META-ANALYSIS EMOTION & DYSREGULATION

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Systematic Review and Meta-analysis: Pharmacological and Nonpharmacological Interventions for Persistent Nonepisodic Irritability

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Objective: This meta-analysis examined the efficacy of available pharmacological and nonpharmacological interventions for irritability among youth with autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorders (DBD), disruptive mood dysregulation disorder (DMDD), and/or severe mood dysregulation (SMD).

Method: Literature searches were conducted in October 2020, resulting in 564 abstracts being reviewed to identify relevant papers, with 387 articles being reviewed in full. A random effects model was used for the meta-analysis, with subgroup meta-regressions run to assess effects of study design, intervention type, medication class, and clinical population.

Results: A total of 101 studies were included (80 pharmacological, 13 nonpharmacological, 8 combined). Despite high heterogeneity in effects ($I^2 = 94.3\%$), pooled posttreatment effect size for decreasing irritability was large (Hedges' $g = 1.62$). Large effects were found for pharmacological ($g = 1.85$) and nonpharmacological ($g = 1.11$) interventions; moderate effects were found for combined interventions relative to monotherapy interventions ($g = 0.69$). Antipsychotic medications provided the largest effect for reducing irritability relative to all other medication classes and nonpharmacological interventions. A large effect was found for youth with ASD ($g = 1.89$), whereas a medium effect was found for youth with ADHD/DMDD/DBD/SMD ($g = 0.64$).

Conclusion: This meta-analysis provides a comprehensive review of interventions targeting persistent nonepisodic irritability among youth with various psychiatric disorders. Strong evidence was found for medium-to-large effects across study design, intervention type, and clinical populations, with the largest effects for pharmacological interventions, particularly antipsychotic medications and combined pharmacological interventions, and interventions for youth with ASD.

Key words: irritability; pharmacological interventions; psychosocial interventions; ASD; ADHD

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Persistent nonepisodic irritability in children is one of the most common reasons for referrals to mental health professionals,[1] and has been linked to a host of negative long-term outcomes.[2,3] Irritability is a mood state, referring to inter-individual differences in proneness to anger that cause significant impairment or distress in the child's daily life.[4,5] In addition, it is an aspect of the negative affectivity domain of temperament, which captures variation in the intensity, duration, and regulation of children's angry mood and behavior.[6] Although irritability is a growing focus for psychiatric research and therapeutic interest,[7,8] there is limited empirical guidance regarding how to treat irritability and how its presence should alter the treatment of comorbid behavioral health disorders.[4,5] As such, there is a clear need for a meta-analysis of available evidence-based pharmacological and nonpharmacological interventions for persistent nonepisodic irritability among children with psychiatric disorders. We focus on irritability specifically in this review, instead of the broader domain of emotion dysregulation (ie, difficulty modifying emotions and behaviors to achieve a desired goal),[9] as the latter is much less frequently used as a treatment outcome in pharmacological interventions.[5]

Role of Irritability in Psychiatric Disorders

The concept of severe mood dysregulation (SMD) was created by the National Institute of Mental Health to foster the systematic assessment of nonepisodic irritability.[10]

Persistent nonepisodic irritability was formalized as a mental health disorder in the *DSM-5* as disruptive mood dysregulation disorder (DMDD), with the core criteria of chronic nonepisodic irritability and severe, recurrent temper outbursts.[11] However, persistent irritability in children and adolescents has been identified as a transdiagnostic marker for psychiatric disorders.[8,12] Specifically, irritability is a listed *DSM-5* symptom of DMDD, disruptive behavior disorders (DBD) such as oppositional defiant disorder, and internalizing disorders such as posttraumatic stress disorder, generalized anxiety disorder, and mood disorders (ie, major depressive and manic episodes). In addition, it is an associated feature of many other *DSM-5* disorders, including neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD).[11,13]

Interventions for Persistent Nonepisodic Irritability

Irritability is typically studied as a treatment outcome within the context of treatment of various *DSM-5* psychiatric disorders. For example, atypical antipsychotics in children with ASD and central nervous system (CNS) stimulants in children with ADHD have been found to reduce irritability.[14-16] A review conducted by Vidal-Ribas *et al.* (2016) conceptualized the status of irritability in psychiatry and focused on whether irritability can be differentiated from other psychiatric symptoms, whether it forms a distinct disorder (ie, able to be distinguished from depression and anxiety), and whether it is a meaningful predictor of clinical outcome.[4] They found that irritability is a distinct dimension with underlying neurophysiological differences (ie, altered activations in the amygdala, striatum, and frontal regions relative to those in youth without SMD, suggesting difficulties in emotion regulation, reward processing, and attentional control) and significant stability across time.[4] This review also highlighted that most knowledge about the treatment of irritability is based on effects of treatments for related conditions (eg, depression) or post hoc analyses of trial data. However, this review did not systematically analyze treatment options for irritability across psychiatric disorders in childhood. Similarly, Stringaris *et al.* (2018) reviewed psychological and pharmacological treatments for irritability.[13] Specifically, their review highlighted that several psychological treatments exist, but largely fall under 1 of 2 umbrella categories—parent management training (also referred to as behavioral parent training) and cognitive−behavioral therapy—with a handful of other, newer treatment approaches such as interpretation bias training still being explored.[13] With regard to pharmacological interventions, Stringaris *et al.* discussed the utility of various medications including CNS stimulants, atypical antipsychotics, selective serotonin reuptake inhibitors, and mood stabilizers (eg, lithium).[13] Although Stringaris *et al.* provided a detailed review of existing pharmacological and nonpharmacological interventions, no study to date has empirically assessed the efficacy of such interventions for improving irritability in children through a meta-analysis. Importantly, they also highlighted that it remains to be determined whether interventions for irritability work differently in youth with various *DSM-5* disorders.

The lack of empirical evidence regarding evidenced-based interventions for youth irritability has been theorized to contribute to the high rates of polypharmacy and associated treatment-related morbidity in children with persistent irritability.[17-21] For example, many youth with ADHD and persistent irritability are being increasingly prescribed mood stabilizers and antipsychotic medications, often before evidence-based interventions for ADHD, including behavioral parent training and CNS stimulants, have been optimized.[22,23] Treatment sequences are ideally derived from the extant literature base. For pediatric irritability, no prior work has examined the comparative efficacy of different intervention modalities across studies. Thus, the present study sought to address this need for a meta-analysis of the efficacy of available evidence-based pharmacological and nonpharmacological interventions for persistent nonepisodic irritability among children with ASD, ADHD, DBD, DMDD, and/or SMD. We chose to focus on youth with neurodevelopmental and externalizing disorders, given the high comorbidity among these disorders, the overlap in pharmacological interventions (eg, stimulants) used within these populations, and that many intervention studies for youth with internalizing disorders do not use measures with irritability specific outcomes (eg, Children's Depression Rating Scale–Revised, Young Mania Rating Scale). In addition, we examined relative effects of study design (open trial vs randomized controlled trial [RCT]) and intervention type (pharmacological, nonpharmacological, vs combined) among youth with ASD relative to youth with ADHD, DBD, DMDD, and/or SMD. These clinical subpopulations were selected given the overlap in etiology and evidence-based treatments (ie, stimulants and behavioral parent training) for youth with ADHD, DBD, DMDD, and SMD.

