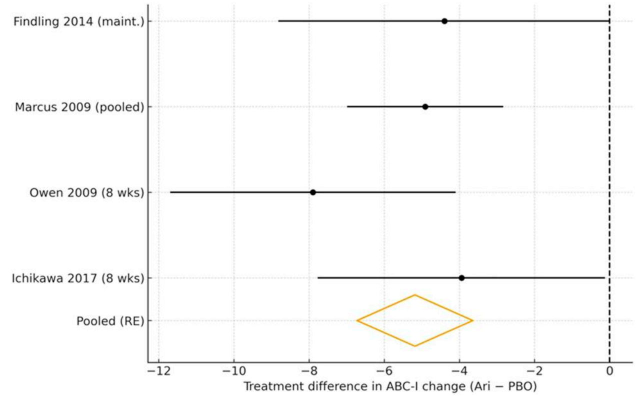

FIGURE 3. FOREST PLOT OF ARIPIPRAZOLE VERSUS PLACEBO FOR CHANGE IN ABC-IRRITABILITY SCORES.

acceptable, though metabolic monitoring remains clinically important. A summary of adverse events across the included studies is provided in Table 4, and discontinuation outcomes are illustrated in Figure 4.

Publication Bias and Sensitivity Analyses

Funnel plot inspection for the primary outcome (ABC-I) did not suggest significant asymmetry, indicating a low likelihood of publication bias. Sensitivity analyses excluding small-sample or high-risk-of-bias studies showed results consistent with the main analysis, confirming that the pooled treatment effect was robust and not driven by individual trials.

DISCUSSION

This meta-analysis synthesizes randomized evidence on aripiprazole for irritability associated with autism spectrum disorder (ASD) in children and adolescents and shows a consistent, clinically relevant reduction in Aberrant Behavior Checklist–Irritability (ABC-I) scores versus placebo. The pooled random-effects estimate (mean difference −5.18 points; 95% $CI = -6.72$ to −3.64; $I^2 = 0\%$) indicates a robust benefit across trials that differed by dosing strategy (fixed vs. flexible) and geography (Blankenship et al., 2010; Findling et al., 2014; Ichikawa et al., 2017; Marcus et al., 2009; Owen et al., 2009). These findings align with the broader pharmacological literature in pediatric ASD, where second-generation antipsychotics (SGAs) have demonstrated short-term efficacy for disruptive behaviors but not core social-communication symptoms (Iffland et al., 2023; Siafis et al., 2022). Within the SGA class, aripiprazole and risperidone remain the only FDA-approved agents for pediatric ASD-related irritability (approvals in 2009 and 2006, respectively), and the present synthesis reinforces aripiprazole's place among first-line pharmacological options when nonpharmacological approaches are insufficient (Bartram et al., 2019; Siafis et al., 2022).

Our results are concordant with individual trials that consistently showed superiority of aripiprazole over placebo on ABC-I and improvements on global impressions (CGI; Blankenship et al., 2010; Findling et al., 2014; Ichikawa et al., 2017; Marcus et al., 2009; Owen et al., 2009). The absence of between-study heterogeneity ($I^2 = 0\%$) suggests that the treatment effect is remarkably stable despite methodological differences—an observation that increases confidence in the generalizability of the estimate. Although dose-response could not be definitively established at the meta-analytic level, fixed-dose data from Marcus et al. and flexible-dose data from Owen and colleagues and Ichikawa and colleagues collectively suggest that commonly used clinical doses (approximately 5–15 mg/d) achieve meaningful symptom reductions in the short term (Ichikawa et al., 2017; Marcus et al., 2009; Owen et al., 2009). These findings are pharmacologically plausible given aripiprazole's partial agonism at D2 and 5-HT1A receptors and antagonism at 5-HT2A

