The Role of Methylphenidate and Aripiprazole in the Treatment of Emotion Dysregulation in Children With ADHD

Pei-Yin Pan, MD, PhD, and Chin-Bin Yeh, MD, PhD

Abstract:

Purpose: In this study, we examined the effectiveness of methylphenidate on emotion dysregulation among children with attention-deficit/hyperactivity disorder (ADHD), and the strategy of switching to or adding aripiprazole for nonresponders.

Methods: We conducted a 3-step, 10-week, open-label trial including children (6–18 years old) with ADHD and emotion dysregulation, defined according to the Child Behavior Checklist-Dysregulation Profile. In step 1, patients received methylphenidate treatment for 4 weeks. In step 2, nonresponders were started on aripiprazole treatment for 4 weeks. Nonresponders in step 2 entered step 3, receiving a combination of methylphenidate and aripiprazole for 2 weeks. The primary outcome was the change from baseline in emotion dysregulation, assessed using the irritability subscale of the Aberrant Behavior Checklist. Secondary outcomes included the change from baseline in ADHD symptoms, cross-domain-associated symptoms, adaptive functioning, and neurocognitive profiles.

Results: Among the 30 enrolled patients, 22 (73.3%) responded to methylphenidate (group MR), while 8 entered step 2 (aripiprazole treatment for methylphenidate nonresponders; group MN). In step 2, 5 patients responded to aripiprazole, while 2 patients entered step 3 and received methylphenidate plus aripiprazole. Patients who responded to methylphenidate or aripiprazole exhibited significant improvements in emotion dysregulation (Hedges' g: 2.62 and 1.30, respectively) and school adaptation. Emotion dysregulation severity was correlated with oppositional defiant disorder symptoms, but not with core symptoms of ADHD.

Conclusions: The nature of emotion dysregulation in ADHD is heterogeneous regarding the response to methylphenidate. For most patients, methylphenidate significantly improved emotion dysregulation. Aripiprazole could be effective and safe for methylphenidate nonresponders.

Key Words: aripiprazole, attention-deficit/hyperactivity disorder, irritability, methylphenidate, emotion dysregulation

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Children with attention-deficit/hyperactivity disorder (ADHD) commonly experience emotion dysregulation, characterized by a range of inappropriate emotional reactivity that is disproportionate to the context.[1] In the literature, emotion dysregulation in ADHD is described using a variety of terms—including emotional lability, emotional impulsivity, irritability, tantrums, emotional negativity, and also excitability or exuberance.[2,3] The prevalence of emotion dysregulation in children with ADHD is estimated to be as high as 50%,[4] and it has been listed as one of the associated features of ADHD in the Diagnostic and Statistical Manual of Mental Disorders, 5 Edition.[5] Converging evidence suggests that emotion dysregulation contributes to subsequent psychiatric comorbidities and cross-domain impairments beyond ADHD symptoms, including substance use, suicidality, and interpersonal difficulties.[4,6–8] Despite the significant impacts on mental health and overall functioning, there is not yet any consensus regarding the concept of emotion dysregulation in children with ADHD, or the therapeutic approaches.

Given the high prevalence of emotion dysregulation among children with ADHD, some researchers have argued that emotion dysregulation is a core feature of ADHD, and that the symptom manifestations may be explained by the same neurocognitive deficits.[9] However, large-scale family analysis has revealed that emotion dysregulation and ADHD do not co-segregate within families, implying that emotion dysregulation and ADHD have different genetic backgrounds.[7] Additionally, compared to children with ADHD alone, those with ADHD and emotion dysregulation have more severe and persistent ADHD symptoms.[10–12] Based on the different genetic underpinnings, clinical courses, and outcomes, the combination of ADHD and emotion dysregulation can be viewed as a distinct entity from ADHD. Further examination of this concept requires additional information regarding the differences in treatment outcomes between ADHD children with and without emotion dysregulation.[2] However, relatively little research has addressed this subject.[11]

The majority of available data regarding the effectiveness of treatment for emotion dysregulation in ADHD has been derived from studies conducted among adults.[13] Although stimulants have shown effectiveness for emotion dysregulation in children with ADHD, a considerable proportion of patients do not respond to stimulants,[14] and this population remains neglected in this field of research. Nonstimulants including guanfacine and atomoxetine have shown small-to-moderate effects on irritability and aggressions in oppositional symptoms in children with ADHD, but there has been no sufficient evidence of their effectiveness on emotion dysregulation.[15] Moreover, previous trials of treatment for emotion dysregulation in children with ADHD exhibit substantial heterogeneity, mainly due to the use of varying measurements to define the target patients and outcomes—for instance, the emotion lability subscale of Conners' Parent Rating Scale,[16,17] the Child Behavior Checklist-Dysregulation profile (CBCL-DP),[11,14] Expression and Emotion Scale for Children,[18] and Emotion Regulation Checklist.[19] These rating scales measure different dimensions of emotional symptoms, but do not capture the full spectrum of manifestations of emotion dysregulation in ADHD.