METHOD

Search Strategy

This systematic review and meta-analysis was not preregistered. Our aim was to identify published literature describing the evidence-based interventions for persistent nonepisodic irritability in youth with ASD, ADHD, DBD, DMDD, and SMD. Search strategies were undertaken across 5 databases, namely, Medline, PsychInfo, Embase, Cochrane Register of Controlled Trials, and Web of Science

Core Collection. Other sources searched were ClinicalTrials.gov, World Health Organization International Clinical Trial, European Union Clinical Trials Register, International Standard Randomized Controlled Trial Number registry, Agency for Healthcare Research and Quality, National Institute of Mental Health, and American Academy of Child and Adolescent Psychiatry. Google Scholar was also searched using the advanced search tool, limiting searches to government and organization domains. Search terms used were a combination of subject headings and text terms. A research librarian (AK) conducted searches using synonyms and combinations of the following search terms: therapy, irritability, and psychiatric disorders, in October 2020. Truncation of terms was used to capture variation in language. We looked at studies in the English language only. The reference sections of identified articles were also examined for additional relevant articles.

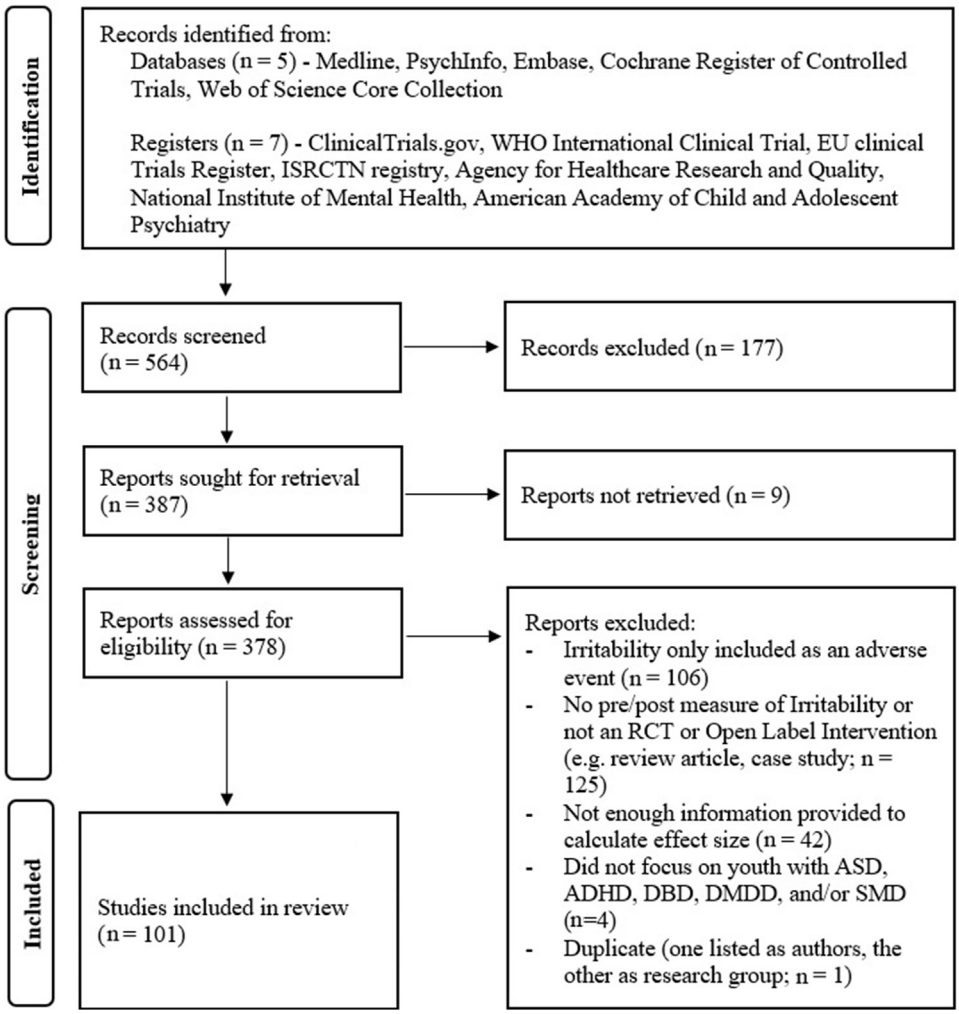
We excluded studies that: (1) were in foreign language, (2) targeted intellectual disability, traumatic brain injury, epilepsy, or an organic brain disorder only, (3) included only adult populations (ie, mean age was 18 years or higher), (4) did not involve an intervention, (5) the population was not diagnosed with 1 of the targeted neurodevelopmental or externalizing disorders (ie, ASD, ADHD, DBD, DMDD, and/or SMD), and (6) did not include a pre and post measure of irritability or did not provide enough information to calculate change in irritability. A 2-phase review process was used. First, 2 screeners, the first and second authors (RB and RB), independently screened the article titles and abstracts to identify relevant papers. Discrepancies were resolved by discussion. Second, full articles were obtained and 2 screeners (HE, DS, AC, CS; articles divided among the 4 screeners, all reviewed by 2) reviewed these to assess inclusion criteria. Discrepancies were resolved by discussion with the first author (RB). Figure 1 provides the full Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for identification of studies.

Pooled Effect Size Analyses

Standardized mean differences were calculated for all intervention studies, regardless of intervention type (ie, pharmacological, nonpharmacological, combined). Pre- and post-intervention means and standard deviations were used to calculate standardized mean differences for all irritability measures, in line with recommendations by Morris (2008),[24] which minimizes bias and enhances precision. When pharmacological interventions assessed irritability at multiple timepoints (eg, 2 weeks, 4 weeks, 6 weeks, 8 weeks), the post-intervention measure was the last time point of active treatment (eg, 8 weeks in this example). Effect sizes were calculated so that reductions in irritability were always scaled positively, whether calculated from pre- to post-intervention or between intervention and control groups. Furthermore, we elected to convert all mean differences to Hedges' g because of the variation in sample size and the significant number of pilot studies with relatively smaller samples.[25] Specifically, Hedges' g is a measure of effect size (sometimes referred to as a corrected effect size) that is similar to Cohen's d, but that outperforms Cohen's d when sample sizes are smaller than 20 (results are roughly equivalent for larger sample sizes). Some papers had multiple effects included because of more than 1 informant rating of irritability or more than 1 active treatment condition. Effects from the same study were weighted to account for nonindependence so that no single study or effect disproportionately accounted for the results.[26] Given the large range in sample sizes and methodological rigor of the included studies, a random effects model was used. and pooled effects were examined separately for all studies using pre and post data.

Subgroup analyses were also computed to compare pharmacological to nonpharmacological and interventions using both modalities (ie, combined interventions). Given that reporting pooled effect sizes from pre to post within only 1 group can yield bias, a second pooled effect was computed for studies with both an intervention and control group using a pre to post change score.[27] Subgroup analyses based on clinical diagnoses (ie, ASD and ADHD/DBD/DMDD/SMD) were conducted to assess intervention effects for different clinical populations. Any studies conducted prior to the publication of the *DSM-5* that used pervasive development disorders or Asperger disorder were included in the ASD subgroup. Studies that used comorbidities (eg, ADHD and ASD) were included in both subgroup analyses. Finally, subgroup analyses within these the 2 clinical subpopulations were conducted to assess relative effects based on medication class, study design, and intervention type. To address issues of nonindependence of effects given that several studies reported more than 1 measure of irritability, a meta-regression was completed for both pooled effect analyses to determine whether the individual studies were accounting for heterogeneity in effect sizes. Heterogeneity was assessed using I^2, which indicates the percentage of total variation in study effect estimates that is due to between-study variability. Analyses were run by HM in R version 3.6.2 using the meta package (version 4.11).