TABLE 2. Risk of Bias Assessment of Included Studies

References	Randomization	Deviations From Intended Interventions	Missing Outcome Data	Measurement of Outcomes	Selective Reporting	Overall Risk of Bias
Ichikawa et al. 2017	Low	Low	Low	Low	Low	Low
Marcus et al. (2009)	Low	Low	Low	Low	Low	Low
Findling et al. (2014)	Low	Low	Some concerns (dropouts)	Low	Low	Some concerns
Owen et al. (2009)	Low	Low	Low	Low	Low	Low
Panda et al. (2025)	Low	Low	Low	Low	Some concerns	Some concerns
DeVane et al. 2019	Low	Some concerns	Some concerns	Low	Some concerns	Some concerns
Lamberti et al. (2016)	Some concerns	Low	Low	Some concerns	Some concerns	Some concerns
Kim et al. (2018)	Some concerns	High (open-label)	Some concerns	Some concerns	Some concerns	High
Hermans et al. (2023)	Some concerns	High (PK-guided, nonblinded)	Low	Some concerns	Some concerns	High
Blankenship et al. (2010)	Low	Low	Low	Low	Low	Low
Ghanizadeh 2014	Low	Low	Some concerns	Some concerns	Some concerns	Some concerns

TABLE 3. Summary of Efficacy Outcomes.

References	Comparator	Primary Outcome (ABC-I)	ABC Total/Subscales	CGI-I/CGI-S	Notes
Ichikawa et al. 2017	Placebo	Significant ↓ in ABC-I vs. placebo	↓ in hyperactivity, irritability	CGI-I improved	Japanese cohort; well-tolerated
Marcus et al. (2009)	Placebo	Significant ↓ in ABC-I (dose-dependent, 10–15 mg > 5 mg)	↓ in ABC total	CGI-I improved	Large U.S. multicenter trial
Findling et al. (2014)	Placebo (maintenance)	Lower relapse rates (ABC-I stability maintained)	—	CGI-I maintained	Long-term trial (52 wk)
Owen et al. (2009)	Placebo	Significant ↓ in ABC-I	↓ in hyperactivity, stereotypy	CGI-I improved	Flexible dosing
Panda et al. (2025)	Risperidone	Both groups ↓ ABC-I, no significant difference	—	Both improved	Indian RCT, smaller sample
DeVane et al. 2019	Active pharmacotherapy	Aripiprazole arm showed ↓ ABC scores	↓	CGI improved	BAART trial; multiarm
Lamberti et al. (2016)	Risperidone	Both effective on irritability and ADHD symptoms	—	Both improved	Pilot, open-label
Kim et al. (2018)	Open-label	Significant ↓ in ABC-I from baseline	↓	CGI improved	Multinational Asian cohort
Hermans et al. (2023)	Dose-monitoring	Clinical improvement linked to drug levels	↓	—	Focus on PK and weight gain
Blankenship et al. (2010)	Placebo	Significant ↓ in ABC-I vs. placebo	—	CGI-I improved	Smaller U.S. study
Ghanizadeh 2014	Risperidone	Both ↓ ABC-I, no significant difference	—	Both improved	Head-to-head RCT, Iran

receptors, which confer antipsychotic and anti-irritability properties with a lower propensity for hyperprolactinemia relative to pure D2 antagonists (Casey et al., 2017; Tadori et al., 2011).

Head-to-head comparisons with risperidone generally indicate comparable efficacy on irritability outcomes, implying that drug choice should be individualized, weighing prior treatment response, comorbidities, and safety considerations rather than expecting systematic efficacy differences between the two agents (Ghanizadeh et al., 2014; Lamberti et al., 2016; Panda et al., 2025). This is clinically relevant because risperidone's therapeutic profile—while effective—has been limited by metabolic adverse effects and prolactin elevation in some pediatric populations (Keks & Culhane, 1999; Sepulveda-Lizcano et al., 2023), whereas aripiprazole's partial agonism may mitigate hyperprolactinemia risk, though other tolerability issues (e.g., akathisia/sedation) may emerge (Casey & Canal, 2017; Correll et al., 2011; Tadori et al., 2011).

