

Pharmacologic Treatment of Severe Irritability and Problem Behaviors in Autism: A Systematic Review and Meta-analysis

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abstract

BACKGROUND: Autism spectrum disorder (ASD) is increasingly recognized as a public health issue. Irritability and aggression (IA) often negatively affect the lives of people with ASD and their families. Although many medications have been tested for IA in ASDs in randomized controlled trials (RCTs), critical quantitative analyses of these trials are lacking in the literature.

OBJECTIVES: To systematically review and quantitatively analyze the efficacy and safety of pharmacologic treatments for IA in youth with ASD.

DATA SOURCES: Studies were identified from Medline, PsycINFO, Embase, and review articles.

METHODS: Original articles on placebo-controlled RCTs of pharmacologic treatments of IA in youth age 2 to 17 years with ASD were included. Data items included study design, study goals, details of study participants, details of intervention, study results, statistical methods, side effects, and risks of bias. The primary study outcome measure was the effect size of reduction in the Aberrant Behavioral Checklist–Irritability (ABC-I) scores in the medication group, as compared with placebo, in RCTs using parallel groups design.

RESULTS: Forty-six RCTs were identified. Compared with placebo, 3 compounds resulted in significant improvement in ABC-I at the end of treatment. Risperidone and aripiprazole were found to be the most effective, with the largest effect sizes. Sedation, extrapyramidal side effects, and weight gain were assessed quantitatively.

CONCLUSIONS: Although risperidone and aripiprazole have the strongest evidence in reducing ABC-I in youth with ASD, a few other compounds also showed significant efficacy with fewer potential side effects and adverse reactions in single studies.



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Dr Fung participated in conceptualizing and designing the study and in data acquisition, analysis and interpretation of the data, and statistical analysis and drafted the initial manuscript; Drs Mahajan, Bernal, and Whitaker participated in conceptualizing and designing the study and in data acquisition and critical revision of the manuscript for important intellectual content; Ms Nozzolillo participated in conceptualizing and designing the study and in data acquisition, and she provided administrative, technical, and material support and reviewed the final manuscript; Dr Krasner participated in data acquisition and reviewed the final manuscript; Dr Jo participated in statistical analysis and critical revision of the manuscript for important intellectual content, and she provided administrative, technical, and

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Autism spectrum disorder (ASD) is characterized by deficits in social communication and interactions, as well as restricted and stereotypic behaviors. In addition to these core symptoms, children and adolescents with ASD often suffer from problem behaviors, such as symptoms of irritability and aggression (IA), which may manifest as tantrums, self-injury, and aggressive behaviors toward others.

Formal definition of *irritability* is scarce in the literature. According to Snaith and Taylor,¹ irritability is defined as a “feeling state characterized by reduced control over temper which usually results in irascible verbal or behavioral outbursts,” although this mood state may be present without observed manifestation. The developmental literature and studies suggest that irritability can be defined as “an excessive response to stimuli.”² Irritability is also a consequence of emotion dysregulation (a dysfunction of evidenced neurobiologic processes), which can lead to change in mood state and aggression (a behavior).¹ Emotion regulation may be defined as “the process of initiating, avoiding, inhibiting, maintaining, or modulating the occurrence, form, intensity, or duration of internal feeling states, emotion-related physiological, attentional processes, motivational states, and/or the behavioral concomitants of emotion in the service of accomplishing affect-related biological or social adaptation or achieving individual goals.”³ Emotion dysregulation, therefore, is the inability to regulate such process effectively.

Aggression is defined as hostile, injurious, or destructive behavior often caused by frustration.⁴ Aggression may be divided into 2 categories: impulsive and premeditated. Impulsive aggression has been shown as a possible consequence of emotion

dysregulation.⁵ In this article we focus primarily on the treatment of impulsive aggression, given its increased relevance in context of ASD. Impulsive aggression and its domains have been described by other terms in the literature. For example, “agitation” has been used to describe impulsive aggression, “self-injurious behaviors” describes inwardly driven aggression, and “temper outbursts/tantrums” is used to describe outwardly driven aggression that may be disruptive to the environment or may involve destruction of property.

Neurobiologically, emotion dysregulation may be considered as a common pathologic process underlying IA. The 2 major components of emotion regulation are top-down inhibition and bottom-up drive.⁴ Generally, the prefrontal cortex (PFC) and anterior cingulate cortex are thought to be the neural substrate for top-down inhibition, whereas the amygdala and insula are often associated with bottom-up drive. When these regions are dysfunctional, affected people may exhibit more severe irritability and impulsivity. In typically developing people, cognitive control has been shown to be associated with optimal functional connectivity between dorsolateral PFC and parietal cortex.⁶ In contrast, in ASD cognitive control has been shown to be controlled by the ventrolateral PFC and anterior cingulate cortex.⁷ Furthermore, recent evidence has shown that alterations of the GABAergic system in ASD were also present in some of the same areas responsible for top-down inhibition and bottom-up drive.^{8,9} Although evidence is emerging, additional research is needed to increase our understanding of the neurobiology of IA to allow the development of more effective interventions.