FIGURE 1 PRISMA Flow Diagram for Systematic Review



Note: *ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DBD = disruptive behavior disorders; DMDD = disruptive mood dysregulation disorder; EU = European Union; ISRCTN = International Standard Randomized Controlled Trial Number; SMD = severe mood dysregulation; RCT = randomized controlled trial; WHO = World Health Organization.*

[a]*One study was identified during the manuscript review process.*

RESULTS

In total, 101 intervention studies were included in the meta-analysis, comprising 6,953 youth with persistent nonepisodic irritability (study sample sizes ranged from 8 to 579; Figure 1 presents the PRISMA flowchart).

Characteristics of Included Studies

Descriptions of the 101 articles (42 open trial, 59 RCT) included in this systematic review and meta-analysis can be found in Table 1.[28-125] (Included studies targeted a range of ages, with youth ages 2+ years being represented in the current meta-analysis, suggesting that results from this meta-analysis are representative of the full preschool through adolescent developmental periods. With regard to measures of irritability, the Aberrant Behavior Checklist–Irritability subscale was the most commonly used measure, being used by 87 of the studies. The only other measures used by multiple studies included in the present review were the Disruptive Behavior Disorder Rating Scale (n = 2), Affective Reactivity Index (n = 2), and Swanson, Nolan, and Pelham, version IV scale (n = 2). Most studies relied on parent ratings (84 total, 74 with parent ratings only); however, 15 included clinician ratings, 9 included teacher ratings, and 3 included patient ratings (ie, child self-report). Study trials ranged in length from 1 week to 84 weeks (mean = 13.11, SD = 12.78), with 44.3% of studies falling between 1 and 9 weeks and 43.3% of studies falling between 10 and 18 weeks; 8 weeks was the most common

TABLE 1 Description of Articles Included in the Systematic Review (N = 101)

Authors, year, reference	Sample size	Age range, y	Country/ race/ethnicity distribution (%)	Intervention type	Clinical disorder	Study design
Akhondzadeh *et al.*, 2010[28]	40	4 to 12	Iran	Pharmacological	ASD	RCT
Aman *et al.*, 2002[29]	118	5 to 12	USA: 61.9 White, 4.8 Hispanic	Pharmacological	DBD	RCT
Aman *et al.*, 2010[30]	316	6 to 17	USA: 72.2 White, ethnicity not provided	Pharmacological	ASD	RCT
Aman *et al.*, 2015[14]	84	5 to 17	USA: 67.9 White, 6 Hispanic	Pharmacological	ASD	RCT
Arnold *et al.*, 2003[15]	94	5 to 17	USA	Pharmacological	ASD	RCT
Arnold *et al.*, 2006[31]	16	5 to 15	USA: 81.3 White, ethnicity not provided	Pharmacological	ASD + ADHD	RCT
Arnold *et al.*, 2012[32]	124	4 to 13	USA: 75 White, ethnicity not provided	Combined[a]	ASD	RCT
Asadabadi *et al.*, 2013[33]	40	4 to 12	Iran	Pharmacological	ASD	RCT
Ayatollahi *et al.*, 2020[34]	64	11 to 17	Iran	Pharmacological	ASD	RCT
Baruth *et al.*, 2010[35]	45	9 to 26	USA: race/ethnicity not provided	Nonpharmacological	ASD	RCT
Baweja *et al.*, 2016[36]	68	6 to 12	USA: 26.3 racial/ethnic minority	Pharmacological	ADHD + DMDD	Open trial
Bearss *et al.*, 2013[37]	16	3 to 6	USA: 81 White, 13 Hispanic	Nonpharmacological	ASD	Open trial
Bearss *et al.*, 2015[38]	180	3 to 7	USA: 86.7 White, 14.4 Hispanic	Nonpharmacological	ASD	RCT
Becker *et al.*, 2016[39]	10	5 to 16	Brazil	Pharmacological	ASD	Open trial
Behmanesh *et al.*, 2019[40]	48	4 to 11	Iran	Pharmacological	ASD	RCT
Bishop *et al.*, 2015[41]	89	4 to 45	USA: 77.5 White, 5.6 Hispanic	Pharmacological	ASD	Open trial
Capano *et al.*, 2018[42]	25	5 to 12	USA: race/ethnicity not provided	Pharmacological	ASD	Open trial
Capone *et al.*, 2008[43]	23	3 to 13	USA: race/ethnicity not provided	Pharmacological	ASD	Open trial
Conner *et al.*, 2019[44]	20	12 to 17	USA: 82.4 White, ethnicity not provided	Nonpharmacological	ASD	Open trial
Dean *et al.*, 2017[45]	98	3 to 9	Australia	Pharmacological	ASD	RCT
de la Cruz *et al.*, 2015[46]	579	7 to 10	USA: 60.8 White, 19.3 Hispanic	Combined[b]	ADHD	RCT
Delion *et al.*, 2018[47]	48	5 to 9	France	Nonpharmacological	ASD	Open trial
DeVane *et al.*, 2019[48]	61	6 to 17	USA: 62.3 White, 16.1 Hispanic	Pharmacological	ASD	RCT
Erickson *et al.*, 2014[49]	32	6 to 17	USA: 96.9 White, 9.4 Hispanic	Pharmacological	ASD	Open trial
Fido and Al-Saad, 2008[50]	40	7 to 17	Kuwait	Pharmacological	ASD	Open trial
Gadow *et al.*, 2014[51]	168	6 to 12	USA: 53.0 White, 5.4 Hispanic	Combined[c]	DBD	Open trial
Ghaleiha *et al.*, 2013[52]	49	5 to 12	Iran	Pharmacological	ASD	RCT
Ghaleiha *et al.*, 2013[53]	40	4 to 12	Iran	Pharmacological	ASD	RCT
Ghaleiha *et al.*, 2014[54]	40	4 to 12	Iran	Pharmacological	ASD	RCT
Ghaleiha *et al.*, 2015[55]	44	4 to 12	Iran	Pharmacological	ASD	RCT
Ghaleiha *et al.*, 2016[56]	46	4 to 12	Iran	Pharmacological	ASD	RCT
Ghanizadeh and Moghimi-Sarani, 2013[57]	40	3 to 17	Iran	Pharmacological	ASD	RCT

(continued)