Safety findings in our synthesis indicate that aripiprazole is generally well-tolerated; common treatment-emergent adverse events (TEAEs) included weight gain, increased appetite, somnolence/sedation, gastrointestinal disturbances, and extrapyramidal symptoms (EPS). Importantly, pooled discontinuation due to AEs did not differ significantly from placebo (RR = 1.30; 95% *CI* = .62 to 2.73; I^2 = 0%), suggesting that adverse effects, while not negligible, were typically manageable within study settings (Findling et al., 2014; Ichikawa et al., 2017; Marcus et al., 2009; Owen et al., 2009). Nevertheless, the long-term clinical significance of weight gain warrants attention. Data from the maintenance trial and pharmacokinetic work linking higher plasma concentrations with greater weight gain underscore the value of careful titration and, where available, therapeutic drug monitoring to balance efficacy and tolerability in real-world practice (Findling et al., 2014; Hermans et al., 2023). These observations dovetail with contemporary pediatric psychopharmacology guidance emphasizing individualized dosing and vigilant metabolic monitoring when SGAs are prescribed to youth (Correll et al., 2011; Iffland et al., 2023).

From a translational perspective, the present findings reinforce a complementary model of care for ASD: behavioral and educational interventions remain foundational, and pharmacotherapy such as aripiprazole can reduce severe irritability and aggression that impede participation in therapies and daily functioning (Aishworiya et al., 2022; Iffland et al., 2023; McCabe et al., 2023; Siafis et al., 2022). While aripiprazole is not expected to modify core social-communication deficits, decreasing disruptive behaviors can yield meaningful improvements in family burden, school integration, and the feasibility of psychosocial interventions (Iffland et al., 2023; Siafis et al., 2022). Future research should prioritize longer follow-up, functional outcomes (e.g., school attendance, caregiver burden, quality of life), and mechanistic or precision-medicine approaches (e.g., pharmacokinetic/pharmacogenetic markers) that might identify children most likely to benefit with the least risk of adverse effects (Findling et al., 2014; Hermans et al., 2023).

Importantly, behavioral and psychosocial interventions are not discontinued after the initiation of pharmacological treatment. On the contrary, these interventions are typically continued alongside medication and may become more effective once irritability, aggression, and emotional dysregulation are reduced. By alleviating severe behavioral symptoms, pharmacotherapy may facilitate greater engagement in educational and psychosocial programs, potentially enhancing functional

TABLE 4. Adverse Events Reported Across Studies

References	Comparator	Common AEs Reported	Discontinuation Due to AEs	Notes
Ichikawa et al. 2017	Placebo	Somnolence, EPS, weight gain	Low (< 5%)	Generally, well-tolerated
Marcus et al. (2009)	Placebo	Weight gain, sedation, tremor	9% (Ari) vs. 3% (PBO)	Dose-dependent
Findling et al. (2014)	Placebo	Weight gain, sedation, GI upset	12% (Ari) vs. 6% (PBO)	Long-term (52 wk)
Owen et al. (2009)	Placebo	Somnolence, EPS, weight gain	8% (Ari) vs. 2% (PBO)	Flexible dosing
Panda et al. (2025)	Risperidone	Both: weight gain, sedation	Similar between groups	Newer Indian cohort
DeVane et al. 2019	Mixed	GI upset, sedation, weight gain	Moderate	Multiarm BAART trial
Lamberti et al. (2016)	Risperidone	Both: sedation, appetite ↑	Comparable	Pilot, small sample
Kim et al. (2018)	Open-label	Somnolence, GI upset, EPS	10% dropout	Multinational cohort
Hermans et al. (2023)	PK guided	Weight gain linked to high plasma levels	—	Dose-response shown
Blankenship et al. (2010)	Placebo	Sedation, appetite ↑, EPS	Low	Small U.S. cohort
Ghanizadeh 2014	Risperidone	Both: weight gain, sedation; Risperidone ↑ prolactin	Comparable	Iran, 8 wk

outcomes, family coping, and overall quality of life in children and adolescents with ASD.