Approximately 20% of people with ASD exhibit IA at moderate to severe levels,¹⁰ with >50% exhibiting

significant emotion dysregulation.¹¹ These symptoms often cause significant challenges to people with ASD and their families and affect treatment implementation and long-term outcomes.¹¹ In an ideal setting, medications for IA in ASD are typically considered after medical problems and comorbid psychiatric disorders have been addressed and behavioral interventions have been unsuccessful or only partially effective. Clinical judgment may override these conditions in the event of emergencies involving severe agitation or aggression to self or others. Once the clinical situation is more stable, however, the clinician may revisit these conditions before committing to longer-term treatment with medication. Clinicians have used a wide variety of medications to treat IA, mostly on an off-label basis. In 2006, the US Food and Drug Administration (FDA) approved risperidone to treat irritability associated with ASD. The agency included the target behaviors (ie, aggression, deliberate self-injury, and temper tantrums) under the general heading of “irritability” based on 2 8-week, placebo-controlled trials of risperidone in 156 patients aged 5 to 16 years.^{12,13} Subsequently, aripiprazole was also approved for this purpose, with evidence from 2 randomized controlled trials (RCTs) supporting its efficacy and safety in the treatment of IA. Currently, risperidone and aripiprazole are the only medications approved by the FDA for the treatment of IA in people with ASD. Various RCTs of other pharmacologic agents have also been conducted for IA symptoms in ASD. The efficacy and safety profiles of both the FDA-approved and off-label medications for IA symptoms have not been quantitatively compared. Therefore, the aims of this study are to conduct a systematic review of the efficacy and safety of pharmacologic treatments targeting IA in youth with ASD and a meta-analysis comparing the efficacy and safety of atypical

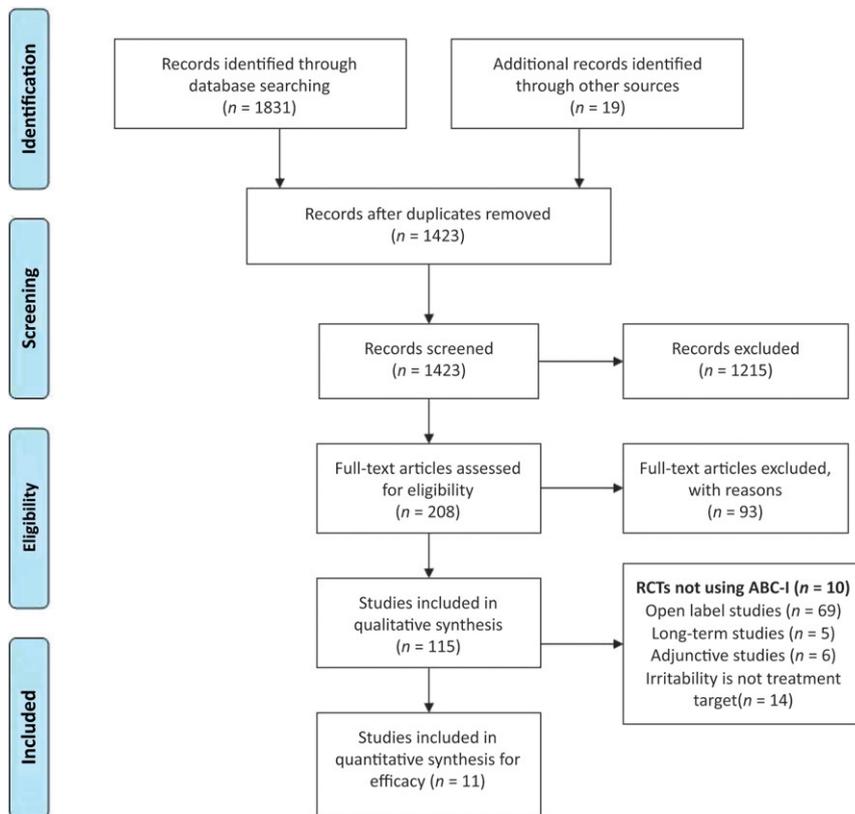


FIGURE 1
Flowchart showing the selection of trials.

antipsychotics versus placebo, as well as other medications (analyzed together) versus placebo.

METHODS

Research Questions

The key questions addressed in this study are: What is the evidence supporting the short- and long-term effectiveness of pharmacologic interventions on IA in youth with ASD? and What are the adverse events (AEs) associated with medications used in treating IA in youth with ASD?

Eligibility Criteria

Eligibility criteria for inclusion in the systematic review were a randomized placebo-controlled clinical trial, monotherapy, ages 2 to 17 years, research participants with ASD, use of a medication or nutraceutical treatment, use of a rating scale to

assess IA symptoms, human studies, >10 subjects in the medication treatment arm, an article presenting original data (ie, not reviews, opinion pieces, or editorials), and written in English. See Fig 1 for the flowchart showing the selection of trials based on the PRISMA format.¹⁴

Search Procedure

Studies were selected through a systematic multistage process. We searched Medline, PsycINFO, and Embase (published from database start date to November 2013) for pertinent articles combining 3 categories (ASD, IA, and treatments) of relevant keywords, Medical Subject Headings, and Emtree terms. (See Supplemental Information for more details.)