TABLE 1 Continued

Authors, year, reference	Sample size	Age range, y	Country/ race/ethnicity distribution (%)	Intervention type	Clinical disorder	Study design
Ghanizadeh and Ayoobzadehshirazi, 2015[58]	59	4 to 18	Iran	Pharmacological	ASD	RCT
Hajizadeh-Zaker *et al.*, 2018[59]	70	4 to 12	Iran	Pharmacological	ASD	RCT
Haller *et al.*, 2021[60]	44	11.96±2.11	USA: 89 White, 14 Hispanic	Nonpharmacological	DMDD	RCT
Handen and Hardan, 2006[61]	16	13 to 17	USA: race/ethnicity not provided	Pharmacological	DBD	Open trial
Handen *et al.*, 2015[62]	128	5 to 14	USA: 82 White, 0 Hispanic	Combined[b]	ASD + ADHD	RCT
Hardan *et al.*, 2012[63]	33	3 to 10	USA: race/ethnicity not provided	Pharmacological	ASD	RCT
Hellings *et al.*, 2005[64]	30	6 to 20	USA: 90.0 White, 3.3 Hispanic	Pharmacological	ASD	RCT
Hellings *et al.*, 2015[65]	16	13 to 39	USA: 87.5 White, ethnicity not provided	Pharmacological	ASD	Open trial
Hendouei *et al.*, 2020[66]	62	4 to 12	Iran	Pharmacological	ASD	RCT
Hollander *et al.*, 2010[67]	27	5 to 17	USA: 29.6 White, 22.2 Hispanic	Pharmacological	ASD	RCT
Ichikawa *et al.*, 2017[68]	92	6 to 17	Japan	Pharmacological	ASD	RCT
Ichikawa *et al.*, 2018[69]	86	6 to 17	Japan	Pharmacological	ASD	Open trial
Ishitobi *et al.*, 2013[70]	9	9 to 22	Japan	Pharmacological	ASD	Open trial
Kemner *et al.*, 2002[71]	25	6 to 16	Netherlands	Pharmacological	ASD	Open trial
Kent, Hough *et al.*, 2013[72]	79	5 to 17	USA: 70 White, ethnicity not provided	Pharmacological	ASD	Open trial
Kent, Kushner *et al.*, 2013[73]	96	5 to 17	USA: 70 White, ethnicity not provided	Pharmacological	ASD	RCT
Khalaj *et al.*, 2018[74]	46	4 to 12	Iran	Pharmacological	ASD	RCT
Kim *et al.*, 2018[75]	67	6 to 17	South Korea, Thailand, and Philippines	Pharmacological	ASD	Open trial
Kircanski *et al.*, 2018[76]	10	9 to 15	USA: race/ethnicity not provided	Nonpharmacological	DMDD	Open trial
Klaiman *et al.*, 2013[77]	46	3 to 7	USA: 45.7 White, 2.2 Hispanic	Pharmacological	ASD	RCT
Krieger *et al.*, 2011[78]	21	7 to 17	Brazil	Pharmacological	SMD	Open trial
Kurz *et al.*, 2018[79]	9	4 to 8	Austria	Nonpharmacological	ASD	Open trial
Leisman *et al.*, 2018[80]	40	5 to 17	Cuba	Nonpharmacological	ASD	RCT
Loebel *et al.*, 2016[81]	160	6 to 17	USA: 77 White, ethnicity not provided	Pharmacological	ASD	RCT
Mahdavinasab *et al.*, 2019[82]	64	3 to 12	Iran	Pharmacological	ASD	RCT
Malek *et al.*, 2020[83]	26	3 to 12	Iran	Pharmacological	ASD	RCT
Malone *et al.*, 2007[84]	15	12 to 18	USA: 73.3 White, ethnicity not provided	Pharmacological	ASD	Open trial
Maloney *et al.*, 2014[85]	14	6 to 17	USA: race/ethnicity not provided	Pharmacological	ASD	Open trial
Marcus *et al.*, 2009[86]	218	6 to 17	USA: 71.1 White, ethnicity not provided	Pharmacological	ASD	RCT
Marcus *et al.*, 2011[87]	199	6 to 17		Pharmacological	ASD	Open trial

(continued)

TABLE 1 Continued

Authors, year, reference	Sample size	Age range, y	Country/ race/ethnicity distribution (%)	Intervention type	Clinical disorder	Study design
			USA: 71.2 White, ethnicity not provided			
Mazahery *et al.*, 2019[88]	73	2 to 8	New Zealand	Pharmacological	ASD	RCT
McCrae *et al.*, 2020[89]	17	6 to 12	USA: 76 White, 0 Hispanic	Nonpharmacological	ASD	Open trial
Mehl-Madrona *et al.*, 2010[90]	44	2 to 28	USA: >80 White, ethnicity not provided	Pharmacological	ASD	Open trial
Miller *et al.*, 2018[91]	19	12 to 17	USA: 57.9 White, 10.5 Hispanic	Nonpharmacological	DMDD	RCT
Miyaoka *et al.*, 2012[92]	40	8 to 40	Japan	Pharmacological	ASD	Open trial
Moazen-Zadeh *et al.*, 2018[93]	70	4 to 12	Iran	Pharmacological	ASD	RCT
Mohammadi *et al.*, 2013[94]	40	4 to 12	Iran	Pharmacological	ASD	RCT
Momtazmanesh *et al.*, 2020[95]	60	4 to 12	Iran	Pharmacological	ASD	RCT
Najjar *et al.*, 2015[96]	44	5 to 44	USA: 75.0 White, 18.2 Hispanic	Pharmacological	ASD	Open trial
Nicolson *et al.*, 2006[97]	13	4 to 17	Canada	Pharmacological	ASD	Open trial
Niederhofer, 2004[98]	14	5 to 11	Italy	Pharmacological	ASD	RCT
Nikvarz *et al.*, 2017[99]	30	4 to 17	Iran	Pharmacological	ASD	Open trial
Owley *et al.*, 2005[100]	28	6 to 17	USA: 68 White, 7 Hispanic	Pharmacological	ASD	Open trial
Pan *et al.*, 2018[101]	24	7 to 17	Taiwan	Pharmacological	ADHD + DMDD	Open trial
Pandina *et al.*, 2007[102]	55	5 to 12	USA: 61.8 White, ethnicity not provided	Pharmacological	ASD	RCT
Pedersen *et al.*, 2018[103]	350	4 to 21	USA: 79 White, 7 Hispanic	Combined[d]	ASD	Open trial
Posey *et al.*, 2006[104]	16	6 to 17	USA: 68.8 White, 12.5 Hispanic	Pharmacological	ASD	Open trial
RUPP Autism Network, 2005[105]	63	5 to 17	USA: 69.8 White, 4.8 Hispanic	Pharmacological	ASD	Open trial
Rezaei *et al.*, 2010[106]	40	4 to 12	Iran	Pharmacological	ASD	RCT
Sanders *et al.*, 2020[107]	36	6 to 17	USA: 88.6 White, 5.7 Hispanic	Nonpharmacological	ASD	RCT
Scahill *et al.*, 2015[108]	62	6 to 12	USA: 64.5 White, 9.7 Hispanic	Pharmacological	ASD + ADHD	RCT
Shea *et al.*, 2004[109]	79	5 to 12	Canada	Pharmacological	ASD	RCT
Smith *et al.*, 2016[110]	117	5 to 14	USA: 81.2 White, ethnicity not provided	Combined[b]	ADHD	RCT
Sprengers *et al.*, 2020[111]	92	7 to 15	Netherlands	Pharmacological	ASD	RCT
Stigler *et al.*, 2009[112]	25	5 to 17	USA: 88 White, ethnicity not reported	Pharmacological	ASD	Open trial
Stigler *et al.*, 2012[113]	25	12 to 21	USA: race/ethnicity not reported	Pharmacological	ASD	Open trial
Taliou *et al.*, 2013[114]	55	4 to 10	Greece	Pharmacological	ASD	Open trial
Towbin *et al.*, 2020[115]	49	7 to 15	USA: 79.6 White, Hispanic not reported	Pharmacological	DMDD	RCT
Veenstra-Vanderweele *et al.*, 2017[116]	150	5 to 21	USA: 76.7 White, 12.7 Hispanic	Pharmacological	ASD	RCT