Antipsychotics have been used as adjuvant to methylphenidate in children with ADHD comorbid with disruptive behavior disorders.[20] While some studies suggest efficacy, this combination treatment has not shown clear superiority over methylphenidate or antipsychotic monotherapy. Among the antipsychotics indicated for pediatric patients, aripiprazole shows good tolerability, with low risks of sedation, extrapyramidal symptoms, and metabolic abnormalities.[21] As a dopamine-serotonin partial agonist,

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aripiprazole is Food and Drug Administration-approved for the treatment of main mood disorders, including bipolar disorder and major depressive disorder (adjunctive treatment), as well as irritability associated with autism.[21] Additionally, the combination of methylphenidate and aripiprazole is reportedly effective for children with ADHD comorbid with disruptive dysregulation mood disorder (DMDD).[22] However, the effectiveness of aripiprazole monotherapy or in combination with methylphenidate for children with ADHD and emotion dysregulation has not been well-studied.

The present trial was designed to develop a practical therapeutic strategy for children with ADHD and emotion dysregulation. A 3-step protocol was adopted to examine the effectiveness of switching to or adding aripiprazole as treatment for patients who did not respond to methylphenidate alone. The target patients with ADHD and emotion dysregulation were defined using the CBCL-DP, which had been widely investigated in epidemiological and genetic research.[23,24] The primary outcome was measured using the irritability subscale of the Aberrant Behavior Checklist (ABC-I), which rates a wide range of features of emotion dysregulation that are linked to relevant clinical outcomes.[25] Finally, we analyzed the effectiveness of methylphenidate on ADHD symptoms and emotion dysregulation symptoms, to further clarify the nature of emotion dysregulation in children with ADHD.

MATERIALS AND METHODS

Trial Design

We conducted an open-label 3-step study over 10 weeks. In step 1, patients received treatment with methylphenidate at an optimal dose for 4 weeks by flexible dosing (starting at IR tablets 5 or 10 mg twice per day and increasing to a maximum of 20 mg 3 times per day or OROS tablet 72 mg per day), 7 days per week without drug holidays. Patients who did not respond to methylphenidate with an improvement of emotional symptoms (ABC-irritability subscale score reduced at least 25% from baseline) were eligible for step 2, in which they were switched to aripiprazole at an optimal dose by flexible dosing for another 4 weeks (starting at 2.5 mg per day and increasing to a maximum of 10 mg per day). Patients who did not exhibit a response in step 2 next entered step 3, where they received a combination of methylphenidate and aripiprazole for 2 weeks (the methylphenidate dose in step 1 added to ongoing aripiprazole). Patient follow-up included in-person outpatient visits with the trial psychiatrist at baseline and every 2 weeks after the first dose of study medication. Evaluated outcomes included the treatment effectiveness, adherence to medication, and adverse events. Dose adjustments were made at each visit according to clinical judgment, based on the severity of ADHD and emotion dysregulation symptoms (clinician's impression), the patients' needs and drug side effects. The primary and secondary outcome measurements were administered at baseline and at the end of each step (Fig. 1).

This trial was conducted at Tri-Service General Hospital (TSGH), a university hospital in Taipei, Taiwan. It was approved by the institutional review board of TSGH. All the patients and their parents/guardians provided informed consents prior to enrollment. The trial was registered at ClinicalTrials.gov (ID: NCT05974241).