Data Extraction for Systematic Review

The evidence from included articles was abstracted systematically

through an adapted method of the US Preventive Services Task Force.¹⁵ All full-length articles were subjected to the eligibility criteria noted earlier, and studies that still met criteria after investigators read the complete article were selected for inclusion in the systematic review and meta-analysis. The risk of bias in individual studies was minimized by the use of a systematic approach in screening and data extraction. Screening of articles was conducted between June 2012 and September 2013 by 8 investigators. Each investigator independently assessed a subset of titles and associated abstracts to select articles for full-text review.

Data extraction from the full-text articles was performed between April and November 2013 by the same 8 investigators. All full-length articles were again subjected to the eligibility criteria noted earlier, and studies that still met criteria after investigators read the complete article were selected for inclusion in the systematic review and meta-analysis. The 8 investigators each independently abstracted one-eighth of the articles, with an overlapping subset (20%) to ensure consistency and to validate the process. Articles with discrepancies between data collected by 2 investigators were examined by a third investigator. Titles of articles were checked to eliminate articles in duplicate. Data items included study design (type of study [eg, RCT, case-control study], number of sites, details on randomization, comparison group(s), crossover or not, inclusion of discontinuation phase), study goals (safety, efficacy, effectiveness, discontinuation), study participants (specific inclusion and exclusion criteria, sample size), details of intervention (name of medication, dose, duration, information on titration), study results (primary and secondary outcomes [eg, Aberrant Behavioral Checklist-Irritability (ABC-I)], reported effect sizes,

means and standard deviations of outcome measures at baseline [ie, pretreatment] and end of treatment), statistical methods, harms (ie, side effects), and risks of bias. All data were captured online through Survey Monkey (see Supplemental Information for the data extraction form).

The criteria for evaluating the quality of each study were based on a modification of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.¹⁶ The overall quality of each study was determined by assessing the risks of bias and indirectness. Factors used to evaluate the risks of bias included carryover effects and factors related to allocation concealment. The main factor used to assess indirectness was the use of ABC-I as the primary outcome. As suggested by the GRADE system, all RCTs are first assigned a score of 4. The score is then lowered if serious risk of bias or indirectness is found; the score is elevated if other desirable factors including large effect size and large sample size are found.¹⁷ Details for the grading of study quality are included in Supplemental Information.

Meta-analysis

The primary outcome measure used by the FDA to approve the use of risperidone in treating IA in ASD was the change from baseline to endpoint on the ABC-I. The ABC-I is 1 of the 5 subscales of the ABC, a standardized parent-reported rating scale originally designed to assess treatment effects on problem behavior in people with intellectual disabilities. The ABC-I measures the emotional and behavioral symptoms of ASD, including aggression toward others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. Since its use in the seminal studies with risperidone,^{12,13} the ABC-I has been accepted as the gold standard for measuring IA in

medication trials for ASD. Therefore, we used the ABC-I as the primary endpoint for our meta-analysis in this study.

Studies using ABC-I with irritability as the treatment target (ie, ABC-I stated as primary endpoint in the manuscripts or baseline ABC-I ≥ 18) were included in the meta-analysis, but those that did not were reviewed only for the systematic review. Effect sizes (Cohen's *d*) for efficacy were calculated from the means and standard deviations at the end of treatment (placebo and medication) reported in the manuscripts.

$$\text{Cohen's } d = \frac{\text{ABC-I}_{\text{mean},p,\text{end}} - \text{ABC-I}_{\text{mean},m,\text{end}}}{\text{ABC-I}_{\text{stdev},\text{pool}}}$$

where

$\text{ABC-I}_{\text{mean},m,\text{end}}$ = Mean of ABCI in the medication group at the end of treatment

$\text{ABC-I}_{\text{mean},p,\text{end}}$ = Mean of ABCI in the placebo group at the end of treatment

$$\text{ABC-I}_{\text{stdev},\text{pool}} = \sqrt{\frac{(\text{ABC-I}_{\text{stdev},p})^2 + (\text{ABC-I}_{\text{stdev},m})^2}{2}}$$

Forest plots were obtained from atypical antipsychotics versus placebo and all other medications versus placebo. To eliminate the potential order effect in crossover studies on side effects, crossover studies were not assessed for side effects. According to Higgins et al,¹⁸ the test for heterogeneity was performed to demonstrate how variable the results are from a selected group of studies (see Supplemental Information for the definition of inconsistency).

The number-needed to treat (NNT) was calculated as the reciprocal of the percentage difference between research subjects who responded to medication compared with placebo. In assessing side effects of medications to patients, we chose to focus on somnolence or sedation, extrapyramidal symptoms (EPSs),

and weight gain because these are the major side effects reported clinically in patients receiving risperidone and aripiprazole. We assessed the magnitudes of weight gain by calculating effect sizes. Relative risks (RRs) and numbers needed to harm (NNHs) were calculated for somnolence or sedation and EPSs of each parallel groups study. The full definitions of NNT, NNH, and RR are presented in the Supplemental Information. In addition to somnolence or sedation, EPSs, and weight gain, we have included all statistically significant AEs, as compared with the placebo group. Furthermore, other AEs with >10% incidence and >25% increase over the placebo group are also reported.