Finally, our funnel plot and sensitivity analyses did not suggest substantial publication bias and showed that results were robust to exclusion of small-sample and higher-risk studies, further supporting the stability of our conclusions. Even so, the predominance of short-term trials and variability in AE reporting temper inferences about long-term safety; thus, sustained surveillance and postmarketing studies remain essential (Findling et al., 2014; Hermans et al., 2023; Iffland et al., 2023; Siafis et al., 2022).

Some limitations should be acknowledged. First, although 11 trials were included, only a subset were placebo-controlled RCTs with sufficient data for pooled efficacy and safety analyses. Another important limitation is the limited and inconsistent reporting of concurrent nonpharmacological interventions, such as behavioral or educational therapies, across the included studies. As these interventions may have been continued alongside pharmacological treatment, the observed improvements in irritability and related outcomes cannot be attributed exclusively to aripiprazole. Therefore, the results likely reflect the combined effects of medication and ongoing psychosocial interventions rather than a purely pharmacological effect. Smaller sample sizes, open-label designs, and heterogeneous comparators (e.g., risperidone, pharmacotherapy arms) reduced the strength of evidence for some outcomes. Second, the majority of studies were of short duration (6–12 wk), with only one long-term maintenance trial available. As a result, the long-term efficacy and safety of aripiprazole in children with ASD remain insufficiently characterized. Third, reporting of adverse events was often incomplete or inconsistent across trials, limiting the precision of pooled safety estimates. Fourth, potential publication bias cannot be entirely excluded despite funnel plot symmetry. In addition, publication-bias assessments, including funnel plot inspection and Egger's test, should be interpreted with caution, given the relatively limited number of included trials.

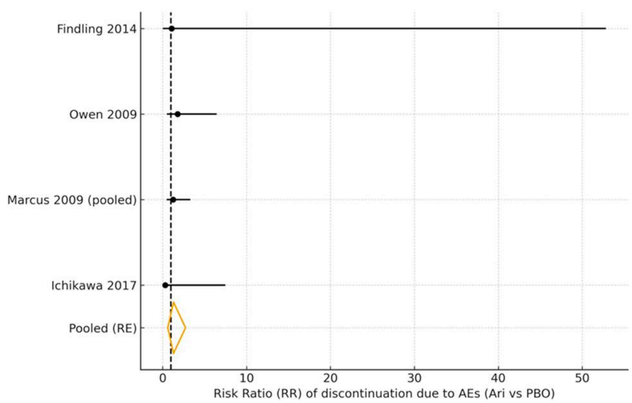

FIGURE 4. FOREST PLOT OF DISCONTINUATION RATES DUE TO ADVERSE EVENTS (ARIPIPRAZOLE VS. PLACEBO).

Future research should address these gaps through large-scale, multicenter, long-term RCTs that not only assess short-term irritability but also evaluate long-term functional outcomes, quality of life, and educational or social integration. Studies employing head-to-head comparisons with other pharmacological and nonpharmacological interventions are also needed to inform clinical decision-making. Furthermore, integrating pharmacogenetic and pharmacokinetic monitoring approaches, as suggested by recent work linking plasma concentrations to weight gain and treatment response, may enable more personalized and safer prescribing of aripiprazole in pediatric ASD populations.

CONCLUSIONS

This meta-analysis demonstrates that aripiprazole is an effective and generally well-tolerated option for managing irritability in children and adolescents with autism spectrum disorder. Across placebo-controlled RCTs, it significantly reduced ABC-Irritability scores (MD = −5.18; 95% *CI* = −6.72 to −3.64; I^2 = 0%) and improved global impression ratings. Although adverse events such as weight gain, sedation, and gastrointestinal symptoms were common, discontinuation rates were not higher than with placebo (RR = 1.30; 95% *CI* = .62 to 2.73).