(continued)

TABLE 1 Continued

Authors, year, reference	Sample size	Age range, y	Country/ race/ethnicity distribution (%)	Intervention type	Clinical disorder	Study design
Wake *et al.*, 2013[117]	20	6 to 17	Japan	Pharmacological	ASD	Open trial
Waxmonsky *et al.*, 2008[118]	101	5 to 12	USA: 41.6, racial/ethnic minority	Combined[e]	ADHD + SMD	RCT
Waxmonsky *et al.*, 2010[119]	56	6 to 12	USA: 80.4 White, 5.4 Hispanic	Combined[a]	ADHD	RCT
Waxmonsky *et al.*, 2016[120]	56	7 to 12	USA: Race/ethnicity not reported	Nonpharmacological	ADHD + SMD	RCT
Wehmeier *et al.*, 2008[16]	421	6 to 17	Germany	Pharmacological	ADHD	Open trial
Willemsen-Swinkels *et al.*, 1995[121]	20	3 to 7	Netherlands	Pharmacological	ASD	RCT
Willemsen-Swinkels *et al.*, 1996[122]	23	3 to 7	Netherlands	Pharmacological	ASD	RCT
Wink *et al.*, 2018[123]	8	12 to 25	USA: 71.4 White, 14.3% Hispanic	Pharmacological	ASD	RCT
Winters *et al.*, 2018[124]	22	9 to 15	USA: 31.8 White, ethnicity not reported	Pharmacological	ADHD + DMDD	Open trial
Wongpakaran *et al.*, 2017[125]	50	2 to 12	Thailand	Pharmacological	ASD	Open trial

Note: For any study conducted outside of the United States, the country is listed without race/ethnicity information, as this was typically not provided. ADHD = attention-deficit/hyperactivity disorder; ASD = autism spectrum disorder; DBD = disruptive behavior disorder; DMDD = disruptive mood dysregulation disorders; RCT = randomized controlled trial; RUPP = Research Units of Pediatric Psychopharmacology; SMD = severe mood dysregulation.

[a]*Combined intervention vs pharmacological intervention.*

[b]*Combined intervention vs nonpharmacological vs pharmacological vs control.*

[c]*Combined intervention with placebo vs combined intervention with pharmacological augmented therapy (ie, risperidone).*

[d]*Pre–post effects of combined intervention only.*

[e]*Effects are comparing various doses of pharmacological (no, low, medium, and high) and nonpharmacological (no, low, and high) interventions.*

study duration (n = 23). Studies included a range of psychiatric disorders required for study participation, although ASD was by far the most represented diagnosis (Table 1). Specifically, 84 studies required an ASD diagnosis for study entry, 3 of which required comorbid ASD and ADHD. The remaining 17 articles required a diagnosis of ADHD, DBD, and/or DMDD/SMD. Of these 17 articles, 3 included ADHD + DMDD and 2 included ADHD + SMD.

With regard to intervention type, a total of 80 studies focused on pharmacological interventions, 13 focused on nonpharmacological interventions, and 8 focused on combined interventions. Of these studies, medications largely fell under 1 of the 5 medication types reviewed by Stringaris *et al.*,[13] with other types of medication including atomoxetine, selective norepinephrine reuptake inhibitors, anti-inflammatory medication, opiate antagonists, diuretics, supplements such as vitamin D and omega-3 fatty acids (Table S1, available online, provides a complete breakdown). Among the 13 nonpharmacological interventions, a range of interventions were used, including parent management training, cognitive–behavioral therapy, emotional awareness and skills enhancement programs, applied behavior analysis, interpersonal psychotherapy, transcranial magnetic stimulation, low-level laser therapy, and therapeutic body wraps (Table S2, available online, includes a complete breakdown). Finally, among the 8 combined interventions, these included parent management training with antipsychotics, stimulants, or nonstimulant ADHD medications, and behavior management training with stimulants or nonstimulants.

Pooled Effect Size and Subgroup Analyses

There were 142 total effects (ie, measures of irritability) included in the overall pooled effect size analysis. All effects were scaled so that positive effect sizes indicated a decrease in irritability. Effect sizes from pre to post treatment across both RCTs and open trials ranged from a Hedges' g of −0.10[119] to 14.30.[30] The overall pooled effect from pre to post treatment on irritability was significantly different from zero (Hedges' $g = 1.62$, 95% CI = 1.25-2.00, $t = 8.54$, $p < .001$). Subgroup analyses did not show a significant difference in effect sizes regarding improvements in irritability for open trials vs

RCTs [$Q = 3.04(1)$, $p = .081$; Hedges' $g = 1.27$, 95% CI = 0.96-1.58, $I^2 = 91\%$ for open trials, and Hedges' $g = 1.85$, 95% CI = 1.26-2.43, $I^2 = 95\%$ for RCTs]. When examining pooled effect size among the pharmacological studies, there were 109 total measures of irritability that resulted in large improvements (Hedges' $g = 1.86$, 95% CI = 1.37-2.35) with effect sizes ranging from a Hedges' g of -0.10[119] to 14.30).[30] When examining pooled effect size among the nonpharmacological studies, there were 20 total measures of irritability that resulted in a large effect (Hedges' $g = 1.11$, 95% CI = 0.74-1.49), with effect sizes ranging from a Hedges' g of 0.08[120] to 3.57.[38] Finally, when examining pooled effect size among the combined intervention effects, there were 13 total measures of irritability with the overall effect being significantly different from zero and medium in strength (Hedges' $g = 0.69$, 95% CI = 0.41-0.96). Effect sizes ranged from a Hedges' g of 0.15[119] to 1.47.[103] Although subgroup analyses indicate significant differences between study type [$Q = 18.86(2)$, $p < .001$], the meta-regression indicated that these differences do not significantly explain heterogeneity in effect sizes, with only 1.81% of the variance in effect size being accounted for by intervention type ($F_{2,139} = 2.29$, $p = .105$).

An additional analysis examined the effects of medication class (ADHD medications, antidepressants, antipsychotics, mood stabilizers, combined, other, and none). There were 26 total effects from ADHD medications, 6 from antidepressants, 53 from antipsychotics, 3 from mood stabilizers, 9 from combined, 27 from other types of medication classes (Table S1, available online, provides a breakdown of classes by study), and 18 with no medications because of being nonpharmacological interventions. The nonpharmacological studies were retained to examine the variance in effect size across all included studies, regardless of medication use. Results indicated the largest overall effect on irritability being from antipsychotics (Hedges' $g = 2.57$, 95% CI = 1.74-3.40), $I^2 = 96\%$), whereas the smallest effect was from ADHD medications (Hedges' $g = 0.50$, 95% CI = 0.38-0.62, $I^2 = 56\%$) (Table S3, available online, provides Hedges' g, 95% CI, and I^2 for all classes). Overall, there was a significant difference in effect sizes between medication classes on improving irritability [$Q = 52.32(6)$, $p < .001$]. The follow-up meta-regression indicated that medication class is accounting for a significant portion of the variance in effect sizes (9%) ($F_{6,135} = 3.33$, $p = .004$). Model results indicated that compared to the reference group (nonpharmacological effects), only antipsychotics remained a significant predictor of the variance in irritability effect sizes ($t_{135} = 2.44$, $p = .016$).