RESULTS

Thirty-five RCTs with 1673 participants were identified for systematic review. Twenty-five of these used ABC-I to assess IA. Eleven of the 25 studies targeted irritability (baseline ABC-I ≥ 18 or ABC-I specified as primary endpoint) as the main outcome measure and were included in the meta-analysis for therapeutic effects of medications on IA (Table 1). These trials represented 5 compounds, with risperidone^{12,13,19-21} being the most tested (5 trials). Aripiprazole^{22,23} and valproate^{24,25} were each tested in 2 placebo-controlled RCTs. N-acetylcysteine and amantadine were tested in 1 RCT each. Among the 25 studies that reported ABC-I, 14 did not target IA as primary outcome (methylphenidate,^{26,27} atomoxetine,²⁸ citalopram,²⁹ clonidine,³⁰ dextromethorphan,³¹ levetiracetam,³² mecamlamine,³³ naltrexone,^{34,35} omega-3 fatty acid,³⁶ secretin,³⁷ tianeptine,³⁸ and venlafaxine³⁹; Supplemental Table 2); 5 studies did not report baseline ABC-I (clonidine, dextromethorphan, levetiracetam, naltrexone, and venlafaxine). The

10 RCTs that did not use ABC-I to assess IA (Supplemental Table 3) represented 8 placebo-controlled trials and 2 head-to-head trials. A baseline ABC-I cutoff for inclusion criteria is typically set at 18. Medications evaluated in trials in which participants had ABC-I ≥ 18 included risperidone (5 studies), aripiprazole (2 studies), valproate (2 studies), amantadine (1 study), haloperidol (1 study), clomipramine (1 study), and omega-3 fatty acid (1 study). The following medication trials had documented baseline ABC-I < 18 : methylphenidate (2 studies), atomoxetine (1 study), citalopram (1 study), mecamlamine (1 study), N-acetylcysteine (1 study), naltrexone (1 study), and tianeptine (1 study).

Efficacy

As shown in Table 1, compared with placebo, 4 compounds, risperidone,^{12,13,19–21} aripiprazole,^{22,23} valproate (1 of 2 studies²⁵), and N-acetylcysteine (NAC⁴¹), were shown to result in significant improvement in ABC-I at the end of treatment. The results of meta-analysis of atypical antipsychotics (risperidone and aripiprazole) are visually illustrated in a forest plot in Fig 2. Three of them showed a moderate to large effect size (risperidone [$d = 0.9$], aripiprazole [$d = 0.8$], and NAC [$d = 0.7$]). Amantadine was not found to show improvement on ABC-I; rather, it resulted in a significant decrease in ABC-Hyperactivity (ABC-H).⁴⁰

Among the studies with ABC-I without IA as treatment target, 3 showed a moderate effect size: clonidine ($d = 0.6$), methylphenidate ($d = 0.6$), and tianeptine ($d = 0.5$). Venlafaxine ($d = 0.4$) and naltrexone ($d = 0.35$) were found to have small effect sizes. Although citalopram revealed statistically significant improvement, its effect size was small ($d = 0.01$) at the end of treatment, with the change

being driven by pretreatment differences between the treatment and placebo groups. Based on ABC-I, atomoxetine,²⁸ dextromethorphan,³¹ levetiracetam,³² mecamlamine,³³ omega-3 fatty acid,³⁶ and secretin³⁷ showed no significant difference from placebo. However, atomoxetine and dextromethorphan were found to effect improvements in hyperactivity and impulsivity (ie, decreases in ABC-H).

Supplemental Table 3 displays the RCTs for irritability in youth with ASD that used measures other than ABC-I. On the Childhood Autism Rating Scale, risperidone was found to be effective in 1 of 2 RCTs.⁴² Haloperidol was effective in 1 of 2 trials when the Childhood Psychiatric Rating Scale was used. Using a parallel groups design, Campbell et al⁴³ failed to show a decrease in angry affect (irritability) in children with ASD. However, using a crossover design, Anderson et al⁴⁴ demonstrated that haloperidol resulted in a significant decrease in angry affect in children with ASD. Risperidone was also found to be superior to haloperidol in a head-to-head trial using ABC-Total.⁴⁵ On the Childhood Psychiatric Rating Scale, clomipramine,⁴⁶ naltrexone,⁴⁷ and a vitamin and mineral supplement (containing 19 vitamins and 9 minerals)⁴⁸ revealed improvement as compared with placebo. High-dose pyridoxine and magnesium (HDPM)⁴⁹ and tetrahydrobiopterin⁵⁰ were not statistically distinguishable from placebo.

Among the 5 RCTs testing risperidone, the heterogeneity was moderate ($I^2 = 40\%$). However, all studies yielded moderate to large effect sizes. Among the RCTs testing aripiprazole, the heterogeneity was substantial ($I^2 = 72\%$). Flexible dosing of aripiprazole appeared to be superior to fixed dosing. Dose-dependent effects were also observed in the study using fixed doses: Dose was positively correlated with effect

size. Overall NNT for risperidone was 2 (range: 2–3 in individual studies) at typical doses (between 1.2 and 1.8 mg), with the exception of 1 study that used a much lower dose (NNT = 9 at 0.15 mg). The NNT for aripiprazole was 3 when flexible dosing was used; however, fixed doses yielded higher NNTs (5–7). NNTs for all other compounds were not available, either because of the lack of response rate data or because of design limitations (we did not calculate NNT for crossover studies).

