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Efficacy of Pharmacological Interventions for Irritability and Emotional Dysregulation in Autism Spectrum Disorder and Predictors of Response:

A Meta-analysis of Placebo-Controlled Randomized Controlled Trials

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ABSTRACT

Introduction: Emotional dysregulation and irritability are common in individuals with autism spectrum disorder (ASD). We conducted the first meta-analysis assessing the efficacy of a broad range of pharmacological interventions for emotional dysregulation and irritability in ASD and predictors of response.

Method: Following a pre-registered protocol (PROSPERO: CRD42021235779), we systematically searched multiple databases until 01/01/2021. We included placebo-controlled randomized controlled trials (RCTs) and evaluated the efficacy of pharmacological interventions and predictors of response for emotional dysregulation and irritability. We assessed heterogeneity using Q statistics and publication bias. We conducted sub-analyses and meta-regressions to identify predictors of response. The primary effect size was the Standardized Mean Difference. Quality of studies was assessed using the “Cochrane Risk of Bias Tool” (RoB2).

Results: 2,856 individuals with ASD in 45 studies were included, of which 26.7% of RCTs were at high risk of bias. Compared to placebo, antipsychotics (1.028, 0.824 to 1.232) and medications used to treat ADHD (0.471, 0.061 to 0.881) were significantly better than placebo in improving emotional dysregulation and irritability, while evidence of efficacy was not found for other drug classes ($p > 0.05$). Within individual medications, evidence of efficacy was found for aripiprazole (1.179, 0.838 to 1.520) and risperidone (1.074, 0.818 to 1.331). Increased rates of comorbid epilepsy ($\beta = -0.049$, $p = 0.026$) were associated with a lower efficacy.

Conclusion: Some pharmacological interventions (particularly risperidone and aripiprazole) have proved efficacy for short-term treatment of emotional dysregulation and irritability in ASD and should be considered within a multimodal treatment plan, taking into account also tolerability profile and families' preferences.

Key words: autism spectrum disorder, irritability, emotional dysregulation, meta-analysis, psychopharmacology

INTRODUCTION

Autism spectrum disorder (ASD) is described as an early-onset chronic condition characterized by persistent deficits in social communication and restricted and repetitive patterns of behavior.¹ Individuals with ASD may present with emotion dysregulation and/or irritability, which have been defined as the failure to regulate emotions appropriately and effectively² and a state of reduced control over temper or an excessive response to stimuli, respectively.^{3, 4} Even if psychopharmacological medications are currently FDA-approved for irritability rather than emotion dysregulation in ASD, emotion dysregulation and irritability are often considered overlapping constructs, and there is no consensus on their scope^{5, 6} or clear differences between them.^{7, 8} Furthermore, there is evidence that families are particularly interested in emotional symptoms,⁹ which highlights the importance of assessing the effects of medications not only on irritability, but also on emotional dysregulation.

Emotional dysregulation and irritability, common in patients with ASD,¹⁰ may manifest as aggression, tantrums, rapidly changing moods, or self-injurious behavior among others.¹⁰ They can profoundly impair functioning¹¹ and lead to a substantial burden on families⁹ and psychiatric services.¹² Several factors may contribute to emotional dysregulation and irritability in ASD, with heterogeneous presentations.^{13, 14} Certain variables as sex¹¹ or age¹⁵ have shown to have an impact on emotion regulation and response to interventions, although not consistently.¹⁶ Currently, the predictors of response to pharmacological interventions that impact emotional dysregulation and irritability in ASD remain unknown since they have not been evaluated by previous meta-analyses.^{4, 17}

Several psychopharmacological interventions targeting symptoms of emotional dysregulation and irritability in ASD have been evaluated, primarily using the Aberrant Behavioral Checklist–Irritability (ABC-I) subscale.¹⁸⁻²⁰ These include antipsychotics,¹⁸ mood stabilizers,¹⁹ and glutamatergic blockers,²¹ among others. However, to date, only two antipsychotics (risperidone and aripiprazole) have been approved by the Food and Drug Administration (FDA) and other regulatory agencies for the pharmacological treatment of irritability in ASD. Still, this indication is limited to children and adolescents, while no recommendations exist for adults.^{22, 23}

A previous study meta-analytically summarized the evidence on the efficacy of aripiprazole and risperidone for severe irritability and problem behaviors in individuals with ASD, including 11 studies published up to 2013.⁴ The effect size fell in a range considered large ($d=0.86$ for risperidone, $d=0.78$ for aripiprazole).⁴ Another meta-

analysis, including eight studies, evaluated the efficacy of these and other atypical antipsychotics for irritability/agitation in individuals with ASD, finding that risperidone and aripiprazole reduced its levels.¹⁷ Other systematic reviews without meta-analytical evidence have addressed the efficacy of other pharmacological interventions such as clonidine.²⁴

To date, no meta-analysis has comprehensively evaluated the efficacy of a broad range of pharmacological interventions for emotional dysregulation and irritability in ASD. There is also a gap of knowledge on the evaluation of predictors of response that needed to be filled. Our aim was to meta-analytically estimate the efficacy of a broad range of pharmacological interventions for emotional dysregulation and irritability in ASD, including children and adults. We also evaluated predictors of response to pharmacological interventions for emotional dysregulation and irritability in ASD at the patient-group level.

METHOD

This pre-registered study (protocol: PROSPERO CRD42021235779) was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)^{25, 26} statement (Table S1, available online).