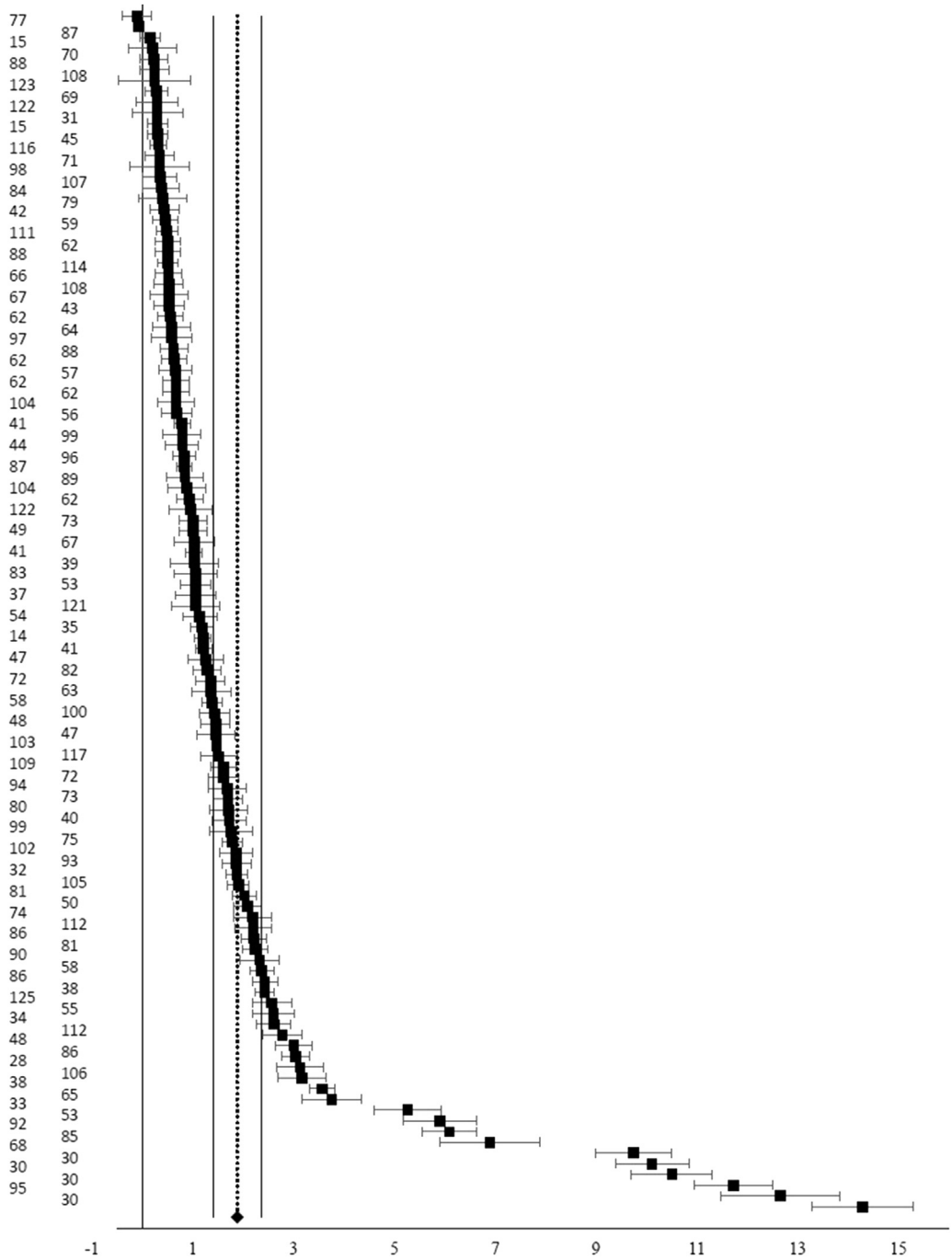
ASD Studies. When examining pooled effect size among the studies with an ASD sample, there were 112 total measures of irritability, with effect sizes from pre to post treatment ranging from a Hedges' g of -0.10[77] to 14.30,[30] and the overall pooled effect was significantly different from zero (Hedges' $g = 1.89$, 95% CI = 1.42-2.36), $t = 7.97$, $p < .001$) (Figure 2). Within the ASD samples, subgroup analyses indicated a nonsignificant difference in effects for the RCT studies vs the open trials (although this difference approached significance in favor of larger effects for the RCTs) [$Q = 3.74(1)$, $p = .053$; Hedges' $g = 1.39$, 95% CI = 0.99-1.80, $I^2 = 91\%$ for open trials and Hedges' $g = 2.18$, 95% CI = 1.47-2.89, $I^2 = 96\%$ for RCTs). In addition, although subgroup analyses indicate significant differences between intervention type [$Q = 7.36(2)$, $p = .025$], the meta-regression indicated that 0% of the variance in effect size is accounted for by intervention type ($F_{2,109} = 0.71$, $p = .496$).

ADHD, DBD, DMDD, and/or SMD Studies. When examining pooled effect size among the studies with an ADHD, DBD, DMDD, and/or SMD sample, there were 39 total measures of irritability, and the overall effect was medium and significantly different from zero (Hedges' $g = 0.64$, 95% CI = 0.51-0.78, $t = 9.47$, $p < .001$). Effect sizes from pre to post treatment ranged from Hedges' g of -0.10[119] to 2.29[61] (Figure 3). Within the ADHD/DBD/DMDD/SMD samples, subgroup analyses indicated a significant difference in effects for the RCT studies vs the open trials, with larger effects being found for the open trials [$Q = 5.27(1)$, $p = .022$; Hedges' $g = 0.88$, 95% CI = 0.58-1.18, $I^2 = 83\%$ for open trials, and Hedges' $g = 0.53$, 95% CI = 0.39-0.66, $I^2 = 49\%$ for RCTs]. Of note, there was a large difference in heterogeneity within the open trials relative to the RCTs, as indicated by their I^2 values. Finally, subgroup analyses did not indicate significant differences based on intervention type [$Q = 0.18(2)$, $p = .912$]; however, it is important to note that there were large differences regarding heterogeneity of effects within intervention types, with the I^2 value for the nonpharmacological interventions ($I^2 = 43\%$) being much smaller than the I^2 values for the combined ($I^2 = 71\%$) and pharmacological ($I^2 = 70\%$) interventions.