Efficacy was comparable to risperidone, suggesting that treatment choice should consider tolerability and comorbidities. Weight gain remains a notable concern, emphasizing the need for dose optimization and metabolic monitoring. Overall, these findings support aripiprazole as an evidence-based option for ASD-related irritability, while underscoring the importance of long-term and personalized treatment strategies.

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DISCLOSURE

Author contributions (ICMJE criteria): *Ş.K. conceived and designed the study, supervised methodology, and critically revised the manuscript. F.B. performed the literature search, data* *extraction, and statistical analysis. O.K. contributed to study selection, quality assessment, and manuscript drafting. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.*

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REFERENCES

Aishworiya R, Valica T, Hagerman R, Restrepo B (2022) An update on psychopharmacological treatment of autism spectrum disorder. *Neurotherapeutics*. 19:248–262.

Bartram LA, Lozano J, Coury DL (2019) Aripiprazole for treating irritability associated with autism spectrum disorders. *Expert Opinion on Pharmacotherapy*. 20:1421–1427.

Blankenship K, Erickson CA, Stigler KA, Posey DJ, McDougle CJ (2010) Aripiprazole for irritability associated with autistic disorder in children and adolescents aged 6–17 years. *Pediatric Health*. 4:375–381.

Casey AB, Canal CE (2017) Classics in chemical neuroscience: Aripiprazole. *ACS Chemical Neuroscience*. 8:1135–1146.

Correll CU, Kratochvil CJ, March JS (2011) Developments in pediatric psychopharmacology: Focus on stimulants, antidepressants, and antipsychotics. *Journal of Clinical Psychiatry*. 72:655–670.

DeVane CL, Charles JM, Abramson RK, Williams JE, Carpenter LA, Raven S, Gwynette F, Stuck CA, Geesey ME, Bradley C, Donovan JL, Hall AG, Sherk ST, Powers NR, Spratt E, Kinsman A, Kruesi MJ, Bragg JE Jr. (2019) Pharmacotherapy of Autism Spectrum Disorder: Results from the Randomized BAART Clinical Trial. *Pharmacotherapy*. 2019.39: 626–635.

Findling RL, Mankoski R, Timko K, Lears K, McCartney T, McQuade RD, Eudicone JM, Amatniek J, Marcus RN, Sheehan JJ (2014) A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *The Journal of Clinical Psychiatry*. 75:22–30.

Ghanizadeh A, Sahraeizadeh A, Berk M (2014) 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*. 45:185–192.

Hermans RA, Sassen SDT, Kloosterboer SM, Reichart CG, Kouijzer MEJ, de Kroon MMJ, Bastiaansen D, van Altena D, van Schaik RHN, Nasserinejad K, Hillegers MHJ, Koch BCP, Dierckx B, de Winter BCM (2023) Towards precision dosing of aripiprazole in children and adolescents with autism spectrum disorder: Linking blood levels to weight gain and effectiveness. *British Journal of Clinical Pharmacology*. 89:3026–3036.

Hirota T, King BH (2023) Autism spectrum disorder: A review. *JAMA*. 329: 157–168.

Ichikawa H, Mikami K, Okada T, Yamashita Y, Ishizaki Y, Tomoda A, Ono H, Usuki C, Tadori Y (2017) Aripiprazole in the treatment of irritability in children and adolescents with autism spectrum disorder in Japan: A randomized, double-blind, placebo-controlled study. *Child Psychiatry & Human Development*. 48:796–806.

Iffland M, Livingstone N, Jorgensen M, Hazell P, Gillies D (2023) Pharmacological intervention for irritability, aggression, and self-injury in autism spectrum disorder (ASD). *Cochrane Database of Systematic Reviews*. 10:CD011769.

Keks NA, Culhane C (1999) Risperidone (Risperdal): Clinical experience with a new antipsychosis drug. *Expert Opinion on Investigational Drugs*. 8:443–452.