Search strategy and selection criteria

A systematic search strategy was used to identify relevant articles, and a two-step literature search was implemented by two independent researchers (GSP, CP). PubMed and Web of Science database (Clarivate Analytics, including Web of Science Core Collection, BIOSIS Citation Index, KCI-Korean Journal Database, MEDLINE, Russian Science Citation Index, and SciELO Citation Index) were searched. We also searched the Cochrane Central Register of Reviews and Ovid/PsycINFO databases from inception until 1st January 2021. For specific search terms, see Supplement 1, available online. First, abstracts of identified references were screened, and then the full text was examined. Interrater reliability was 86%. We also hand-searched the references of previously published articles and extracted any additional relevant titles.

We included: a) randomized controlled trials (RCTs), either parallel studies or cross-over studies (for which only the pre cross-over data were included to avoid the carry-over effect), b) including individuals with an ASD diagnosis as per DSM/ICD criteria, established with or without support from other widely used tools and interviews (e.g.,

ADI-R, ADOS, Childhood Autism Rating Scale), c) evaluating emotional dysregulation and irritability (see definitions in Supplement 2, available online) with an established instrument; several instruments have been used to evaluate emotional dysregulation and irritability, being the ABC-I the most common but including other instruments which can be found in the Supplement 3, available online, d) with at least an intervention group/arm receiving a pharmacological intervention and a control group receiving placebo, e) in which the effect of the pharmacological intervention and the placebo in the emotional dysregulation and irritability scores was evaluated and either raw results for both groups or computed effect sizes on the difference between both groups was provided, f) published in any language (although search terms included only words in English). Exclusion criteria were a) reviews, clinical cases, or study protocols, b) studies evaluating psychosocial interventions, c) studies with overlapping samples. Overlap was systematically assessed looking at the study name, location, and recruitment periods. When overlap was unclear, authors were contacted. When overlap was found, the largest study was included. For overlapping studies with the same sample size, the most recent was included.

Data extraction

Two researchers (JVS and AC) independently extracted data from all the included studies into a Microsoft Excel spreadsheet. This database was cross-checked by a third author (GSP or CP). Extracted variables included: first author and year of publication, program/study name and recruitment period, country/countries, sample size, age (mean, SD, range), sex (% females), pharmacological group (Supplement 4, available online), trial duration (in weeks), design (parallel RCT, cross-over RCT), concomitant medication (not allowed, allowed if stable, allowed), emotional dysregulation and irritability threshold (inclusion limited to individuals over a certain threshold of emotional dysregulation and irritability, no limitation according to this), IQ (ASD with low IQ excluded or not, mean IQ value), percentage of comorbid epilepsy, percentage of comorbid attention-deficit/hyperactivity disorder (ADHD), quality assessment (see below) and emotional dysregulation and irritability results. As per protocol, whenever the data from two or more instruments was provided within the same study, the datum from the ABC-I was extracted as this is the most frequently used instrument to evaluate emotional dysregulation and irritability and includes “irritability”, “agitation”, and “crying” (arguably the closest to the emotional dysregulation construct).^{4, 17, 27}

Strategy for data synthesis

The primary effect size (ES) was the Standardized Mean Difference (SMD) between the intervention and the placebo group. When available, mean \pm SD pre- and post-intervention in both groups were extracted to obtain the SMD. Whenever this information was not fully available, the mean \pm SD difference post-intervention between the groups, the mean \pm SD in both groups post-intervention only, or the effect sizes of the differences computed by the studies (in this hierarchy order) were extracted. We evaluated the overall “intention to treat” efficacy of any pharmacological intervention and the stratified efficacy according to the different pharmacological classes (antipsychotics, antidepressants, mood stabilizers, medications used to treat ADHD: stimulant ADHD medications, non-stimulant ADHD medications, opioid antagonists, glutamatergic blockers, diuretics, neuropeptides, fatty acids, others), whenever two or more studies were available per group. As an additional analysis, for the interventions that improved emotional dysregulation and irritability, we estimated the number needed to treat (NNT),²⁸ defining the bad outcome (i.e., significant emotional dysregulation and irritability levels) through the control event rate (CER) as the score at the top 10%, 30% and 50% percentile for emotional dysregulation and irritability levels.²⁹

We further conducted other sub-analyses according to a) medication subgroup for those families in which statistical power was enough to conduct a sub-analysis (risperidone, aripiprazole, other antipsychotics; stimulants, non-stimulant medications with indication for ADHD), b) design of the RCTs (parallel, cross-over), c) population age range (studies conducted in children and adolescents, studies conducted in adults, studies conducted including both) d) use of concomitant medication (concomitant medication not allowed, concomitant medication allowed if dose stable only, any concomitant medication allowed) e) emotional dysregulation and irritability threshold for being included into the study (studies including only individuals over certain emotional dysregulation and irritability threshold, studies not establishing this criterion) f) instrument used (studies using ABC-I,³⁰ studies using other instruments) g) IQ exclusion (studies excluding individuals with low IQ as defined by the studies, studies not excluding individuals with low IQ) and h) study quality (low risk of bias, some concerns, high risk of bias).