Patients

Trial patients were 6–18 years of age, drug-naive, and had ADHD and emotion dysregulation. We recruited only drug-naive patients for the possible long-term effects of previous pharmacological treatments on patients' neuropsychiatric symptoms and outcomes.[26] All patients were recruited at the child psychiatric outpatient clinic, and underwent a diagnostic interview with the corresponding author, Dr. Chin-Bin Yeh, a senior child psychiatrist who also administered all the treatments throughout the trial. ADHD was defined using the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Emotion dysregulation was determined based on the CBCL-Dysregulation Profile, which is the sum of T scores of 3 subscales—anxious/depressed, attention problems, and aggressive behaviors—ranging from 180 to 210.[6] Patients were excluded if they had significant medical problems, intellectual disability (IQ < 70), epilepsy, schizophrenia, bipolar disorder, or uncontrolled suicidal risk. Patients with DMDD were also excluded. While frequently co-occurring, DMDD has been categorized as an independent diagnostic entity for its specific irritability symptom dimension and developmental trajectory.[5] The emotion dysregulation in ADHD is rather short-lived and reactive, but the cardinal symptoms of DMDD include tonic irritability and behavioral outbursts of intense anger.[27] This trial focused on patients with ADHD and thus excluded those comorbid with DMDD.

Outcomes

The primary effectiveness outcome was the ABC-I subscale. The ABC is an instrument developed to assess emotional and behavioral difficulties in individuals with developmental disabilities. The ABC-I is a proven, well-validated, and widely used rating

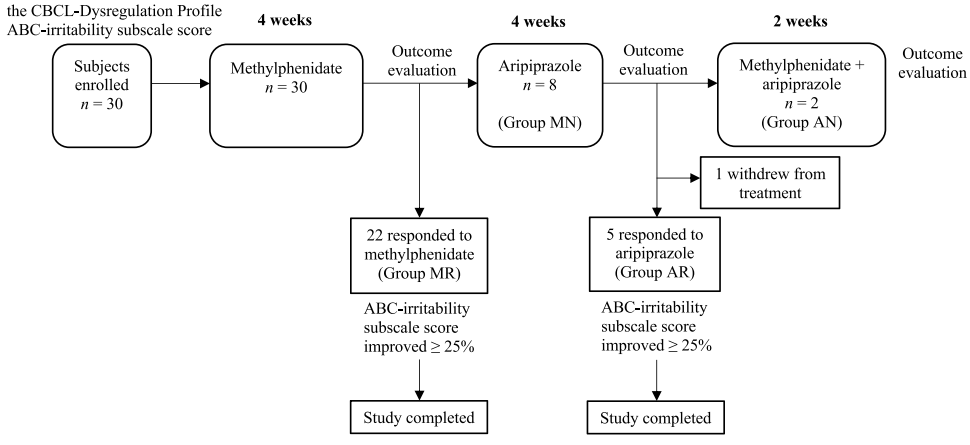

FIGURE 1. Flow diagram of patient disposition during the study. CBCL, Child Behavior Checklist.

inventory for measuring irritability in children.[25] This subscale comprises 15 items regarding irritability, aggression, tantrums, agitation, and unstable mood, which map to the common manifestations of emotion dysregulation in children with ADHD. The total score ranges from 0 to 45, with higher scores indicating greater emotional symptoms.[28]

Secondary effectiveness outcomes included remission from irritability, assessed based on changes (from baseline to the end of each step) in the following scores: the self- and parent-report Affective Reactivity Index (ARI; higher scores indicate greater irritability),[25] the Swanson, Nolan, and Pelham, version IV scale (SNAP-IV; 3 subscales measuring inattention and hyperactivity of ADHD and oppositional defiant disorder [ODD] symptoms; higher scores indicate more severe symptoms);[29] the self- and parent-report Strengths and Difficulties Questionnaire (SDQ; 5 subscales measuring emotional symptoms, conduct problems, hyperactivity, peer problems, and prosocial behavior; higher scores indicate worse problems for the first four listed subscales, but more prosocial behaviors),[30] and the Social Adjustment Inventory for Children and Adolescents (4 subscales measuring adaptive function in school, spare-time activities, peer relations, and home life; higher scores indicate poorer adaptation).[31]

Patients' neurocognitive characteristics were assessed using 3 subtests from the Cambridge Neuropsychological Test Automated Battery (CANTAB):[17] Emotion Recognition Task (ERT; 6 emotions; overall response latencies), One Touch Stockings of Cambridge (a test of spatial planning and working memory; latency to correct and the number of problems solved on first choice), and Spatial Working Memory (a test of executive function; the number of times a new search pattern used; lower scores indicate high strategy use).

