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Drug Holidays May Attenuate Beneficial Effects of Treatment on Emotion Regulation and Recognition Among Children with ADHD: A Single-Center, Prospective Study

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ABSTRACT

Background: In this study, we aimed to evaluate the effects of drug holidays during summer vacations on children with attention deficit/hyperactivity disorder (ADHD) treated with methylphenidate in terms of ADHD symptoms and emotion regulation (ER).

Methods: This single-center, naturalistic, prospective cohort study included pre-, post-, and post-drug holiday evaluations. All patients diagnosed with ADHD and included in our study were administered the Clinical Global Impression Scale, Affective Reactivity Index-parent and child, reading the mind in the eyes test (RMET), Faces test and Cognitive Emotion Regulation Questionnaire for Children 3 times. Fifty-six patients met the inclusion criteria and ten were lost to follow-up. Thirty-nine participants had complete evaluations at all time points.

Results: Both parent and self-report ratings of child irritability were significantly reduced after methylphenidate (MPH) treatment (P=.003 and .002, respectively), although they returned to baseline after drug holidays (P=.618 and .974, respectively). The use of self-blame as a cognitive emotion regulation strategy increased significantly after treatment and remained significantly elevated even after drug holidays (P=.024 and .022, respectively). Children used planning as a cognitive strategy significantly more frequently during MPH treatment (P=.034), although this elevation was temporary and returned to baseline levels after the drug holidays (P=.890). Reading the mind in the eyes test performance was significantly improved after MPH treatment and did not change after drug holidays (P=.009 and .006, respectively), while there was a tendency for facial emotion recognition abilities to improve at the last visit (P=.051).

Conclusion: Our results suggest that MPH treatment improves child- and parent-reported irritability, clinician-rated disorder severity, RMET performance, and the use of planning as a cognitive ER strategy, although only improvement in RMET performance continued after drug holidays. Our results may support the importance of continuing treatment over the holidays for most children with ADHD unless necessitated by adverse events, growth problems, or development of tolerance.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder of childhood onset with potentially life-long consequences that is characterized by developmentally inappropriate and impairing symptoms of inattention, hyperactivity, and impulsivity.[1] Recent reviews suggest that its prevalence among children aged 4-18 years is 3.7%, with a global prevalence of 7.6% in prepubertal children and 5.6% among adolescents.[2,3] Attention deficit/hyperactivity disorder is believed to have a complex etiology, although significant heredity and a favorable response to psychopharmacological treatments point to a neurobiological component as the primary cause.[4] The majority of treatment guidelines suggest psychostimulants, primarily methylphenidate (MPH) and the non-stimulant atomoxetine (ATX), as initial interventions.[5,6]

Emotion regulation (ER) is a complex and multifaceted process that involves the modulation of emotional arousal for personal and social purposes. It is based on the basic

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neurobiological processes underlying arousal and is constrained by temperamental individuality. Conceptual understanding of emotions, strategies to manage them, and self-regulation, as more complex components, emerge later under social influences.[7] Emotion recognition and understanding pertain to understanding one's and others' emotions correctly by using emotional cues inherent in communication domains such as faces, gestures, postures, and speech. This skill is crucial for understanding messages conveyed during social interactions and for generating appropriate responses.[8] Emotional recognition and understanding are closely associated with academic skills and social functioning among children and adolescents.[9,10] Most studies conducted to date suggest that children and adolescents with ADHD may be impaired in emotion recognition from facial and auditory stimuli and that these impairments may be more pronounced for fear and anger.[11,12] Emotional recognition deficits may also worsen from childhood to adolescence.[9]

Emotion dysregulation (ED), defined as failure to regulate one's own emotions, may lead to behavioral problems and impair academic/vocational/social functioning and quality of life. Early signs and symptoms of ED may include exaggerated emotional reactivity, impulsivity, irritability/temper tantrums, reduced tolerance to frustration, hyperarousal, inappropriate emotional expressions, emotional lability, and increased sensitivity to negative experiences.[11-13] Studies conducted to date suggest that ED is common among individuals with ADHD, with a rate of 30.0-45.0% among children receiving the diagnosis. Conversely, among child samples with clinically significant ED, ADHD rates may exceed 85.0%.[13] The mechanisms underlying this comorbidity are currently not clear, although treatment of ADHD symptoms with psychostimulants and other approved agents has been reported to reduce ED in the short term, although their long-term effects are not clear.[13]