Two studies were conducted to establish the efficacy of long-term treatment with risperidone^{51,52} (Supplemental Table 4). Both studies included an open-label plus extension phase (32 weeks) followed by an 8-week randomized double-blind discontinuation phase. The mean ABC-I showed only a minor increase from 9.5 at the start to 10.8 at the end of the extension phase.⁵¹ Relapse rates after the discontinuation phase (without allowing all participants to return to baseline) in the placebo groups (62.5%⁵¹ and 66.7%⁵²) were significantly higher than in the risperidone groups (12.5%⁵¹ and 25.0%⁵²). Long-term efficacy and safety of aripiprazole in the treatment of IA of youth with ASD were assessed in a recent study⁵³ (Supplemental Table 4), which included a single-blind phase of flexibly dosed (2–15 mg/day) aripiprazole for 13 to 26 weeks, followed by a randomized placebo-controlled withdrawal phase. The primary endpoint was time from randomization to relapse, which was found to be the same between aripiprazole and placebo.

AEs

As demonstrated in Supplemental Table 5 and 6 among the 25 RCTs, 18 of them were parallel groups studies representing 11 compounds. Haloperidol⁴³ (NNH = 1), risperidone^{12,13,19,21,42,54} (NNH = 2), amantadine⁴⁰ (NNH = 10), and

TABLE 1 Characteristics of the 11 RCTs

| Source | Intervention | Mean Final Daily Dose | Duration (wk) | Crossover Study? | Primary Endpoints | N | Mean Age at Baseline, y | % Male | Baseline ABC-I, Mean (SD) | ABC-I at End of Treatment, Mean (SD) | P | Effect Size (Cohen's <i>d</i>) | NNT |
|-----------------------------------|------------------|-----------------------|---------------|------------------|-------------------|----|-------------------------|--------|---------------------------|--------------------------------------|-------|---------------------------------|------------------|
| RUPP Autism Network ¹² | Placebo | | 8 | No | ABC-I | 52 | 8.8 | 83 | 25.5 (6.6) | 21.9 (9.5) | <.001 | | |
| | Risperidone | 1.8 mg | | | | 49 | | 80 | 26.2 (7.9) | 11.3 (7.4) | | 1.24 | 2 |
| Pandina ¹³ | Placebo | | 8 | No | ABC-I | 28 | Range: 5–12 | NA | 21.6 (10.2) | 14.1 (11.3) | | | |
| | Risperidone | 1.4 mg | | | | 27 | | | 20.6 (8.1) | 7.2 (5.9) | .002 | 0.76 | 3 |
| Shea ¹⁹ | Placebo | | 8 | No | ABC-I | 39 | 7.3 | 82 | 21.2 (9.7) | 14.7 (8.4) | .001 | | |
| | Risperidone | 1.2 mg | | | | 40 | 7.6 | 73 | 18.9 (8.8) | 6.8 (5.8) | | 1.10 | 3 |
| Kent ²¹ | Placebo | | 6 | No | ABC-I | 30 | 9 | 89 | 28.9 (6.1) | 25.4 (10.7) | | | |
| | Risperidone | 0.15 mg | | | | 30 | 10 | 83 | 27.1 (6.3) | 19.7 (8.2) | .164 | 0.60 | 9 |
| | | 1.5 mg | | | | 31 | 9 | 90 | 28.0 (7.8) | 15.6 (6.5) | <.001 | 1.11 | 2 |
| Hellings ²⁰ | Placebo | | 4 | Yes | ABC-I | 40 | 22 (range: 8–56) | 58 | 19.2 (10.0) | 18.2 (12.4) | | | N/A ^a |
| | Risperidone | 1 mg | | | | | | | 19.2 (10.0) | 11.2 (9.3) | .000 | 0.65 | |
| | | 2 mg | | | | | | | 19.2 (10.0) | 13.3 (8.9) | .000 | 0.46 | |
| Owen ²² | Placebo | | 8 | No | ABC-I | 51 | 8.8 | 86 | 30.8 (6.5) | 25.8 (6.5) | | | |
| | Aripiprazole | Flexible | | | | 47 | 9.7 | 89 | 29.6 (6.4) | 16.7 (6.5) | <.001 | 1.41 | 3 |
| Marcus ²³ | Placebo | | 8 | No | ABC-I | 52 | 10.2 | 92 | 28.0 (6.9) | 19.6 (7.3) | | | |
| | Aripiprazole | 5 mg | | | | 53 | 9.0 | 89 | 28.6 (7.6) | 16.2 (7.3) | .032 | 0.47 | 5 |
| | | 10 mg | | | | 59 | 10 | 85 | 28.2 (7.4) | 15.0 (7.2) | .008 | 0.64 | 7 |
| | | 15 mg | | | | 54 | 9.5 | 83 | 28.9 (6.4) | 14.5 (6.7) | .001 | 0.77 | 6 |
| Hollander ²⁵ | Placebo | | 12 | No | ABC-I, CGI-I | 11 | 9.0 | 90 | 20.3 (7.4) | 17.7 (7.9) | .048 | 0.44 | N/A ^b |
| Hellings ²⁴ | Valproate | ^c | | | | 16 | 9.7 | 81 | 22 (7.8) | 14.5 (6.7) | | | |
| | Placebo | | 8 | No | ABC-I | 14 | 12.1 | 78 | 21.9 (11.6) | 15.5 (10.4) | .650 | –0.28 | N/A ^d |
| King ⁴⁰ | Valproate | 20 mg/kg | | | | 16 | 10.3 | 67 | 23.3 (8.6) | 18.2 (8.8) | | | |
| | Placebo | | 4 | No | ABC-I, ABC-H | 20 | 7 | 95 | 18.7 | 17.5 | | NA ^e | NS ^b |
| Hardan ⁴¹ | Amantadine | 2.5 mg/kg | | | | 19 | | 79 | 19.1 | 17.0 | .180 | | |
| | Placebo | | 12 | No | ABC-I | 18 | 7.2 | 100 | 14.8 (9.6) | 13.1 (9.9) | | 0.71 | N/A ^b |
| | N-acetylcysteine | 2700 mg | | | | 15 | 7 | 83 | 16.9 (7.9) | 7.2 (5.7) | <.001 | | |