Statistical Analysis

A paired *t* test was used to compare the effectiveness measurements of trial drugs in each step. For the step 1 responders (group MR) and nonresponders (group MN), and the step 2 responders (group AR) and nonresponders (group AN), the baseline and end-of-treatment clinical and cognitive profiles were compared by independent t test. Because of the small number of patients, we did not perform a paired *t* test for the nonresponders in step 2 and the patients in step 3 (group AN). We used the Pearson correlations test to examine the relationships between emotion dysregulation (ABC-I and ARI scores) and ADHD symptoms (SNAP-IV scores). A P value <0.05 was considered to indicate statistical significance. Bonferroni correction was used to adjust multiple comparisons. All statistical analyses were conducted using Rstudio, version 4.3.0.[32]

RESULTS

Patient Enrollment, Disposition, and Characteristics

A total of 30 patients were enrolled and received the 4-week treatment of methylphenidate, between April 21, 2017, and March 24, 2022. Of these patients, 22 (73.3%) were responders in step 1 (group MR; ABC-I score was reduced by at least 25% from baseline). The remaining eight patients were nonresponders to methylphenidate in terms of emotion dysregulation, and entered step 2 (group MN). After 4 weeks of aripiprazole treatment, 5 patients (62.5%) were responders with at least 25% reduction of emotion dysregulation (group AR), and 2 patients were nonresponders to aripiprazole and entered step 3 (group AN). One patient withdrew from the study during step 2. The 2 patients in step 3 completed the 2-week combination treatment (Fig. 1).

The mean age of the patients in this study was 8.98 years, 83.3% were male, and 73.3% had ODD (Table 1). The mean IQ was 100.13. The mean subscale scores of SNAP-IV at baseline were 18.33 for inattention, 14.97 for hyperactivity, and 13.90 for ODD. Group MR and group MN did not significantly differ in the baseline SNAP-IV and ABC-I scores, or in the scores of other secondary effectiveness outcomes (Table S1, Supplemental Digital Content, http://links.lww.com/JCP/A955).

Effective Outcomes of Emotion Dysregulation and ADHD Symptoms

The 4-week methylphenidate treatment (step 1) yielded significant improvements of emotion dysregulation among the total patients and in group MR, but not in group MN. The change in ABC-I score from baseline was −9.03 (95% confidence interval [CI], −12.04 to −6.82; Hedges' g, 1.31; $P < 0.001$) among total patients; −12.00 (95% CI, −13.96 to −10.04; Hedges' g, 2.62, $P < 0.001$) in group MR; and while −2.78 (95% CI, −9.18 to 4.43; $P = 0.437$) in group MN (Table 1). Consistent with the ABC-I score, scores on the 3 SNAP-IV subscales were significantly reduced with large effect sizes in group MN (Hedges' g, 1.11, 0.82, 0.79 for inattention, hyperactivity, and ODD, respectively), while these scores were not significantly changed compared to baseline in group MN.

In step 2, among the seven patients who completed the aripiprazole treatment (group AR), 5 showed significant improvement of ABC-I score (Hedges' g, 1.30; $P = 0.022$), while 2 patients did not respond to aripiprazole. Additionally, group AR patients exhibited large improvement of hyperactivity symptoms on SNAP-IV (Hedges' $g = 1.38$, $P = 0.018$). The 2 patients who entered step 3 both responded to the combination of methylphenidate and aripiprazole. Figure 2 illustrates the changes of irritability and ADHD symptoms among the patients at each step, based on the responses of emotion dysregulation to treatment.

Effective Outcomes of Other Clinical Symptoms and Cognitive Profiles

After 4 weeks of methylphenidate treatment, patients in group MR exhibited significant improvement in scores of the self-report ARI ($t = −5.03$, $P < 0.001$), parent-report ARI ($t = −5.51$, $P < 0.001$), conduct problem subscale of the self-report SDQ ($t = −3.88$, $P < 0.001$) and parent-report SDQ ($t = −3.13$, $P = 0.004$), hyperactivity subscale of parent-report SDQ ($t = −2.99$, $P = 0.005$), and school domain of Social Adjustment Inventory for Children and Adolescents ($t = −2.88$, $P = 0.008$). Additionally, patients in group MR exhibited improved adaptation at home ($t = −2.65$, $P = 0.014$) and faster facial expression recognition of happiness ($t = −2.38$, $P = 0.025$) and surprise ($t = −2.39$, $P = 0.024$), although these changes were not significant after Bonferroni correction (Table S2, Supplemental Digital Content, http://links.lww.com/JCP/A955).

Compared to group AN, the patients who responded to aripiprazole in step 2 exhibited improved irritability on the parent-report ARI ($t = −3.89$, $P = 0.011$), hyperactivity symptoms on the self-report SDQ ($t = −3.42$, $P = 0.019$), and adaptation at school ($t = −4.40$, $P = 0.007$) and in peer relationships ($t = −9.16$, $P < 0.001$).