Since high heterogeneity was expected, random-effects meta-analyses were conducted.³¹ To assess publication bias, we first inspected the funnel plot and then conducted Egger’s test,³² complemented by the “trim and fill” method to correct for the presence of missing studies in case of risk of publication bias (i.e., small sample bias) detected with the Egger’s test. Heterogeneity among study point estimates was assessed using the Q statistics. The proportion of the total true variability in the effect size estimates was evaluated with the I² index.³³ We conducted meta-analytical

regressions whenever ten or more studies were available³⁴ to estimate the association between the efficacy of the interventions and (i) mean age (ii), sex (percentage of females), (iii) duration of the intervention, (iv) percentage of individuals with comorbid epilepsy and (v) quality of the study. All p values reported in the meta-analysis were two-sided, and the level of significance was $p < 0.05$. Comprehensive Meta-analysis (CMA) v3³⁵ was used to perform the analyses selecting a pre-post correlation of 0.5 (results using pre-post correlations of 0.3 and 0.7 do not significantly change $< 5\%$ variation- and can be provided by the authors upon request).

Risk of bias (quality) assessment

The quality of studies was independently assessed using the “Cochrane Risk of Bias Tool” (RoB2)³⁶ by two researchers (JVS and AC). Two different versions of the Rob2 were used for parallel studies and for cross-over trials. The overall quality was rated in three categories: low risk of bias, some concerns, or high risk of bias according to the following items: randomization process, deviations from intended interventions, measurement of the outcome and selection of the reported result (Supplement 5, available online). For a study to be rated at overall low risk of bias, all the domains need to be rated at low risk of bias.

RESULTS

The literature search yielded 3,612 records after removing duplicates, and after the exclusion of non-relevant titles or abstracts, 319 full-text articles were screened. After excluding 274 studies at full-text stage (Table S2, available online), 45 studies were finally included (Figure 1). The overall database, considering all independent studies, comprised 2,856 individuals with ASD (mean age 11.2 ± 6.3 years; 13.6% females). 66.2% of the participants were white and the mean IQ was 66.7. 21 studies included children and adolescents (< 18 years), 14 studies including children only (< 12 years), five studies including children, adolescents and adults, four studies including adults only and one study including adolescents only. Most studies ($K=32$, 71.1%) were carried out in North America, followed by Europe ($K=7$, 15.6%), Asia ($K=4$, 8.9%), Australia ($K=1$, 2.2%) and South America ($K=1$, 2.2%). Most frequently provided pharmacological groups were antipsychotics ($K=13$, 28.9%), followed by neuropeptides ($K=5$, 11.1%), antidepressants ($K=4$, 8.9%), mood stabilizers ($K=4$, 8.9%), medication used to treat ADHD ($K=4$, 8.9%), fatty acids ($K=4$, 8.9%), glutamatergic blockers ($K=3$, 6.7%), opioid antagonists ($K=3$, 6.7%), diuretics ($K=2$, 4.4%) and others ($K=4$, 8.9%). Most studies ($K=41$, 93.2%) used the ABC-I to evaluate emotional dysregulation and irritability. The

mean duration of the interventions was short (10.6 ± 7.9 weeks, range=1-48 months) (Table 1). Nineteen studies (42.2%) only included individuals with ASD whose emotional dysregulation and irritability levels were over a certain threshold (which varied), while 26 studies (57.8%) did not establish a threshold for inclusion.

Efficacy of pharmacological interventions for emotional dysregulation and irritability

Compared to placebo, overall, pharmacological interventions (Figure 2, Table 2) significantly improved emotional dysregulation and irritability (SMD=0.611, 95% CI=0.458-0.764, K=45, N=2,856). Significant within subgroup heterogeneity was found between the pharmacological groups evaluated ($Q=34.481$, $p<0.001$). Within the pharmacological groups, there was also significant heterogeneity. Among the pharmacological groups (in descending order of efficacy), antipsychotics (1.028, 0.824 to 1.232, K=13, n=1,425) and medications with indication for ADHD (0.471, 0.061 to 0.881, K=4, n=94) were significantly better than placebo for emotional dysregulation and irritability. Stimulant medication (0.544, -0.058 to 1.146, K=2, n=46) and non-stimulant medication (0.405, -0.167 to 0.978, K=2, n=48) considered separately did not reach statistical significance. There were no statistically significant differences between the active intervention and the placebo group for opioid antagonists (1.014, -0.686 to 2.714, K=3, n=82), diuretics (0.584, -0.111 to 1.279, k=2, n=130), others (0.550, -0.179 to 1.279, K=4, n=199), glutamatergic blockers (0.431, -0.107 to 0.969, K=3, n=122), fatty acids (0.297, -0.084 to 0.678, K=4, n=139), neuropeptides (0.287, -0.109 to 0.683, K=5, n=295) or mood stabilizers (0.153, -0.277 to 0.583, K=4, n=105) (Table 1).

Significant differences in efficacy were found among the antipsychotic medications evaluated ($Q=30.381$, $p<0.001$) (Table S3, available online). The efficacy of aripiprazole (1.179, 0.838 to 1.520, K=5, n=808) and risperidone (1.074, 0.818 to 1.331, K=6, n=372), compared to placebo, was nominally higher than the efficacy of other antipsychotics ($p<0.001$). The subgroup with other antipsychotics (including two studies, one with haloperidol and one with lurasidone) did not reach statistical significance (0.869, -0.011 to 1.749).