"Drug holidays" are deliberate interruptions of ADHD pharmacotherapy for a definite period and for a specific clinical purpose and available guidelines recommend that treatments over a year may be accompanied by drug holidays on an individualized basis. The aims of these drug holidays may include evaluating the necessity of continuing treatments, managing adverse effects, controlling the possibility of tolerance, and increasing the awareness of children and their parents regarding the advantages of treatment.[14-17] Despite the widespread use of drug holidays in routine clinical practice, knowledge concerning their effects on ADHD symptoms, quality of life, and adverse effects is limited, and the available results are mainly related to drug holidays on weekends.[17] According to the literature, short-term drug holidays may be beneficial to control treatment-related adverse events although ADHD symptoms may worsen with longer-term cessations of treatment.[17] A recent retrospective chart-review study also suggested that drug holidays might not have an impact on growth in children with ADHD.[18] A previous prospective study from our group suggested that drug holidays over the summer may not affect the beneficial effects of stimulant treatment on psychomotor speed among Turkish children with ADHD, while resistance to interference was reduced after holidays.[19] To the best of our knowledge, no study to date has evaluated the effects of drug holidays on emotion recognition and regulation among children with ADHD using a naturalistic, prospective design. Emotion dysregulation in ADHD is rarely addressed despite its importance for quality of life and prognosis.[13] Therefore, the purposes of this study were to assess the impact of drug holidays on emotion regulation and ADHD symptoms in children receiving methylphenidate treatment for ADHD during their summer break and to increase the awareness of children and parents regarding the advantages of treatment. We hypothesized that ED and ADHD symptoms would change after drug holidays.

MAIN POINTS

- Our results suggest that MPH treatment improves child- and parent-reported irritability, clinician-rated disorder severity, RMET performance, Use of planning as a cognitive ER strategyin children with ADHD. According to our results, only the improvement in RMET performance continued after drug holidays. According to our results, the use of self-blame increased after treatment, which may reflect the effects of internalized stigmatization
- Our results suggest that prolonged drug holidays may increase clinician-rated disorder severity.
- As recommended in the AACAP, CADDRA, and NICE guidelines, it would be appropriate for the clinician to take an individualized approach to the decision-making process and discuss the risks, benefits, and alternative coping strategies for each patient.

MATERIAL AND METHODS

Study Center, Sampling, and Ethics

Pre-, post-, and post-drug holiday assessments were part of this single-center, naturalistic, prospective cohort study. Between January 2022 and November 2022, the Abant İzzet Baysal University Medical Faculty Child and Adolescent Psychiatry outpatient clinic served as the site of this investigation. The study center's Clinical Research Ethics Committee granted the IRB approval (date/no.:2021/40). Potential participants of the study included patients who applied to the study center with complaints of "inattention" and/or "hyperactivity/impulsivity" during the study period. The criteria for inclusion were age between 8 and 12 years, diagnosis of ADHD according to the K-SADS-PL Turkish version, acceptance of MPH treatment for ADHD symptoms, being either treatment-naïve or with a history of treatment for ADHD in the past (with no treatment in the last 6 months prior to participation in the study), and giving parents' informed consent and children's

verbal or written approval to participate in the study. The criteria for exclusion were age younger than 8 years or older than 12 years, previous diagnosis of ADHD, receiving treatment for the past 6 months prior to participation, and chronic medical/neurological diseases requiring treatment. Comorbid anxiety, mood, disruptive behavior (i.e., oppositional defiant disorder, ODD; conduct disorder, CD), tic and learning disorders (LDs) were allowed and their effects were controlled in analyses. Autism spectrum disorders, intellectual disabilities, trauma-related disorders, and active psychosis was another criterion for elimination, as was parental psychopathology or illiteracy.