Relationships Between Emotion Dysregulation and ADHD symptoms

In our sample, ODD symptoms on SNAP-IV (but not inattention symptoms) were correlated with scores on the ABC-I ($P = 0.002$), self-report ARI ($P = 0.011$), and parent-report ARI ($P < 0.001$). Additionally, the hyperactivity score on SNAP-IV

TABLE 1. Outcomes Regarding Emotion Dysregulation and ADHD Symptoms After Each Step in This Trial

			Group MR	Group MN	Group MR vs Group MN		Group AR	Group AN	Group AR v. Group AN
		Total Patients Enrolled ($N = 30$)	Patients Responding at Step 1 ($n = 22$)	Patients Entering Step 2 ($n = 8$)	*t/P*	Total Patients Completing Step 2 ($n = 7$)	Patients Responding At Step 2 ($n = 5$)	Patients Entering Step 3 ($n = 2$)	*t/P*
Male, *n* (%)		25 (83.3)	18 (81.8)	7 (87.5)		6 (85.7)	5 (100.0)	1 (50.0)	
ODD, *n* (%)		22 (73.3)	15 (68.2)	7 (87.5)		7 (100.0)	5 (100.0)	2 (100.0)	
Age in years, mean (SD)		8.98 (2.08)	9.19 (2.14)	8.40 (1.90)	0.93/0.362	8.01 (1.68)	7.87 (1.59)	8.38 (2.53)	−0.33/0.752
IQ, mean (SD)		100.13 (11.39)	100.41 (12.81)	99.38 (6.67)	−0.22/0.830	98.14 (6.15)	97.40 (7.23)	100.00 (2.83)	−0.47/0.657
Outcome									
ABC-I									
Baseline	Mean (SD)	20.03 (6.47)	20.38 (4.21)	21.38 (8.58)	−0.68/0.503	21.71 (9.21)	18.40 (5.41)	30.00 (14.14)	−1.74/0.742
Week 4 (Step 1)	Mean (SD)	10.06 (6.80)	7.54 (4.58)	19.00 (4.31)	−6.14/**<0.001**	19.57 (4.31)	18.60 (4.39)	22.00 (4.24)	−0.93/0.394
	Change from baseline (95% CI)	−9.43 (−12.04 to −6.82)	−12.00 (−13.96 to −10.04)	−2.78 (−9.18 to 4.43)		−2.14 (−10.25 to 5.96)	0.20 (−3.01 to 3.41)		
	Hedges' g/*P* value	1.31/**<0.001**	2.62/**<0.001**	NA/0.437		NA/0.542	NA/0.871		
Week 8 (Step 2)	Mean (SD)					9.14 (6.12)	6.00 (3.61)	17.00 (0)	−4.08/**0.010**
	Change from baseline (95% CI)					−12.57 (−20.42 to −4.73)	−12.40 (−21.84 to −2.96)		
	Hedges' g/*P* value					1.29/**0.008**	1.30/**0.022**		
Week 10 (Step 3)	Mean (SD)							14.00 (5.66)	
SNAP-IV Inattention									
Baseline	Mean (SD)	18.33 (5.05)	17.82 (5.21)	19.75 (4.26)	−0.92/0.364	20.29 (4.72)	21.20 (4.66)	18.00 (5.66)	0.78/0.468
Week 4 (Step 1)	Mean (SD)	11.40 (6.56)	8.82 (5.28)	18.50 (4.00)	−4.70/**<0.001**	19.43 (3.26)	18.00 (2.55)	23.00 (1.41)	−2.52/0.053
	Change from baseline (95% CI)	−6.93 (−9.94 to −3.93)	−9.00 (−12.48 to −5.52)	−1.25 (−6.08 to 3.58)		−0.86 (−6.52 to 4.80)	−3.20 (−9.73 to 3.33)		
	Hedges' g/*P* value	0.84/**<0.001**	1.11/**<0.001**	NA/0.590		NA/0.724	NA/0.246		
Week 8 (Step 2)	Mean (SD)					16.57 (5.50)	15.20 (5.72)	20.00 (4.24)	−1.05/0.341
	Change from baseline (95% CI)					−3.71 (−12.10 to 4.67)	−6.00 (−16.82 to 4.82)		
	Hedges' g/*P* value					NA/0.320	NA/0.199		
Week 10 (Step 3)	Mean (SD)							12.50 (6.36)	
SNAP-IV Hyperactivity									
Baseline	Mean (SD)	14.97 (6.57)	14.36 (6.88)	16.63 (5.68)	−0.83/0.414	16.43 (6.11)	15.80 (5.45)	18.00 (9.90)	−0.40/0.706
Week 4 (Step 1)	Mean (SD)	10.10 (6.70)	8.05 (6.28)	15.75 (4.27)	3.20/**0.003**	16.00 (4.55)	14.20 (4.09)	20.50 (0.71)	−2.05/0.095
	Change from baseline (95% CI)	−4.87 (−7.53 to −2.20)	−6.32 (−9.60 to −3.04)	−0.88 (−4.78 to 3.03)		−0.43 (−4.92 to 4.07)	−1.60 (−5.18 to 1.98)		
	Hedges' g/*P* value	0.66/**<0.001**	0.82/**<0.001**	NA/0.613		NA/0.823	NA/0.282		
Week 8 (Step 2)	Mean (SD)					10.29 (5.96)	8.40 (5.46)	15.00 (5.66)	−1.43/0.211
	Change from baseline (95% CI)					−6.14 (−13.13 to 0.85)	−7.40 (−12.71 to −2.09)		
	Hedges' g/*P* value					NA/0.075	1.38/**0.018**		
Week 10 (Step 3)	Mean (SD)							9.00 (5.66)	