Sub-analysis of the efficacy of pharmacological interventions according to moderating factors

The efficacy of the pharmacological interventions was higher in trials including only individuals with ASD in which emotional dysregulation and irritability levels were significant (i.e., over a certain threshold), compared to those including individuals with

ASD without restricting the participation of individuals with ASD according to their emotional dysregulation and irritability levels ($Q=15.268$, $p<0.001$). There were no statistically significant differences in efficacy according to between-group heterogeneity analyses between 1) parallel RCTs and cross-over RCTs ($p=0.053$, favoring cross-over RCTs); 2) RCTs conducted in children and adolescents and RCTs conducted in adults or including both children and adolescents and adults ($p=0.509$); 3) RCTs allowing concomitant medications, RCTs not allowing any concomitant medications and RCTs allowing concomitant medications only when the concomitant medication and the dose were stable ($p=0.180$); 4) RCTs using the ABC-I compared to RCTs using other instruments ($p=0.067$); 5) RCTs including individuals with any IQ compared to those excluding subjects with low IQ ($p=0.174$); 6) RCTs at “low risk of bias” compared to those rated as with “some concerns” or at “high risk of bias” ($p=0.905$) (Table S4, available online).

Number needed to treat (NNT) for pharmacological interventions that showed efficacy for emotional dysregulation and irritability

We provide here the values of the NNT for CER set at 10%, 30% and 50%, respectively: any antipsychotic: 11 (95% CI=11-12), 4 (95% CI=4-5) and 3 (95% CI=3-3); risperidone: 11 (95% CI=10-12), 4 (95% CI=4-5) and 3 (95% CI=2-3); aripiprazole: 11 (95% CI=10-12), 4 (95% CI=4-5) and 3 (95% CI=2-3); medications with indication for ADHD: 17 (95% CI=12-106), 7 (95% CI=5-52) and 6 (95% CI=3-45) (Table S5, available online).

Heterogeneity, publication bias

Heterogeneity across the included studies was statistically significant ($Q=127.233$, $I^2=65.414$ $p<0.001$). Among the pharmacological groups, heterogeneity was statistically significant for antipsychotics ($Q=28.327$, $I^2=57.638$ $p=0.005$) and opioid antagonists ($Q=7.957$, $I^2=87.433$ $p=0.005$), but not for antidepressants, mood stabilizers, medications used for ADHD, glutamatergic blockers, diuretics, neuropeptides, fatty acids or other medications (all $p>0.05$).

Publication bias was not detected in either the funnel plot inspection (Figure S1, available online) or in the Egger’s test ($t=1.016$, $p=0.316$).

Meta-regressions

A higher percentage of individuals with epilepsy was associated with significantly lower efficacy of the interventions for emotional dysregulation and irritability ($\beta=-0.049$,

$p=0.026$). There were no significant associations with any of the other outcomes, including the percentage of females, mean age, duration of the intervention, or quality of the studies (all $p>0.05$) (Table S6, available online).

Quality assessment

The quality of the clinical trials ranged from low risk of bias to high risk of bias. Twelve studies (26.7%) were at “high risk of bias,” 18 (40.0%) were rated as with “some concerns,” and 15 (33.3%) were at “low risk of bias”. Two studies (50%) evaluating mood stabilizers, 2 studies (40%) evaluating neuropeptides, 2 studies (15.4%) evaluating antipsychotics, 1 study (50%) evaluating stimulant medication, 1 study (50%) evaluating diuretics, 1 study (25.0%) evaluating antidepressants, 1 study (33.3%) evaluating glutamatergic blockers, 1 study (25%) evaluating fatty acids and 1 study (25%) evaluating other medications were at high risk of bias (Figure 3 and Table S7, available online).

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis assessing the efficacy of a broad range of pharmacological interventions for emotional dysregulation and irritability in individuals with ASD. It is also the first meta-analysis evaluating the influence of a large number of moderating factors on the response to pharmacological interventions. Overall, pharmacological interventions for individuals with ASD, including antipsychotics (risperidone and aripiprazole) and overall medications used for ADHD (stimulants plus non-stimulants), were significantly more efficacious than placebo for emotional dysregulation and irritability. In the context of low sample sizes, the evidence about the efficacy of stimulants and non-stimulants considered separately, opioid antagonists ($K=3$, $n=82$), diuretics ($K=2$, $n=130$), fatty acids ($K=4$, $n=139$), neuropeptides ($K=5$, $n=195$), and mood stabilizers ($K=4$, $n=105$) for emotional dysregulation and irritability in ASD is insufficient at the moment.

The largest effect sizes and the lowest NNTs were observed for two antipsychotics: aripiprazole ($ES=1.179$, 0.838 to 1.520 ; $NNT=3-11$) and risperidone ($ES=1.074$, 0.818 to 1.331 ; $NNT=3-11$), respectively. As an example, to illustrate the implications of our CERs, the estimated average number of individuals with ASD that need to receive aripiprazole or risperidone so the intervention decreases the levels of emotional dysregulation and irritability in one of those individuals to the levels observed across the

less impaired 30% percentile would be 4 (95% CI, 4–5) for both medications. Our effect sizes are in line with the results of a previous meta-analysis.⁴ However, in the earlier meta-analysis, this effect was reversed and slightly larger for risperidone than aripiprazole. Still, the difference is overall small, so they can be considered comparable in terms of efficacy.