Study Procedures

The first 71 cases with symptoms of ADHD who applied were interviewed by the resident child psychiatrist. The DSM-5.1 was used to confirm the ADHD diagnosis. Later on, the study's objectives, course of therapy, and diagnosis were disclosed to the patients and their parents. Seven patients declined to take part in the trial, while 8 patients and their parents declined MPH treatment. In order to confirm the diagnosis of ADHD and rule out concomitant psychiatric problems, the remaining individuals (n=56) had additional evaluation using a semi-structured interview (i.e., Schedule for Affective Disorders and Schizophrenia for School-Aged Children Kiddie-SADS-Lifetime Version; K-SADS-PL-Turkish). Anxiety disorder comorbidity was determined in 7 patients (generalized anxiety, n=4; social anxiety, n=3), two patients each were diagnosed with tic disorders and major depressive disorders. Learning and disruptive behavior disorders were diagnosed in 8 and 20 patients (ODD, n=13; CD, n=7), respectively. Thirty-nine patients in all (69.6%) had more than one diagnosis. In this study, 56 patients who met the inclusion criteria were considered. Self-report forms and parents forms were given out at the study's inclusion and follow-up visits (T1: 60 days after initiation of MPH, T2: 60 days after suspension of MPH). Ten patients (17.9%) did not undergo post-treatment evaluation. The reasons for attrition were as follows: no contact with the phone (n=3, 5.4%), discontinuation of treatment due to adverse effects (n=3, 5.4%), poor compliance (n=3, 5.4%), and choice to continue treatment at another center (n=1, 1.8%, Figure 1). The clinicians evaluated participants at each visit using clinical global impressions scale (CGI), reading the mind in the eyes test (RMET) and faces test (FT), while parents reported affective reactivity. The children completed self-reports on affective reactivity and emotion regulation at each visit.

Measures

1. **Sociodemographic Data Form:** The researchers created this form to collect data on the age, gender, grade, history of ADHD interventions, number of siblings, total family size, parent's age, educational background, and occupations of the participants. Included were diagnoses and physical/psychiatric conditions in the parents that needed to be treated (if any).
2. **Schedule for Affective Disorders and Schizophrenia for School-Aged Children Kiddie-SADS Lifetime Version (K-SADS-PL):** K-SADS-PL is a semi-structured interview used to evaluate lifetime and current psychopathology among children and adolescents according to DSM-IV-TR criteria.[20] It was later revised to reflect DSM-5 criteria and both the initial and the revised versions were found to be valid and reliable among Turkish children.[21,22]
3. **Clinical Global Impressions Scale (CGI):** The American National Mental Health Institute created the clinician-rated Clinical Global Impressions Scale (CGI).[23] It consists of 3 sections in which disease severity, improvement, and treatment-related side effects are evaluated. Before and during therapy, we applied the severity part, and in the post-treatment phase, we applied the recovery section.[23]