SNAP-IV ODD										
Baseline	Mean (SD)	13.90 (6.60)	12.77 (6.77)	17.00 (5.32)	−1.59/0.123	16.86 (5.73)	14.60 (4.10)	22.50 (6.36)	−2.03/0.098	
Week 4 (Step 1)	Mean (SD)	8.97 (6.54)	6.18 (4.79)	16.63 (4.10)		16.29 (4.31)	14.40 (3.21)	21.00 (2.83)	−2.51/0.054	
	Change from baseline (95% CI)	−4.93 (−7.77 to −2.09)	−6.59 (−10.16 to −3.02)	−0.38 (−3.34 to 2.59)		−0.57 (−0.47 to −2.92)	−0.20 (−5.42 to 5.02)			
	Hedges' *g*/*P* value	0.63/**0.001**	0.79/**<0.001**	NA/0.773	−5.47/**<0.001**	NA/0.703	NA/0.921		−3.75/**0.013**	
Week 8 (Step 2)	Mean (SD)					9.71 (5.79)	6.80 (3.56)	17.00 (1.41)		
	Change from baseline (95% CI)					−7.14 (−13.08 to −1.21)	−7.80 (−16.10 to 0.50)			
	Hedges' *g*/*P* value					0.97/**0.026**	NA/0.060			
Week 10 (Step 3)	Mean (SD)							9.50 (3.54)		

was moderately correlated with the scores on the ABC-I and ARI parent-report, but the correlations were no longer significant after multiple comparison correction (Table S3, Supplemental Digital Content, http://links.lww.com/JCP/A955).

Pharmacological Treatment Dosages and Safety Outcomes

In step 1, the mean (SD) daily dosage of methylphenidate was 19.40 (5.65) mg among all patients, 19.44 (6.16) mg for group MR, and 19.29 (4.50) mg for group MN. In step 2, the mean (SD) daily dosage of aripiprazole was 2.81 (0.88) mg. The adverse events reported in step 1 with an incidence over 10% were decreased appetite (56.7%), headache (33.3%), dizziness (20.0%), fatigue (13.3%), and nausea (13.3%). No adverse events were reported in step 2 (Table S4, Supplemental Digital Content, lists all adverse events, http://links.lww.com/JCP/A955).

DISCUSSION

In this pilot trial, we investigated the efficacies of methylphenidate and aripiprazole treatment for children with ADHD and emotion dysregulation, in 3 steps, over a 10-week period. We examined emotion dysregulation as the primary effectiveness outcome, and explored the relationships between emotion dysregulation and ADHD symptoms, as well as other clinical and cognitive profiles. Our analysis yielded 3 key findings. First, methylphenidate effectively treated emotion dysregulation in most children with ADHD, with a large effect size. However, about one-fourth of the patients did not respond to methylphenidate, but responded to aripiprazole alone or combined with methylphenidate. Second, compared to the responders in step 1, the patients whose emotional symptoms did not respond to methylphenidate also exhibited different treatment outcomes in terms of ADHD symptoms, conduct problems, and school adaptation. Third, emotion dysregulation and irritability in children with ADHD were highly correlated with ODD symptoms, but not with the core symptoms of ADHD. These results suggest that the nature of emotion dysregulation among children with ADHD may be heterogeneous in terms of responses to pharmacological treatment, and did not entirely overlap with the nature of ADHD symptoms. To our knowledge, this is the first trial to demonstrate the role of aripiprazole for the treatment of emotion dysregulation in ADHD, especially among nonresponders to methylphenidate.