Our results provide rigorous and up-to-date evidence supporting the approval of risperidone and aripiprazole for the pharmacological treatment of irritability in ASD, suggesting that these agents should be considered first-line within pharmacological agents for the management of emotional dysregulation and irritability in ASD. However, unfortunately, the lack of response for aripiprazole and risperidone can be significant in ASD, reaching 50% in one study.³⁷ The tolerability and safety are additional essential factors to be taken into consideration in the clinical decision-making process when selecting agents. One or more adverse events were observed in up to 61% of the individuals with ASD taking aripiprazole and 77% of the individuals with ASD taking risperidone,³⁸ although the rates of side effects being similar has also been suggested.³⁹ For instance, two of the most differential side effects between both medications are weight gain along with other symptoms of metabolic syndrome (these are more frequent for risperidone) and akathisia (more frequent for aripiprazole).⁴⁰ In an individual study, an increase of more than 7% of their baseline weight appeared in 26% of individuals with ASD taking aripiprazole against 70% of those taking risperidone.³⁸ However, the half-life of aripiprazole is more prolonged,⁴¹ and the weight difference became nonsignificant after the 3-month extension phase.³⁸ In any case, individuals who do not respond to aripiprazole can be switched to risperidone, but potential weight gain after the change is implemented may concern some prescribers. Different treatments, including pharmacological interventions, are being tested and can be useful to target such side effects.⁴² However, psychosocial approaches might be considered prior to or in addition to the pharmacological interventions.^{43, 44} Furthermore, although we have not been able to assess their efficacy, the psychosocial approaches may also be used in combination with pharmacological interventions. This may include cognitive-behavioral therapy,⁴⁵ mindfulness-based treatments,⁴⁵ acceptance-based approaches,⁴⁶ applied behavior analysis-based interventions⁴⁷ or parent-mediated behavioral interventions.⁴⁸ Psychoeducation should also be considered as part of an holistic approach.⁴⁶ The individual variables and preferences of patients with ASD and their families need to be considered in order to provide the most appropriate and holistic intervention possible for individuals with ASD, and advance in the implementation of precision psychiatry for these patients, in which efforts to do so have been limited.⁴⁹

Given possible tolerability issues with aripiprazole and risperidone and considering that not all individuals with ASD may benefit from them, having alternative pharmacological options to offer to our patients is recommendable. According to our results, another group that showed to be superior to placebo for emotional dysregulation and irritability was the one with medications used to treat ADHD, although the number of studies was limited (K=4). Recent meta-analytical evidence shows that approved ADHD medications (particularly methylphenidate and atomoxetine) are the most efficacious for ADHD symptoms in children and youth with ASD.⁵⁰ There is limited evidence that ADHD medications, when properly optimized, may avoid using additional agents (such as antipsychotics and mood stabilizers) to manage emotional dysregulation and irritability in children with ADHD.⁵¹ Likewise, prescribing ADHD medications could be a suitable option for the management of emotional dysregulation and irritability for some individuals with ASD with concomitant (and impairing) ADHD features. Of note, except for one of the included studies,⁵² the other studies evaluating ADHD medication focused on individuals with concomitant ADHD symptoms.⁵³⁻⁵⁵ However, the analyses evaluating separately stimulant medication and non-stimulant medication did not reach statistical significance, and the sample size and number of studies evaluating these medications were limited, so this finding should be interpreted with caution.

The evidence on the efficacy of opioid antagonists, diuretics, fatty acids, neuropeptides, and mood stabilizers for emotional dysregulation and irritability in ASD is currently insufficient, so more research would be needed before these interventions can be widely implemented into clinical practice. The nonsignificant findings for these molecules should be understood within the context of small sample sizes and the limited number of studies evaluating the efficacy of these interventions. At the moment, none of them can be considered first-line interventions for individuals with ASD suffering emotional dysregulation and irritability. However, some of them (e.g., mood stabilizers) are used in clinical practice and require further study to detect subgroups of ASD in which they could potentially be beneficial.

In terms of predictors of response, a higher percentage of individuals with epilepsy was associated with a lower efficacy of the interventions for emotional dysregulation and irritability in our meta-regression analyses. Concerns about the risk of seizures with pharmacological interventions⁵⁶ may difficult an optimum pharmacological approach for individuals with ASD and emotional dysregulation and irritability. Also, reduced blood levels of antipsychotics caused by antiepileptic drugs that act as metabolism inductors (e.g., phenytoin or carbamazepine) may result in decreased efficacy of antipsychotics.⁵⁷ Furthermore, emotional dysregulation and irritability may have different neurobiological

underpinnings in individuals with epilepsy, thus making them prone to better respond to medications with different mechanisms of action (e.g., antiepileptic drugs). Of note, seizures are more frequent in individuals with ASD and low cognitive ability, dysmorphic features, and motor impairment, which may act as confounding factors.⁵⁸ In any case, this finding is important since epilepsy and seizures are common and have been associated with ASD in 10% to 30% of young patients.⁵⁹ Considering their apparently lower efficacy for individuals with epilepsy and that seizures are considered dangerous and life-threatening side effects,⁶⁰ the use of other medications may be considered. Carbamazepine and lamotrigine have shown to be more efficacious than other antiepileptic drugs for epilepsy in children and adolescents with ASD in two network meta-analyses.^{61, 62} Thus, despite the results of this meta-analysis, being carbamazepine and lamotrigine both mood stabilizers and antiepileptic drugs, they could be therapeutic alternatives worth studying in the future for individuals with both ASD and either epilepsy or personal history of seizures.

We further evaluated a wide range of predictors of response to pharmacological interventions for emotional dysregulation and irritability in ASD. According to our sub-analyses, the factor with the most significant effect was the baseline presence of emotional dysregulation and irritability levels over a specific threshold, which was a positive predictor of response. This finding is in line with previous evidence showing that baseline severity of emotional dysregulation and irritability was the only significant moderating factor for treatment response to risperidone in individuals with ASD, with higher severity associated with greater improvements and a better benefit-risk ratio.⁶³ However, we cannot discard a floor effect (although this is not specific to this field)⁶⁴ or 66.7% of our studies establishing emotional dysregulation and irritability as the primary outcome having an effect on this result. Considering our results and that pharmacological interventions do not alter the course of ASD but provide symptomatic relief,⁶⁵ pharmacological interventions for emotional dysregulation and irritability seem to be more useful in individuals with ASD who have emotional dysregulation and irritability features.