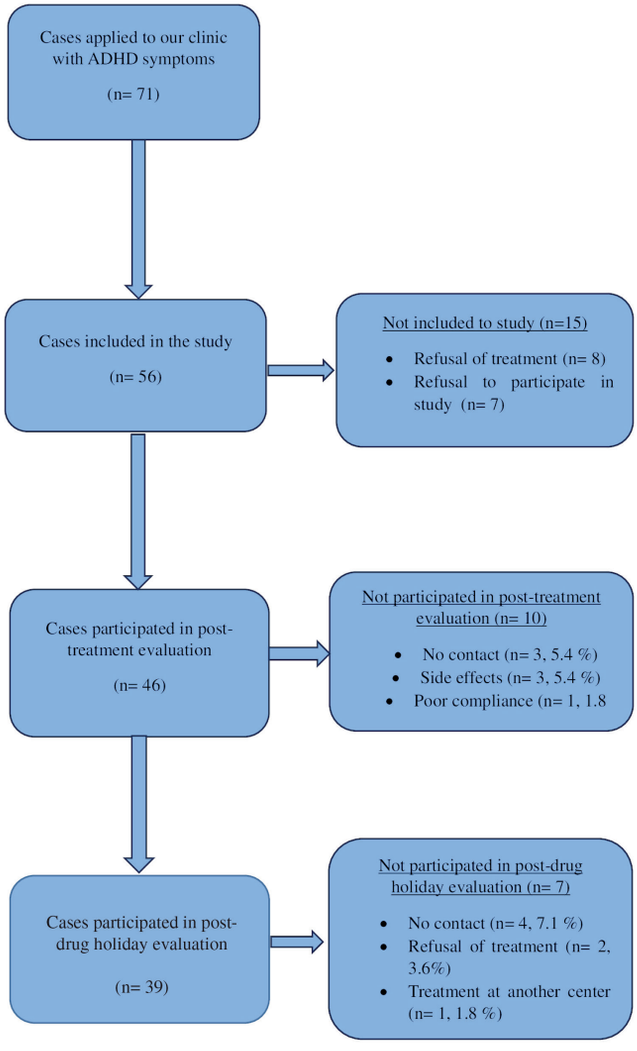

Figure 1. Study flow-chart.

4. **The Affective Reactivity Index (ARI)-Parent (ARI-P) and Child (ARI-C) Forms:** The ARI was developed by Stringaris et al[24] to evaluate the severity of irritability and the effects of interventions. Both the parent and child forms evaluate irritability with 6 items and the impairment due to it in a separate item. Each item is evaluated on a 3-point Likert-type scale (0 = "not true" to 2 = "certainly true"), and the sum of the first 6 items denotes the total ARI score. The Turkish versions of the ARI parent and child forms were previously found to be valid and reliable and used in studies on community and clinical populations.[25,26] Affective reactivity index-parent and child were selected in the study due to their brevity and feasibility. Cronbach alphas of ARI-P and C in the current sample were; 0.89 and 0.81, respectively.
5. **Cognitive Emotion Regulation Questionnaire for Children (CERQ-K):** The CERQ-K was developed by Garnefski et al[27] to evaluate emotion regulation strategies in children aged 9-12 years, and its Turkish translation was found to be valid and reliable.[26] The CERQ-K consists of 36 5-point Likert-type items (1 = never to 5 = always) tapping nine cognitive emotion regulation domains (i.e., self-blame, other-blame, acceptance, planning, positive refocusing, rumination-focus on thought, positive reappraisal, putting into perspective, and catastrophizing). Among those self-blame, other-blame, rumination- focus on thought and catastrophizing are classified as maladaptive while the remainder are judged to be adaptive. The scores for each domain may vary between 4 and 20 with elevated scores denoting more frequent use of the strategy. Cognitive emotion regulation questionnaire for children was selected to evaluate a broad domain of cognitive emotion regulations strategies and applicability in the age range of the sample. Cronbach alpha in the current sample was 0.82.
6. **Reading the Mind in the Eyes Test (RMET):** The RMET evaluates the ability to understand mental states and emotions by viewing eye expressions. It was developed by Baron-Cohen et al and later revised.[28] A Turkish reliability study was conducted by Yıldırım et al,[29] while Girli[30] later established the psychometric properties of the child and adult forms. Greater RMET scores are thought to reflect better social cognition and emotion recognition abilities. Cronbach *α* of RMET in the current sample was 0.66.
7. **Faces Test (FT):** This test was developed by Ekman[31] to evaluate the ability to recognize facial expressions of emotions. Greater FT scores are thought to reflect higher facial emotion recognition abilities. Guttman Lambda-2 of FT in the current sample was 0.56. Reading the mind in the eyes test and FT were used in the study due to their practicality and to evaluate emotion recognition skills.

Statistical Analysis

Study data were analyzed using IBM SPSS Statistics for Windows™ version 23.0 (IBM Corp., Armonk, NY, USA). Quantitative data were reported as means and standard deviations or as medians and inter-quartile ranges (IQR), depending on the ordinality and normality assumptions. Nominal data were summarized as frequencies with percentages. Due to the non-normality of the data, non-parametric tests were used in the analyses (Shapiro-Wilk test, $P < .05$). To summarize the sociodemographic and clinical factors, descriptive analyses were performed. The Wilcoxon test was applied for bivariate comparisons within patients, and the Mann-Whitney *U*-test was utilized to compare treatment completion rates with attrition rates. The Chi-square test was utilized to assess bivariate associations between nominal variables, while Spearman's correlation coefficients were used to evaluate the relationships between quantitative and ordinal variables. Bonferroni-Holm correction for controlling family wise error was used in bivariate comparisons between children with ADHD and comorbid disruptive behavior/learning disorders and those without (p', Gaetano, J. (2018). Holm-Bonferroni sequential correction: An Excel calculator (1.3) [Microsoft Excel workbook]. Retrieved from: https://www.researchgate.net/publication/322568540_Holm Bonferroni_sequential_correction_An_Excel_calculator_13. DOI:10.13140/RG.2.1.3920.0481]. *P* was set at .05 (2-tailed). Because there were limited studies in the literature on drug holidays and due to the naturalistic design of the study no a priori power analysis was undertaken.