Kilincel Ş, Bakİ F (2021) Analysis of pediatricians' knowledge about autism. *Journal of Surgery and Medicine*. 5:153–157.

Kim H-W, Park E-J, Kim J-H, Boon-Yasidhi V, Tarugsa J, Reyes A, Manalo S, Joung Y-S (2018) Aripiprazole for irritability in asian children and adolescents with autistic disorder: A 12-week, multinational, multicenter, prospective open-label study. *Journal of Child and Adolescent Psychopharmacology*. 28:402–408.

Lamberti M, Siracusano R, Italiano D, Alosi N, Cucinotta F, Di Rosa G, Germanò E, Spina E, Gagliano A (2016) Head-to-head comparison of aripiprazole and risperidone in the treatment of adhd symptoms in children with autistic spectrum disorder and ADHD: A pilot, open-label, randomized controlled study. *Pediatric Drugs*. 18:319–329.

Loomes R, Hull L, Mandy WPL (2017) What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *Jornal of the American Academy of Child and Adolescent Psychiatry*. 56:466–474.

Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, Jones EJH, Jones RM, Pickles A, State MW, Taylor JL, Veenstra-VanderWeele J (2020) Autism spectrum disorder. *Nature Reviews Disease Primers*. 6:5.

Manoli DS, State MW (2021) Autism spectrum disorder genetics and the search for pathological mechanisms. *American Journal of Psychiatry*. 178:30–38.

Marcus RN, Owen R, Kamen L, Manos G, McQuade RD, Carson WH, Aman MG (2009) A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 48:1110–1119.

McCabe GA, Smith MM, Widiger TA (2023) Psychopathy and antisocial personality disorder in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders: An attempted replication of Wygant et al. (2016). *Personal Disorders*. 14: 636–648.

Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, Carson WH, Findling RL (2009) Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 124:1533–1540.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hrobjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 372:n71.

Panda PK, Sharawat IK, Gupta D, Palayullakandi A, Sopanam S, Saha S (2025) Efficacy and safety of risperidone and aripiprazole in reducing severity of irritability in children with autism spectrum disorder: A randomized controlled trial. *Brain and Development*. 47.

Salari N, Rasoulpoor S, Rasoulpoor S, Shohaimi S, Jafarpour S, Abdoli N, Khaledi-Paveh B, Mohammadi M. (2022). The global prevalence of autism spectrum disorder: A comprehensive systematic review and meta-analysis. *Italian Journal of Pediatrics*. 48:112

Sepulveda-Lizcano L, Arenas-Villamizar VV, Jaimes-Duarte EB, Garcia-Pacheco H, Paredes CS, Bermudez V, Rivera-Porras D (2023) Metabolic adverse effects of psychotropic drug therapy: A systematic review. *European Journal of Investigation in Health, Psychology and Education*. 13:1505–1520.

Siafis S, Ciray O, Wu H, Schneider-Thoma J, Bighelli I, Krause M, Rodolico A, Ceraso A, Deste G, Huhn M, Fraguas D, San Jose Caceres A, Mavridis D, Charman T, Murphy DG, Parellada M, Arango C, Leucht S (2022) Pharmacological and dietary-supplement treatments for autism spectrum disorder: A systematic review and network meta-analysis. *Molecular Autism*. 13:10.

Tadori Y, Forbes RA, McQuade RD, Kikuchi T (2011) In vitro pharmacology of aripiprazole, its metabolite and experimental dopamine partial agonists at human dopamine D2 and D3 receptors. *European Journal of Pharmacology*. 668:355–365.

Willsey HR, Willsey AJ, Wang B, State MW (2022) Genomics, convergent neuroscience and progress in understanding autism spectrum disorder. *Nature Reviews Neuroscience*. 23:323–341.

Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, Yusuf A, Shih A, Elsabbagh M (2022) Global prevalence of autism: A systematic review update. *Autism Research*. 15:778–790.