In the current meta-analysis, we included only RCTs, which are considered the gold standard individual study design to assess efficacy. Placebo response (which can also be found in the active arm)⁶⁶ can be substantial in ASD,⁶⁷ and we only included placebo-controlled studies. Other sub-analyses were carried out to test the methodological robustness of our results. The lack of differences between the subgroups in our sub-analyses indicate that the efficacy of pharmacological interventions for emotional dysregulation and irritability in ASD is sound, and there is no evidence of methodological

issues or biases playing a significant role in our results. These include lack of differences between parallel RCTs and cross-over RCTs; between RCTs allowing concomitant medication and those not allowing them or allowing them when the dose was stable; between RCTs using the ABC-I and those using other instruments; or between RCTs at “low risk of bias” and those rated as with “some concerns” or at “high risk of bias.” Furthermore, although aripiprazole and risperidone have only been approved for the pharmacological treatment of children and adolescents with ASD,^{22, 23} according to both our sub-analyses and meta-regressions, there is no evidence of the efficacy being lower for adults. We hope that this finding will be considered in future guidelines.

This study has some limitations that must be taken into consideration when interpreting its results. Some of them were inherent to our research question and the evidence available. First, the evidence was limited for some pharmacological classes, such as opioid antagonists and diuretics, for which only two studies were available. However, this is the most comprehensive meta-analytical evidence in the field to date, and the database was the largest yet. Second, there was high statistical heterogeneity among the studies included; we accounted for it in meta-regression analyses, although other significant sources of heterogeneity may exist, including expressive language, trait severity or IQ, which were not reported in most of the included studies, or even the measurements or instruments used. Furthermore, we were underpowered to test some of the meta-regressors as we did not have the minimum threshold recommended by Cochrane to conduct meta-regressions (10 studies per regressor). One example would be the percentage of comorbid ADHD, which was only provided by five studies.^{53, 54, 68-70} Third, in the stratified analyses, the emotional dysregulation and irritability and IQ thresholds considered by the included studies were distinct. Fourth, we were unable to quantify the differential efficacy of specific drugs pooled within each pharmacological group except for antipsychotics and medications with an indication for ADHD. Thus, the possibility of some individual pharmacological agents being efficacious, even if the overall group did not show significant differences compared to placebo, exists. Fifth, due to the heterogeneity of the included studies regarding pharmacological agents used, it was not possible to fully use neuroscience-based nomenclature.^{71, 72} Sixth, 66.2% of the participants were white. Further research on individuals from other races and ethnicities to develop diversity sensitive guidelines are needed. Seventh, it was not possible to ascertain the long-term efficacy of the interventions, due to the fact that included RCTs lasted on average 10.6 weeks. Withdrawal RCTs should be conducted in the future for those medications with evidence of efficacy in short-term trials. As for the limitations of the review per se, we did not meta-analytically evaluate the adverse effects or the reason for attrition in the included studies, which were heterogeneously reported and beyond

the scope of the present work. We also did not address the cost-effectiveness and social benefits of the interventions. A final significant limitation or consideration is related to the operationalization of the outcomes (i.e., emotional dysregulation and irritability) and related instruments to measure it. Emotional dysregulation is commonly presented by individuals with ASD but has not been used as a term to capture co-occurring symptoms using current outcome measures. Instead, most studies in ASD have operationalized emotional dysregulation behavioral symptoms using an Aberrant Behavior Checklist subscale that was originally termed Irritability/Agitation/Crying and which has some limitations including the inappropriate use of total scores;^{27, 73} the rationale for the use of the current operationalization is detailed in the introduction. We hope the evidence provided by this meta-analysis highlights the need for mental health professionals to carry out a more comprehensive and systematic assessment of complex features such as emotion dysregulation and irritability in individuals with ASD. Consequently, based on the evidence provided, professionals may provide a better management of these features for individuals with ASD.

CONCLUSION

Some pharmacological interventions (particularly risperidone and aripiprazole) have proved efficacy for short-term treatment of emotional dysregulation and irritability in ASD. They should therefore be considered, together with adverse events and families' preferences, within first-line treatments for this target. A new generation of pharmacological interventions for irritability and emotional dysregulation targeting new pathophysiological mechanisms such as inflammation or oxidative stress may be beneficial but require further research

Figure 1. PRISMA Flowchart Outlining Study Selection Process

Note: ^aReasons for exclusion of each paper during the full text screening are reported in Table S2, available online.

Figure 2. Forest Plot Showing the Efficacy of Pharmacological Interventions for Emotional Dysregulation and Irritability in Individuals With Autism Spectrum Disorder

Figure 3. Quality Assessment Results

Note: Studies with cross-over design (A) Studies with parallel design (B).