RESULTS

Fifty-six children (75.0% male, n = 42) with a median age of 115.0 (IQR = 39.5) months were included in the study. Most children (91.1%, n = 51) lived in nuclear families. The majority of both mothers (57.1%, n = 32) and fathers (51.8%, n = 29) had graduated from secondary school. The sample resided in Western Black Sea Region and most (75.0%) had low socioeconomic status. More than half of the sample were diagnosed with the ADHD-combined subtype (55.4%, n = 31) while the rest were diagnosed with ADHD-inattentive subtype (44.6%, n = 25). Methylphenidate treatment was initiated in all participants and ten (17.9%) were lost to follow-up. Most children had moderate to severe symptoms at baseline (Mean CGI-S = 4.8, SD = 0.8). The median daily doses of MPH at baseline and after titration were 15.0 (IQR = 10.0) mg and 21.3 (IQR = 9.3) mg, respectively. Sensitivity analyses revealed that those continuing follow-up used the cognitive strategies of putting into perspective ($P = .016$) and positive reappraisal ($P = .018$) significantly more frequently than those lost to attrition (Mann-Whitney *U*-test for both). Apart from these, there were no significant differences between patients continuing treatment and those lost to attrition in terms

Table 1. Symptom Severities of Children with ADHD According to Clinicians Assessed Pre-/Post-Treatment and After Drug Holidays

Median (IQR)	T0 (n=56)	T1 (n=46)	T2 (n=39)	*P**		
				T0-T1	T1-T2	T0-T2
CGI-S	5.0 (1.0)	3.0 (1.0)	3.0 (1.0)	<.001	<.001	<.001

*Wilcoxon signed ranks test.
CGI-S, Clinical Global Impressions-Severity; IQR, inter-quartile range; T0, pre-treatment; T1, post-treatment; T2, after drug holiday.

of sociodemographic data, ADHD types, comorbidities, CGI, ARI-P, ARI-C, RMET, FT, or the remaining subtests of the CERQ-K. Seven patients were lost to follow-up for the post-drug holiday evaluation, resulting in 39 participants with complete evaluations at all time points. There was no statistically significant difference between ADHD subtypes in terms of ER, RMET, Faces test, ARI-P, and ARI-C at baseline.

The study was designed to reflect the academic period in a year with children receiving their diagnoses in the Autumn and treatment with any form of MPH initiated thereafter. Immediate release from was dosed twice daily at the morning and noon while extended release forms were given once daily in the morning. The mean dose of MPH at initiation was 15.6 mg/day which was titrated to 21.9 mg/day at the second visit which took place after 2 months of treatment. Parents of patients were contacted at the beginning of the summer holiday and they were interviewed on their intent to continue/ discontinue treatment. All the parents reported that they would stop treatment during the summer. At the end of the summer holiday the patients and their parents were evaluated again after 2 months of drug holiday.

All patients with an ADHD diagnosis who participated in our study received CGI, ARI-P, ARI-C, RMET, FT, and CERQ-K 3 times: before treatment (T0), after treatment for 8 weeks (T1), and after a drug holiday of 8 weeks (T2). Symptoms were significantly reduced (i.e., 40.0% from baseline) according to clinicians after treatment, with no effect from drug holidays (Table 1).

Both parent and self-report ratings of child irritability were significantly reduced after MPH treatment, although they returned to baseline after the drug holidays. Children rated their irritability as significantly elevated after drug holidays compared to when they were using MPH. The use of self-blame as a cognitive emotion regulation strategy increased significantly after treatment and remained significantly elevated even after drug holidays (i.e., 25.0% from baseline). Children used planning as a cognitive strategy significantly more frequently during MPH treatment, although this elevation was temporary and returned to baseline levels after the drug holiday (Table 2). Lastly, children used catastrophizing significantly more frequently during the last evaluation than during previous evaluations (i.e., 9.1% from baseline).