N/A, not available; NS, not significant; RUPP, Research Units on Pediatric Psychopharmacology.

^a Cannot be determined because of crossover design.

^b Cannot be determined because of lack of response rate data.

^c 25.5 mg/kg (responders); 22.7 mg/kg (nonresponders).

^d Response rates between placebo and medication arms are not statistically significant.

^e Cannot be determined because of lack of standard deviations of ABC-I data.

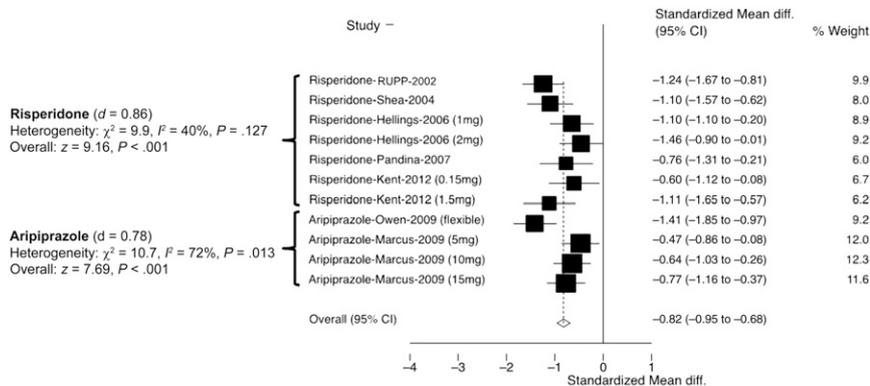


FIGURE 2

Mean score of aberrant behavioral checklist: irritability at end of treatment in RCTs of atypical antipsychotics for the treatment of irritability in autism spectrum disorder. Heterogeneity test: $\chi^2 = 28$, $df = 10$, $I^2 = 52\%$, $P = .022$. CI, confidence interval.

aripiprazole^{22,23} (NNH = 16) were found to cause somnolence or sedation. Risperidone^{12,13,19,21,42,54} (NNH = 6), haloperidol⁴³ (NNH = 10), and aripiprazole^{22,23} (NNH = 20) were shown to cause EPSs. A single EPS episode (drug relatedness is uncertain) was reported for NAC, yielding an NNH of 90. Finally, compared with placebo, aripiprazole ($d = 3.1$), risperidone ($d = 0.8$), and valproate ($d = 0.3$) were found to cause the most weight gain. Details on adverse events are included in the Supplemental Information.

Quality of Evidence

The determination of the quality of evidence for the 25 RCTs presented in Table 1 and Supplemental Table 2 is summarized in Supplemental Table 7. All RCTs of risperidone were found to have high quality of evidence (exception: moderate quality of evidence for Hellings et al²⁰). The quality of evidence for both RCTs on aripiprazole and a single RCT on NAC were also classified as high. With regard to the 2 RCTs on valproate, one was found to have high quality (Hollander et al²⁵), and the other revealed moderate quality of evidence (Hellings et al²⁴). The quality of evidence in the RCT on citalopram and secretin was classified as moderate. All other studies were found to have low quality of evidence.

DISCUSSION

This study is the most comprehensive systematic review and meta-analysis of pharmacologic treatments for IA in ASD to date. We analyzed 11 RCTs, consisting of 811 youth, to test whether pharmacologic monotherapy could improve ABC-I, a gold standard in evaluating IA, in people with ASD. Only 3 compounds showed moderate to large effect sizes for treating irritability in ASD: 2 atypical antipsychotic medications (risperidone and aripiprazole) and 1 antioxidant/glutamatergic modulator (NAC). Among the medications tested for target symptoms other than IA and whose assessments included ABC-I, 1 α_2 adrenergic agonist (clonidine), 1 psychostimulant (methylphenidate), and 1 tricyclic antidepressant (tianeptine) demonstrated moderate effect sizes in decreasing ABC-I. Many more compounds ($n = 8$) did not have evidence to support their efficacy for IA in ASD. The reason for more compounds failing to show efficacy is not clear, but some of the negative studies had small sample sizes. Therefore, it is possible that some of these negative studies may represent false negatives. Furthermore, as discussed earlier, the baseline ABC-I scores for participants in some studies (eg, atomoxetine, citalopram, mecamylamine, naltrexone) were

lower than the typical cutoff (ABC ≥ 18) for inclusion of a treatment study focusing on irritability.