Table 1: Characteristics of the Included Studies

First author and year of publication	Country	Sample size	Age: mean, SD (range)	Sex (% females)	Pharmacological agent/ group	Race/Ethnicity	IQ mean±SD or % intellectual disability)	Trial duration (in weeks)	Risk of bias
Aman 2010 ³⁰	USA	316	9.6, 3.0	11.1	Aripiprazole/ antipsychotic	-	-	8	High risk of bias
Benton 2011 ¹⁸	USA	218	9.7, 3.1 (6-17)	10.5	Aripiprazole/ antipsychotic	-	-	8	Low risk of bias
Findling 2014 ⁷⁴	USA	85	10.4 (2.8)	20	Aripiprazole/ antipsychotic	69.4% White; 22.4% African American, 3.5% Asian, 1.2% American Indian and Alaska native, 3.5% other	-	16	Low risk of bias
Ichikawa 2017 ⁷⁵	Japan	92	10.1, 3.2 (6-17)	18.5	Aripiprazole/ antipsychotic	-	63.0%	8	Low risk of bias
Owen 2009 ⁷⁶	USA	98	9.3, 3.0	12.2	Aripiprazole/ antipsychotic	74.5% White, 18.4% African American, 2.0% Asian, 5.1% other	-	8	Low risk of bias
Kent 2013 ⁷⁷	USA	96	9.0, 3.1	13.1	Risperidone/ antipsychotic	70% White, 20% African American, 7% Asia, 3% other	-	6	Some concerns
McCracken 2002 ⁷⁸	USA	101	8.8, 2.7 (5-17)	19	Risperidone/ antipsychotic	66% White, 11% African American, 7% Hispanic, 8% Asian, 8% Other	73.3%	8	Low risk of bias
McDougle 1998 ⁷⁹	USA	31	28.1, 7.3	29	Risperidone/ antipsychotic	64.9% White, 35.5% African American, 3.2% Hispanic	54.6±23.9	12	Some concerns
Nagaraj 2006 ⁸⁰	India	39	5.0, 1.7 (2-9)	12.8	Risperidone/ antipsychotic	-	56.4%	26	Low risk of bias
Ramerman 2019 ⁸¹	Netherlands	25	29, 17.5 (10-68)	24	Risperidone/ antipsychotic	-	100%	24	Low risk of bias

Shea 2004 ⁸²	Canada	79	7.4, 2.3 (5-12)	21.5	Risperidone/ antipsychotic	69.6% White, 15.2% African American, 15.2% other	63.6%	8	Some concerns
Loebel 2016 ⁸³	USA	150	10.7 (6-17)	18	Lurasidone/ antipsychotic	77% White, 16.2% African American, 6.8% Other	-	6	Some concerns
Remington 2001 ⁸⁴	Canada	36	16.3 (10-36)	16.7	Clomipramine/ antidepressant; haloperidol/ antipsychotic	-	-	7	High risk of bias
King 2009 ⁸⁵	USA	149	9.4, 3.1	14	Citalopram/ antidepressant	72.5% White, 11.4% African American, 9.4% Asian, 1.3% American Indian and Alaska native, 6.7% other, 11.4% Hispanic/Latino, 0.7% Hawaiian	100%	12	Low risk of bias
Neiderhofer 2003 ⁸⁶	Austria	12	7.3, 3.3 (4.2–14.9)	0	Tianeptine/ antidepressant	-	65±16	12	Low risk of bias
Niederhofer 2004 ⁸⁷	Italy	14	7.1, 3.0 (5.2 -11.7)	0	Venlafaxine/ antidepressant	-	67±12	6	Some concerns
Belsito 2001 ⁸⁸	USA	28	5.8, 1.75 (3-11)	3.6	Lamotrigine/ mood stabilizer	-	-	18	High risk of bias
Hellings 2005 ⁶⁹	USA	30	11.2, 4.2 (6-20)	27.8	Valproate/ mood stabilizer	-	-	8	Low risk of bias
Hollander 2010 ¹⁹	USA	27	9.5, 2.6 (4.8–14.9)	16.4	Divalproex sodium/ mood stabilizer	29.6% White, 22.2% African American 22.2% Hispanic, 11.1% Asian, 7.4% other, 7.4% mixed	63.3±23.9	12	Low risk of bias
Wasserman 2006 ⁸⁹	USA	20	8.7, 3.2, (5-17)	15	Levetiracetam/ mood stabilizer	50% White, 35% African American, 5% Asian, 10% Hispanic	75.7±33.4	10	Some concerns
Arnold 2006 ⁵³	USA	16	9.3, 2.9 (5-15)	25	Atomoxetine/ ADHD medication	81.3% White, 12.6% African American, 6.3% Asian	-	13	Some concerns