The emotion recognition abilities of children, as evaluated with the RMET, were significantly improved after MPH treatment and did not change after post-drug holidays (i.e., 22.6% from baseline), while there was a tendency for facial emotion recognition abilities to improve at the last visit (Table 3).

Child-reported affective reactivity correlated positively, moderately, and significantly with parent-reported affective reactivity at baseline (*P*: 0.42, $P < .010$), while it was weakly correlated with catastrophizing strategy (*P*: 0.32, $P < .050$). Other CERQ-K subtests did not display significant correlations with clinician rated severity, parent and child

Table 2. Parents and Children Rated Irritability and Cognitive Emotion Regulation Strategies of Children with ADHD Pre-/Post-Treatment and After Drug Holidays

Median (IQR)	T0 (n=56)	T1 (n=46)	T2 (n=39)	*P**		
				T0-T1	T1-T2	T0-T2
ARI-parent total	3.0 (5.8)	2.0 (5.3)	3.0 (4.0)	*.003*	.196	.618
ARI-child total	4.0 (5.5)	3.0 (4.0)	4.0 (6.0)	*.002*	*.034*	.974
CERQ-K self-blame	8.0 (4.8)	10.0 (4.7)	10.0 (6.0)	*.024*	.773	*.022*
CERQ-K other blame	7.5 (8.0)	10.0 (3.5)	9.0 (6.0)	.241	.474	.054
CERQ- K acceptance	10.0 (6.0)	12.0 (3.0)	11.0 (6.0)	.165	.467	.185
CERQ- K planning	13.0 (6.0)	14.0 (4.3)	13.0 (6.0)	.097	*.034*	.890
CERQ- K positive refocusing	13.0 (6.0)	14.0 (7.0)	12.0 (4.0)	.203	.251	.086
CERQ-K- rumination/ focus on thought	12.0 (7.7)	13.0 (4.2)	13.0 (6.0)	.065	.648	.151
CERQ- K positive reappraisal	15.0 (6.0)	12.0 (6.0)	12.0 (4.0)	.438	.956	.337
CERQ-K putting into perspective	12.0 (4.7)	13.0 (6.0)	12.0 (7.0)	.359	.607	.346
CERQ-K catastrophizing	11.0 (4.0)	11.0 (6.0)	12.0 (5.0)	.118	.708	*.039*

*Wilcoxon signed ranks test.
ARI, Affective Reactivity Index; CERQ-K, Cognitive Emotion Regulation Questionnaire for Children; IQR, inter-quartile range; T0, pre-treatment; T1, post-treatment; T2, after drug holiday.

Table 3. Emotion Recognition Abilities of Children with ADHD Assessed Pre/ Post-Treatment and After Drug Holidays

Median (IQR)	T0 (n=56)	T1 (n=46)	T2 (n=39)	*P**		
				T0-T1	T1-T2	T0-T2
Reading the mind in the eyes test	15.5 (8.8)	16.0 (9.0)	19.0 (8.0)	*.009*	.979	.006
Faces test	15.0 (5.0)	15.0 (3.3)	15.0 (3.0)	.428	.102	.051

*Wilcoxon signed ranks test.
IQR, inter-quartile range; T0, pre-treatment; T1, post-treatment; T2, after drug holiday.

reported affective reactivity and emotion recognition tests at baseline (Supplementary Table 1). The RMET and Faces test scores were also positively, moderately, and significantly correlated, respectively (*P*: 0.57, *P* < .010).

After treatment, no significant correlations were found between child- and parent-rated affective reactivity, clinician-rated disorder severity, and the CERQ-K (apart from rumination with child affective reactivity, *P*: 0.32, *P* < .050), RMET, and Faces tests. Similar to the baseline evaluations, the RMET and Faces test scores correlated positively, moderately, and significantly (*P*: 0.55, *P* < .010, Supplementary Table 2). After the drug holidays, no significant correlations were found between child- and parent-rated affective reactivity and clinician-rated disorder severity and the CERQ-K, RMET, and Faces tests, whereas the RMET and Faces test correlated significantly between themselves (*P*: 0.60, *P* < .010, Supplementary Table 3).