The response rate of emotion dysregulation in ADHD to methylphenidate within our sample was higher than in 2 previous studies that defined the response according to T scores of Conners' Teacher Rating Scale and CBCL-DP.[14,17] In our present study, we defined response using a relatively low threshold, which could exaggerate the response rate; however, the effect size of emotion dysregulation symptom improvement was large and supported the efficacy. We measured the primary outcome in a manner that encompassed the full range of features of emotion dysregulation—including emotional lability, irritability, and negativity.[28] Our results suggested that methylphenidate generally mitigated that emotional reactivity profile, along with the patients' core symptoms of ADHD. Additionally, the patients exhibited significantly improved conduct problems, in line with the literature showing that methylphenidate is efficacious for disruptive behaviors in ADHD.[33] Taken together, the available evidence suggests that ADHD, emotion dysregulation, and cooccurring conduct problems might share a root in dopaminergic dysfunction,[34] which can be partially resolved by methylphenidate treatment, although the exact brain mechanisms are not completely understood.

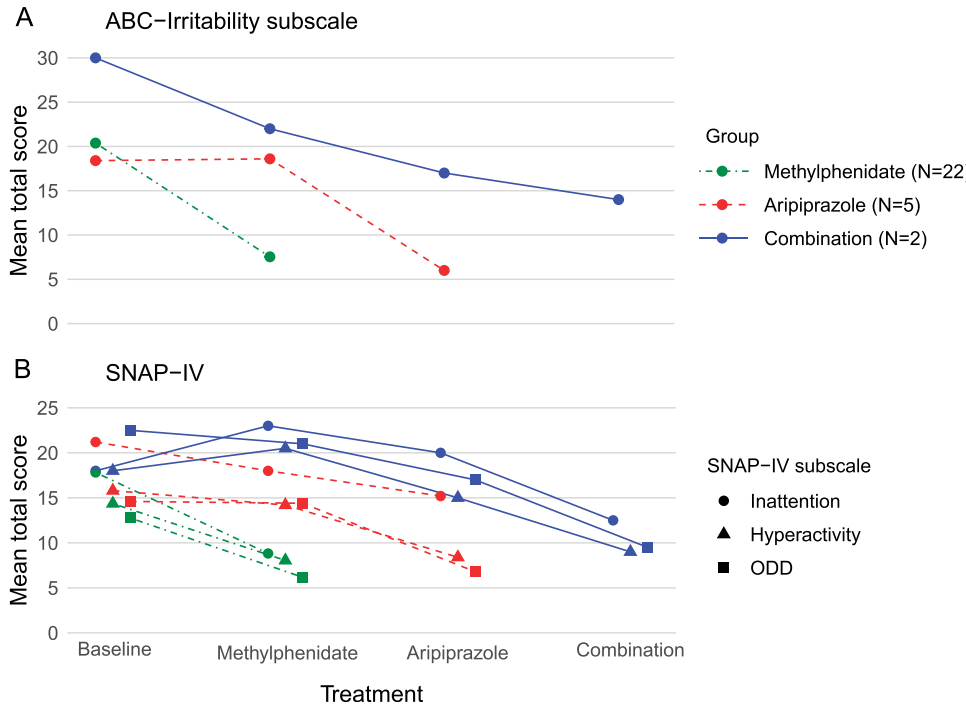

FIGURE 2. Severity of patients' emotion dysregulation and ADHD symptoms, according to their responses to the treatment at each step.

On the other hand, at least one-fourth of the patients did not respond to the 4-week methylphenidate treatment, either in terms of emotion dysregulation or ADHD symptoms. The different treatment profiles might imply that the nonresponders had distinct pathophysiology underlying their emotional and behavior manifestations. These results highlight the heterogeneity of emotion dysregulation in ADHD, and the need for individualized therapeutic strategies. Our study demonstrated that switching to aripiprazole or combination treatment was effective for the methylphenidate nonresponders. The patients who responded to aripiprazole exhibited a reduction of emotion dysregulation symptoms, and improved school adaptation and peer relationships. Considering the additional impairments associated with emotion dysregulation, alternative pharmacological treatments, other than methylphenidate, may be crucial in clinical approaches for children with ADHD. Notably, alternative strategies, such as switching to atomoxetine, have previously been reported to be beneficial for some patients.[18] There remains a need for future trials focusing on treatment for nonresponders, to guide the clinical practice for this understudied population.