Handen 2000 ⁵⁴	USA	13	7.4 (5.6-11.2)	23.1	Methylphenidate/ ADHD medication	30.7% White, 53.8% African American, 15.3% Hispanic	-	1	High risk of bias
Jaselskis 1992 ⁵⁵	USA	8	8.1, 2.8 (5-13.4)	0	Clonidine/ ADHD medication	-	59±16	13	Some concerns
Quintana 1995 ⁵²	USA	10	8.5, 1.3 (7-11)	40	Methylphenidate/ ADHD medication	-	64.3±9.9	4	Some concerns
Woodard 2007 ⁷⁰	USA	8	13 (9-17)	12.5	Dextromethorphan/ Opioid antagonist	-	-	10	High risk of bias
Willemsen-Swinkels 1996 ⁹⁰	Netherlands	20	5.5, 1.2 (3-7)	20	Naltrexone/ opioid antagonist	-	-	8	High risk of bias
Chez 2020 ⁹¹	USA	13	21.9, 3.3 (18-60)	21.4	Dextromethorphan quididine/ Opioid antagonist	57.1% White, 7.1% African American, 7.1% Hispanic, 21.4% Asian, 7.1% other	56.7±19.8	8	Low risk of bias
King 2001 ⁹²	USA	39	(5-19)	12.8	Amantadine hydrochloride/ glutamatergic agent	77% White, 33% Other	-	3	Low risk of bias
Martsenkovsky 2016 ⁹³	Ukraine	76	(1.5-3)	Na	Memantine hydrochloride/ glutamatergic agent	-	-	16	High risk of bias
Wink 2018 ²¹	USA	7	16.0, 1.9 (13.5-18.5)	14.3	Riluzole/ glutamatergic agent	71.4% White, 14.3% African American, 14.3% Hispanic	-	12	Low risk of bias
Sprengers 2020 ⁶⁸	Netherlands	92	10.5, 2.4 (7-15)	32	Bumetanide/ diuretic	-	101.0± 20.4	13	Some concerns
Umbricht 2017 ⁹⁴	USA	19	23.4, 5.1	0	RG7713*/ diuretic	-	100±14.5	2	High risk of bias
Carey 2002 ⁹⁵	USA	8	5.0, 1.5 (3-8)	0	Secretin/ neuropeptide	-	-	4	Some concerns
Marchezan 2017 ⁹⁶	Brasil	10	6.7, 1.5 (4-9)	0	Gastrin-Releasing Peptide/ neuropeptide	-	-	4	Some concerns

Munesue 2016 ⁹⁷	Japan	29	22.5, 5.9	0	Oxytocin/ neuropeptide	-	100%	16	High risk of bias
Owley 2001 ⁹⁸	USA	56	6.7, 1.9	14.3	Secretin/ neuropeptide	80.3% White, 7.1% African American, 1.8% Asian, 10.7% Hispanic	32.6 ± 14.7 56.5±21.9	8	Low risk of bias
Unis 2002 ⁹⁹	USA	85	6.4, 2.1 (3-12)	Na	Secretin/ neuropeptide	-	55±13	4	High risk of bias
Bent 2014 ¹⁰⁰	USA	57	7.2, 1.1	14	Omega-3 Fatty Acids/ fatty acids	82.5% White, 7% African American, 3.5% Asian, 1.7% American Indian and Alaska native, 5.2% Other	-	6	High risk of bias
Amminger 2007 ¹⁰¹	Austria	13	11.2, 3 (5-17)	0	Omega-3 fatty acids/ fatty acids	-	-	6	Low risk of bias
Mazahery 2019 ¹⁰²	New Zeland	56	5.1, 1.4 (2.5-8)	20.5	Omega-3 and vitamin D/ fatty acids	48.6% White, 51.3% Other	-	48	Some concerns
Yui 2012 ¹⁰³	Japan	13	14.6, 6.0 (6-28)	7.7	Arachidonic acid docosahexaenoic acid/ fatty acids	-	0%	16	Some concerns
Hardan 2012 ¹⁰⁴	USA	29	7.1, 2.1 (3.2–10.7)	6.1	N-acetylcysteine/ others	-	-	12	Low risk of bias
Lewis 2018 ¹⁰⁵	USA	8	24, 3 (20-28)	14.3	Nicotine/ others	-	-	3	High risk of bias
Veenstra-VanderWeele 2017 ¹⁰⁶	USA	150	11.6 (5-21)	17.3	Arbaclofen/ others	-	49.3%	12	Some concerns
Arnold 2012 ¹⁰⁷	USA	20	7.4, 2.5 (4-12)	15	Mecamylamine/ others	85% White, 10% Asian, 5% other	71.6±26.5	14	Some concerns

Table 2. Efficacy of Pharmacological Interventions for Emotional Dysregulation and Irritability

Group, subgroup*	No. of Studies	N INT	N CTRL	Standardized Mean Difference			z Score	P	Test for Heterogeneity		
				Mean	95 CI				Q	I ²	
Any pharmacological group	45	1527	1329	0.611	0.458	0.764	7.830	<0.001	127.233	65.418	<0.001
Antipsychotics	13	812	613	1.028	0.824	1.232	9.885	<0.001	28.327	57.638	0.000
Antidepressants	4	131	134	0.238	-0.004	0.480	1.925	0.054	0.176	0.000	0.000
Mood stabilizers	4	56	49	0.153	-0.277	0.583	0.698	0.485	3.703	18.980	0.000
ADHD medication	4	47	47	0.471	0.061	0.881	2.254	0.024	0.466	0.000	0.000
<i>Stimulant medication</i>	2	23	23	0.544	-0.058	1.146	1.771	0.076	0.044	0.000	0.000
<i>Non-stimulant medication</i>	2	24	24	0.405	-0.167	0.978	1.387	0.165	0.315	0.000	0.000
Opioid antagonist	3	41	41	1.014	-0.686	2.714	1.169	0.242	7.957	87.433	0.000
Glutamatergic blockers	3	62	60	0.431	-0.107	0.969	1.570	0.116	3.929	49.098	0.000
Diuretics	2	66	64	0.584	-0.111	1.279	1.646	0.100	3.170	68.450	0.000
Neuropeptides	5	141	154	0.287	-0.109	0.683	1.421	0.155	7.458	46.364	0.000
Fatty acids	4	71	68	0.297	-0.084	0.678	1.529	0.126	3.585	16.316	0.000
Others	4	100	99	0.550	-0.179	1.279	1.479	0.139	4.069	50.851	0.000

*Bold font refers to any pharmacological group.

Italic font refers to subgroup within the same pharmacological group.

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