Compared with placebo, risperidone and aripiprazole showed the most evidence of efficacy in treating irritability in youth with ASD. Both compounds showed large effect sizes for treating IA ($d = 0.9$ and 0.8 , respectively). Aripiprazole appeared to have a large heterogeneity in effect size, probably because of the differences in study design (ie, flexible dosing vs fixed dosing at 3 dose levels). Data from the long-term studies suggested that risperidone^{51,52} is effective in treating irritability and aggressive behaviors in children with ASD for up to 6 months.

Both risperidone and aripiprazole showed elevated rates of AEs in published RCTs. With regard to EPS, risperidone and aripiprazole showed NNHs of 7 and 20, respectively, in short-term (≤ 8 weeks) studies, with similar results in long-term studies.^{42,53} These NNHs are lower than those reported in RCTs in children with bipolar disorder, which could indicate more sensitivity to EPSs in children with ASD. Additionally, with regard to sedation, risperidone and aripiprazole yielded NNHs of 2 and 16, respectively, in short-term studies, with similar rates in long-term studies.^{42,53,54}

Based on effect size calculations for weight gain, aripiprazole results in larger burden on weight than risperidone (3.1 vs 0.9) in short-term studies. However, this finding was complicated by the lower (twofold) mean weight gain in the placebo groups of the aripiprazole studies compared with the risperidone studies and by the fact that the absolute excess over placebo in mean weight gain was greater for risperidone (1.6 kg) than for aripiprazole (1.1 kg). Interestingly, the weight gains associated with risperidone (5.3 kg) and aripiprazole

(4.4 kg) were found to be higher in another cohort composed primarily of youth with mood or psychotic disorders.⁵⁵ Longer-term studies^{42,54} both showed similar weight gain in the risperidone group (3.0 and 2.8 kg, respectively) at 6 months. In the only long-term (52-week) open-label trial of aripiprazole, mean change in body weight of participants from baseline to endpoint was 6.3 kg.⁵⁶ These results are counter to a prevailing clinical impression that aripiprazole causes less weight gain than risperidone. In a recent naturalistic study examining the ASD population in a tertiary care setting, the effects of risperidone and aripiprazole on body weight gain in long-term treatment were not significantly different.⁵⁷ Weight gain caused by these medications probably increases the risk of metabolic abnormalities, with 1 study finding that children with ASD treated with risperidone had significant rates of lipid elevations, including low-density lipoprotein (7%) and triglycerides (5%).⁵⁶ Furthermore, atypical antipsychotic medications were associated with an elevated risk of diabetes in a large sample of children with or without ASD.^{58,59}

As indicated earlier, the NNT for efficacy of IA treatment with risperidone was generally lower than that of aripiprazole. However, the NNH for EPSs and sedation with risperidone was also generally lower than that of aripiprazole. Both medications appeared to have similar impact on weight gain. However, in selecting between risperidone and aripiprazole, it is advisable that clinicians take into account the relative benefits and risks for each potential adverse effect in individual patients.

Eight medications in this study (Table 1 and Supplemental Table 2) were reported to reduce ABC-I significantly more than placebo.^{12,13,19–23,25–27,29,30,34,35,38,39,41,60} NAC, clonidine, methylphenidate, and tianeptine

yielded moderate to large effect sizes.^{26,27,30,38,41} In contrast to risperidone and aripiprazole, NAC, methylphenidate, and tianeptine did not cause significant somnolence, EPSs, or weight gain.^{26,27,38,41} However, findings from these studies are limited by the lack of replication because demonstrated efficacy and tolerability generally came from only 1 RCT (exception: methylphenidate). Furthermore, the treatment targets for clonidine, methylphenidate, and tianeptine were not irritability (ie, ABC-I was not indicated as primary endpoint and baseline ABC-I was ≤ 18). Additional large RCTs are needed to confirm that these medications are indeed effective in reducing IA. Furthermore, these medications lack long-term efficacy and safety data to support long-term use.

The antidepressant medications citalopram²⁹ (selective serotonin reuptake inhibitor) and venlafaxine³⁹ (serotonin–norepinephrine reuptake inhibitor) showed small effect sizes in efficacy for IA in 2 investigations, but IA was not the primary outcome measure in either study. Another tricyclic antidepressant, clomipramine, was found to be indistinguishable from placebo in 1 study.⁶⁰ Atomoxetine, a selective norepinephrine reuptake inhibitor, failed to show an effect in reducing IA in ASD.²⁸ Opioid receptor antagonists naltrexone and dextromethorphan showed mixed results: Naltrexone^{34,35} revealed a small effect size, and dextromethorphan³¹ showed no difference from placebo. Two antiepileptic medications (valproate^{24,25} and levetiracetam³²) had mixed results. Whereas one of the RCTs of valproate showed significant improvement in ABC-I,²⁵ the other did not.²⁴ The only RCT for levetiracetam in ASD was a negative study.³² Mecamylamine, a nicotinic acetylcholine receptor antagonist used for treating hypertension, failed to show an effect in treating IA in ASD.³³ Amantadine, a dopaminergic

agent used for treating Parkinson's disease, was also indistinguishable from placebo.⁴⁰ Omega-3 fatty acid³⁶ (antioxidant) and secretin³⁷ (endogenous hormone regulating secretions from the stomach and pancreas) also showed no significant advantage over placebo.