DISCUSSION

This systematic review and meta-analysis investigated the efficacy of pharmacological and nonpharmacological interventions for persistent, nonepisodic irritability among youth with neurodevelopmental and externalizing disorders, namely, ASD, ADHD, DBD, DMDD, and SMD. It provides an updated and a more comprehensive review than the

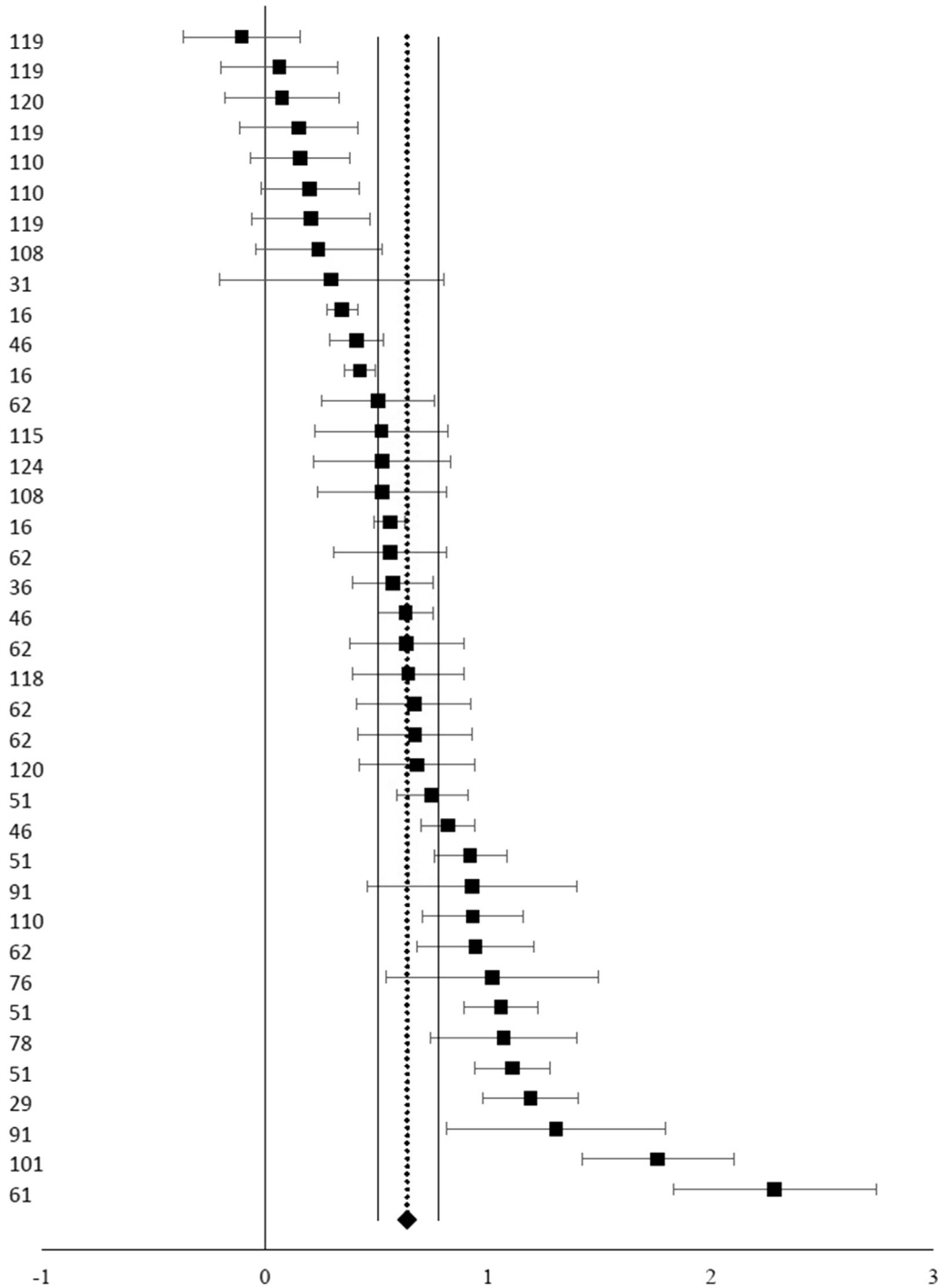
FIGURE 2 Forest Plot of Pooled Effect Size Analysis for Pre- and Post-Effects for Autism Spectrum Disorder Studies



Note: Overall effect = 1.89, 95% CI = 1.42-2.36; Prediction interval = −3.08 to 6.86. Heterogeneity: I^2 = 95%, τ^2 = 6.23, H = 4.32, 95% CI = 4.08-4.58]. Numbers correspond to citation numbers in the References.

Stringaris *et al.* review,[13] including a meta-analysis and meta-regressions, which provide insight into which intervention types are most effective in improving irritability among youth with various psychiatric disorders. Importantly, despite significant heterogeneity between studies (Hedges' g of −0.10 to 14.30; I^2 = 94.3%), with some studies finding a negative or nonsignificant effect and others finding very large effects, the pooled post-treatment effect size for decreasing irritability overall was large (Hedges' g = 1.62), with this effect being driven by the large effect found

FIGURE 3 Forest Plot of Pooled Effect Size Analysis for Pre and Post Effects for Attention-Deficit/Hyperactivity Disorder, Disruptive Behavior Disorders, Disruptive Mood Dysregulation Disorder, and Severe Mood Dysregulation Studies



Note: *Overall effect = 0.50, 95% CI = 0.37-0.63; Prediction interval = −.09 to 1.80. Heterogeneity: I^2 = 52%, τ^2 = 0.08, H = 1.45, 95% CI = 1.17-1.80. Numbers correspond to citation numbers in the References.*

among studies with and ASD sample ($g = 1.89$) relative to studies with an ADHD, DBD, DMDD, and/or SMD sample ($g = 0.64$). Subgroup analyses suggest that intervention type (pharmacological, nonpharmacological, vs combined) did not significantly explain variance in effect sizes for the total sample or for either clinical subsample.

This is likely because large effects were found for both pharmacological and nonpharmacological interventions, with evidence for moderate effects for combined interventions relative to monotherapy (ie, a pharmacological or nonpharmacological intervention only). In contrast, subgroup analyses found study design (open trial vs RCT) to marginally predict heterogeneity overall and for the ASD subsample and significantly predict heterogeneity in the ADHD/DBD/DMDD/SMD subsample. Specifically, RCTs had marginally larger effects for the overall and ASD subsample, but open trials had significantly larger effects in the ADHD/DBD/DMDD/SMD subsample. The fact that the RCTs for our ASD subsample had marginally larger effects than the open trials gives us increased confidence that existing interventions are effective in reducing irritability relative to a placebo or treatment as usual in youth with ASD; however, it is important to note that the prediction interval for this clinical population is still quite large (Figure 2). Finally, a major contribution of this meta-analysis was our finding that antipsychotics and combined pharmacological interventions (eg, antipsychotics used with stimulants, antidepressants with stimulants) appear to provide the largest effects for reducing irritability. However, there was significant heterogeneity across studies using antipsychotics and combined pharmacological interventions ($I^2 = 96\%$ and 93%, respectively). These findings and their clinical implications are discussed further below.