Among the methylphenidate responders, stimulants showed the potential to improve recognition of facial expressions of happiness and surprise, but not other cognitive profiles. The literature includes reports that patients with ADHD show anomalies in orienting to emotional stimuli, and this emotional misperception could contribute to emotion dysregulation, especially the overperception of negative stimuli.[2] Our present findings supported that impaired emotion recognition might be involved in the psychological process of emotion dysregulation in ADHD, which could be mitigated with methylphenidate. However, similar effects were not found with aripiprazole treatment, indicating that the pathways of emotion dysregulation in ADHD likely comprise multiple levels of neural mechanisms.[2] Our findings emphasize the need for refinement of the emotion dysregulation phenotypes linked to deficits in specific regulatory process, which could facilitate potential tailored interventions based on a more nuanced understanding of emotion dysregulation in ADHD.

Emotion dysregulation was highly correlated with ODD symptoms, but not with inattention symptoms, and only moderately correlated with hyperactivity with weak significance. These findings were in accordance with the results of a previous study,[7] indicating that emotion dysregulation was more closely related to ODD than to core ADHD symptoms, and not supporting that emotion dysregulation was integral to ADHD.[2] Compared to children with ADHD alone, those with ADHD and emotion dysregulation also reportedly exhibit more severe ADHD symptoms,[7,11,16] differing neurobiology, neural connectivity, and peripheral physiology,[10] and distinct genetics.[2] Regarding the clinical course, these patients exhibit distinct profiles regarding their increased risks for psychiatric comorbidities and worse functions across multiple domains.[4] Nevertheless, there are only limited data regarding the trajectory of ADHD symptoms in children with ADHD and emotion dysregulation. To further determine whether emotion dysregulation is a subtype of ADHD or if these 2 disorders are correlated but distinct dimensions, there remains a need for longitudinal studies contrasting the developmental courses of dimensions of ADHD between children with and without emotion dysregulation.[8]

Limitations

There are several limitations to the present trial. First, the sample size was relatively small, promoting vulnerability to type II error, with inadequate statistical power to detect true significant findings. For example, we cannot exclude the possibility that baseline characteristics may have differed between the responders and nonresponders to methylphenidate. Additionally, in step 2 and step 3, the numbers of subjects were too small to perform statistical analysis, ie, comparison of the treatment profiles among the 3 regimens. Second, this trial did not include a placebo group, so we cannot evaluate the effects of any other factors that may have contributed to improvement of the primary outcome. Third, each step of the trial lasted 4 or 2 weeks; thus, we cannot assess the effectiveness of longer exposure to the trial regimens. Fourth, we did not include

a group of children with ADHD alone, to examine the effects of emotion dysregulation on the clinical manifestations and treatment response of ADHD. Fifth, we do not know whether our findings may apply to other stimulants, or ADHD drugs with different pharmacodynamics. Sixth, we were unable to examine the possible effects of drug-drug interactions between methylphenidate and aripiprazole.[35] Seventh, this trial included both children and adolescents. Since adolescence has been reported to be a critical transition period for both ADHD and emotion dysregulation symptoms,[36] the large age range of subjects may confound our results.

CONCLUSIONS

This pragmatic trial among children with ADHD and emotion dysregulation revealed that methylphenidate treatment generally yielded significant improvement in the severity of emotional symptoms. Moreover, the methylphenidate responders and nonresponders also exhibited distinct treatment responses in terms of their ADHD symptoms, implying the heterogeneous nature and potentially distinct entity of severe emotion dysregulation in ADHD. Among the methylphenidate nonresponders, switching to or adding aripiprazole could be effective and safe for a short-term treatment period. Our results indicate the potential role of aripiprazole treatment for children with ADHD and emotion dysregulation resistant to methylphenidate. These findings could provide professionals with preliminary evidence to guide pharmacological approaches for this population in clinical settings. There remains a need for future studies with larger sample size and longitudinal follow-up, to validate our results and further elucidate the developmental associations between emotion dysregulation and ADHD.

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AUTHOR DISCLOSURE INFORMATION

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DATA AVAILABILITY STATEMENT

The dataset generated during and/or analyzed during the current study are not publicly available due to the protection of participant anonymity.

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