Finally, adjunctive treatments have been used to treat irritability in ASD. However, a discussion of these treatments was not included because the focus of this systematic review was primarily to capture the beneficial and adverse effects of pharmacologic monotherapies in ASD. Adjunctive treatments to atypical antipsychotics are emerging (Supplemental Table 8), but limited data are available to judge their efficacy.

We note several limitations of the current study. First, all studies used in the meta-analytic calculations were based on ABC-I. Other instruments for IA symptoms were used in only a handful of studies of disparate medications. Second, ABC-I captures an array of items associated with IA, but we are unable to determine which individual symptoms were most improved. There is only 1 published item-level analysis of the ABC-I in response to treatment in ASD: Compared with placebo, aripiprazole showed statistically significant improvement in 3 specific items of ABC-I.⁶¹ Third, our study did not control for differences in baseline ABC-I scores between active and placebo groups. This decision was made because of the lack of reporting of baseline scores in many studies. Fourth, many studies (eg, of citalopram) included in this systematic review did not have participants with substantial symptoms of irritability (typically with baseline ABC-I ≥ 18). On one hand, for studies with ABC-I ≤ 18 (eg, NAC), the studied participants did not have high enough IA-related symptoms. On the other hand, for other studies that showed lack of efficacy, the negative results might

be caused by the low irritability threshold for inclusion in the study, not the lack of therapeutic effect. Fifth, the primary endpoints for a number of included studies were not related to irritability. For example, the effects of methylphenidate on ABC-I may be secondary to the treatment of hyperactivity and impulsivity. Sixth, this meta-analysis did not control for treatment duration. The majority of the studies were between 6 and 12 weeks in duration. Seventh, the meta-analytic calculations for efficacy measures were obtained from acute treatment data only. Because of the differences in study designs, we did not compare data from short-term studies with long-term maintenance treatment studies. Eighth, ABC-I is an informant-based measure, and we are therefore limited to parents' subjective assessments of their child's behavior, albeit obviously sensitive to treatment effects. Ninth, AEs in most studies were not tracked with similar methods, and therefore it is possible that specific AEs might be missed because of differences in how they were tracked and documented. Finally, we did not include a discussion on behavioral treatment, because it is beyond the scope of the current study.

Second-generation antipsychotic medications are the only treatment to have shown support in more than a single study in the treatment of IA in ASD, but they are associated with significant AEs. Medications such as NAC and clonidine may have significantly better side effect profiles, but their beneficial effects have been reported only in single studies with small sample sizes. In addition to pharmacological treatments, behavioral and educational approaches in treating IA are crucial in practical settings; however, these interventions have not been examined in large trials. Furthermore, because the combination of appropriate medication and

cognitive behavioral therapy has been shown to have potential additional benefits over either treatment alone of other disorders (eg, depression and attention-deficit/hyperactivity disorder), testing combination strategies in ASD, especially in the higher-functioning youth, may potentially be more effective than pharmacologic or behavioral treatment alone.^{62,63} The only such study in ASD found that the addition of parent training in behavior management strategies to risperidone provided a small to medium additional benefit over risperidone alone ($d = 0.48$ on ABC-I), but the benefit was not significantly sustained >6 months later.⁶⁴

Several questions deserve additional study. Are there any identifiable changes early in the treatment phase that predict treatment outcomes? What are the outcome measures from short-term studies that predict long-term functional outcomes? Is there evidence supporting the effectiveness of some agents in 1 setting and not others? Is there evidence of effective augmentation strategies in the treatment of IA in ASD? What is the optimal duration of treatment?

Beyond practical questions about response to current treatments, the field needs to focus on the development of new treatments, including both behavioral and medication strategies. Advances in our understanding of the risk factors and underlying pathophysiology of ASD may provide avenues for new treatment approaches that may benefit core symptoms or associated IA symptoms. A specific understanding of the neural mechanisms that underlie IA symptoms in ASD could lead to new, targeted treatments, as well as allowing better prediction of response to current interventions.

In conclusion, we performed a systematic review and

meta-analysis of RCTs that showed efficacy of pharmacologic interventions in treating IA in ASD. Although risperidone and aripiprazole have the strongest evidence for reducing ABC-I in youth with ASD, they also have evidence for significant AEs for a subset of patients. A few compounds show promise in single pilot studies (clonidine and NAC), with less evidence of associated harms. Additional investigations of these compounds are warranted to confirm the preliminary findings.

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ABBREVIATIONS

| | |
|--------|-------------------------------------------------------------------|
| ABC: | Aberrant Behavioral Checklist |
| AE: | adverse event |
| ASD: | autism spectrum disorder |
| EPS: | extrapyramidal symptom |
| FDA: | Food and Drug Administration |
| GRADE: | Grading of Recommendations Assessment, Development and Evaluation |
| HDPM: | high-dose pyridoxine and magnesium |
| IA: | irritability and aggression |
| NAC: | N-acetylcysteine |
| NNH: | number needed to harm |
| NNT: | number needed to treat |
| PFC: | prefrontal cortex |
| RCT: | randomized controlled trial |
| RR: | relative risk |

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