The majority of studies in the current review used pharmacological interventions (ie, 80 of 101 included studies), with an additional 8 implementing combined interventions. Large effects were found for pharmacological and nonpharmacological interventions, with medium effects found for combined interventions relative to monotherapy (Table 1 footnotes include a breakdown of effect comparisons for the combined interventions). However, meta-regression analyses indicated that intervention type was not a significant predictor of overall effects, accounting for only 1.14% of variance in all effects. Despite this, analyses examining effects based on medication class indicated that antipsychotic medications and combined pharmacological interventions produced the largest effects overall (ie, Hedges' g values were >2.00) and in both clinical subsamples, relative to other medication classes and nonpharmacological interventions. The decision to use a specific treatment should always include a consideration of tolerability, which was not assessed here and may be particularly relevant for prescription of antipsychotics to children.[126] In youth with ADHD/DBD/DMDD/SMD, the risk to benefit balance of adjunctive antipsychotics may alter over time, emphasizing the importance of ongoing reassessment of treatment effects.[127] Future research should use cutting-edge methodologies such as a sequential multiple assignment randomized trial (SMART)[128] to systematically test the effects of independent and combined interventions, and ordering of such interventions for persistent, nonepisodic irritability. SMART designs allow for explicit examination of optimal adaptive intervention approaches by individualizing sequences of treatments. For research on the treatment of ADHD, SMART studies have found that the optimal and most cost-effective sequence began with low-intensity behavioral therapy, followed by adjunctive medication in participants with persistent impairment.[129] When behavioral therapy was added after medication, attendance of therapy sessions was significantly lower, which may have reduced the efficacy of this sequence.[130] Although they did not use formal SMART methodology, several studies of atypical antipsychotics and mood stabilizers in youth with ADHD and comorbid DBD or DMDD have observed that initial treatment with behavioral therapy and CNS stimulants leads to substantive improvement in up to half of participants, and to the degree that these participants did not meet criteria for advancing to treatment with additional pharmacological interventions with antipsychotics.[51,131] This will be an important area for future research to continue to explore, particularly among other psychiatric populations besides persons with ADHD.

With regard to effects for different psychiatric diagnoses, a large effect was found for youth with ASD($g = 1.89$), whereas a medium effect was found for youth with ADHD/DBD/DMDD/SMD ($g = 0.64$). It is noteworthy that DMDD was added to the *DSM-5* in 2013 to classify impairing irritability among youth without other primary causes of irritability (eg, ASD, major depression); however, the majority of treatment studies included in the current meta-analysis were for youth with ASD. Given overlapping but divergent neural mechanisms mediating irritability in ASD, ADHD, DBD, and DMDD,[132] it will be important for future research to explore whether treatments for youth with ASD that led to large effects (eg, aripiprazole) might be effective for youth with ADHD/DBD/DMDD/SMD. Alternatively, there is recent evidence that treating irritability transdiagnostically (rather than focusing on a particular clinical disorder), such as through the Modular Approach to Therapy with Children with Anxiety, Depression, Trauma, and Conduct Problems (MATCH),[133] is effective. Specifically, MATCH can be used to flexibly implement parent training and cognitive–behavioral therapy in a personalized format to target severe irritability. As such, it will be critical for future intervention research to examine the potential of such interventions for a range of clinical populations, including those not included in the current meta-analyses (eg,

persons with generalized anxiety disorder, post-traumatic stress disorder, major depressive disorder).

These findings should be interpreted with several limitations in mind. First, there was high heterogeneity across studies included in the meta-analysis. Specifically, despite large effects overall, 2 studies in the ASD subsample found negative effects (ie, increases in irritability) [77,87]; these studies were both pharmacological studies (tetrahydrobiopterin and aripiprazole, respectively). For the ADHD, DBD, DMDD, and SMD subsample, there was only 1 study that found a negative effect.[119] This study used a single-item teacher-rated measure of irritability meant to assess medication-related adverse events and observed low baseline ratings, leaving little room for improvement. It is possible that the wide range of treatments used (from antipsychotics and mood stabilizers to vitamin D and omega-3 supplements for pharmacological interventions, and from parent training and cognitive–behavioral therapy to laser therapy and therapeutic body wraps for nonpharmacological interventions) are driving the observed heterogeneity. However, heterogeneity remained high even when intervention type was compared in meta-regression analyses. There are a variety of other factors that likely contribute and could confound associations between observed effects and the specific interventions. For example, a wide range of informants were used to assess treatment effects—clinician, parent, self, and teacher ratings—with parent ratings being the most commonly used measure. Measures also ranged from the well validated measures, such as the Aberrant Behavior Checklist–Irritability subscale or Affective Reactivity Index, to re-purposed measures for other conditions such as oppositional defiant disorder (eg, Disruptive Behavior Disorder Rating Scale),[36,46,51,101,118,120] to single-item ratings of irritability.[45,115,119] The role of informant when assessing irritability is also unclear and merits further study. Study design may have also affected the results, as several studies used stepped designs with RCT starting after initial lead-in care received by all participants. These adjunctive designs are likely to produce smaller effects than those using only a single phase of treatment.[134] Of note, several of the studies requiring participants to have a diagnosis of ADHD used these designs,[51,119,120] which may have contributed to the relatively lower effect sizes seen in the ADHD subsample. Similarly, as previously noted, almost all of the effects for the combined interventions compared combined pharmacological and nonpharmacological interventions to monotherapy (ie, either a pharmacological or nonpharmacological intervention only), rather than compared to a placebo. As such, we caution against interpreting the medium effect for combined treatments as less effective than monotherapy; rather, our findings document moderate additional benefit to adding a second treatment type to an existing treatment. Finally, all studies included in this meta-analysis needed to directly examine changes in irritability or provide enough information on irritability as a secondary outcome to calculate changes in irritability as a result of the intervention, potentially limiting the generalizability of our findings. For example, studies reporting on aggression or emotion dysregulation that did not report separate changes in irritability were not included.

In summary, this systematic review and meta-analysis provides strong support (ie, medium to large effects across study designs, intervention types, and clinical populations) for the efficacy of pharmacological and nonpharmacological interventions for preschool children through adolescents with various psychiatric disorders. Of note, pharmacological and nonpharmacological interventions both delivered large effects, with evidence for additional moderate effects for the use of combined therapy relative to monotherapy. In addition, the largest effects were found for interventions for youth with ASD, and for antipsychotic and combined pharmacological interventions. Despite this, given the wide range of treatment options with strong efficacy that are available, and given the current lack of evidence-based tailoring variables to match a patient with a particular treatment, it seems prudent to start with low-cost, well-tolerated treatments before escalating to treatments associated with appreciable burden and morbidity (eg, atypical antipsychotics); future research exploring this possibility and treatment sequencing such as through SMART designs is critical. In an effort to optimize outcomes, upcoming trials should attempt to identify additional potential moderators of effects, given the high heterogeneity.

This article is a part of a special review series devoted to child and adolescent emotion dysregulation as part of the presidential initiative of AACAP President Gabrielle A. Carlson, MD (2019-2021). Articles were selected to cover a range of topics in the area, including reviews of genetics, neuroimaging, pharmacological and nonpharmacological treatment, screening tools, and prevention, among others. The series was edited by Guest Editor Daniel P. Dickstein, MD, Associate Editor Robert R. Althoff, MD, PhD, and Editor-in-Chief Douglas K. Novins, MD.

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Formal analysis: Eadeh
Funding acquisition: Baweja
Methodology: Breaux

Supervision: Breaux, Waxmonsky
Writing — original draft: Breaux, Shroff, Cash, Swanson
Writing — review and editing: Breaux, Baweja, Eadeh, Shroff, Cash, Swanson, Knehans, Waxmonsky

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