Finally, we compared children diagnosed with ADHD having comorbid disruptive behavior/learning disorders with those without using the Mann-Whitney *U*-test and used Holm-Bonferroni correction to control family wise error. The groups did not differ significantly in terms of sociodemographic, clinical, self-reported, or parent-reported variables (*P*' > .611).

DISCUSSION

In this single-center, naturalistic, prospective, clinic-based study, we evaluated the effects of drug holidays during summer vacations among children with ADHD treated with MPH in terms of clinician-rated disorder severity, parent- and child-rated irritability, child-reported cognitive emotion regulation strategies, and emotion recognition abilities as measured by RMET and FT. These variables were evaluated at baseline (T0), after MPH treatment (T1), and after drug holiday (T2). According to our results, clinician-rated disorder severity, along with parent- and child-rated irritability, reduced with treatment, returning to baseline after drug holidays. Children used self-blame as a cognitive ER strategy significantly more frequently after baseline along with planning, although the increase in the latter strategy was temporary and returned to baseline levels after drug holidays. They also used catastrophizing significantly more frequently during the last visit than during previous evaluations. The emotion recognition abilities of children, as evaluated with the RMET, significantly improved after MPH treatment and did not change after drug holidays, while there was a tendency for facial emotion recognition abilities to improve at the last visit, although this was not significant.

Previous studies on children, adolescents, and adults with ADHD from our country as well as from others found that they were impaired in terms of emotion and facial recognition and that treatment may ameliorate these impairments.[8,9,11-13,32-36] Poor performance in emotion and facial recognition was correlated with social-emotional impairment among participants with ADHD, and the beneficial effects of stimulant treatment on ER/emotion recognition seemed to accrue over time.[37] The relationships between executive functioning, IQ, language/pragmatics skills, and the relative importance of hyperactivity/impulsivity versus inattention symptoms and emotion/facial recognition abilities among those with ADHD are still debated.[8,9,32-37] Our findings, which partially corroborate earlier research, indicate that emotion recognition abilities, as evaluated with RMET, may benefit from at least 8 weeks of treatment with MPH, while part of those gains may remain stable after drug holidays. However, MPH treatment did not significantly affect the FT performance. FT involves the evaluation of a gestalt stimulus, while RMET involves the evaluation of a specific stimulus (i.e., faces versus eyes). In addition, responses in the FT are coded as "true" or "false" while the RMET requires a forced choice between four items.[28,29,31,33] These differences across tasks may explain the different results obtained. Additionally, the exclusion of intellectual disabilities may introduce "floor" and "ceiling" effects for this task, thereby reducing variability.[38] The trend of increasing FT performance at the last evaluation may reflect the effects of maturation and reduced intra-group variability. Also, lower levels of reliability of both tests in our sample may have affected our results. We did not evaluate the effects of executive functioning, IQ, and language/pragmatic skills on RMET/FT performance, and our study was not adequately powered to evaluate the relative importance of inattentive/ hyperactive-impulsive symptom domains on emotion/facial recognition. The limited sample size also precluded analyses of emotional valence at baseline and after treatment, as assessed by RMET and FT. Finally, we excluded adolescents and focused on children with ADHD attending primary school to reduce the variance in the tests. Further studies evaluating the effects of MPH treatment and drug holidays on these constructs may involve larger and more diverse samples from both sexes and consist of different ADHD subtypes.

Attention deficit/hyperactivity disorder is frequently associated with ED/irritability, and this relationship may be reciprocal, with clinically significant ED/irritability

being associated with ADHD.[11-13,39] Treatment of ADHD with stimulants or other agents was reported to reduce irritability.[11-13,39] Our results are in accordance with those of previous studies, and both children and their parents reported that irritability/affective reactivity reduced after treatment. Although parents reported no significant increase in irritability after drug holidays, the children reported that their irritability increased after holidays. This discrepancy may reflect greater awareness of children's internal experiences or their expectations of academic and peer-related difficulties during the academic year. Their parents on the other hand may have limited awareness of this irritability if it is not expressed as anger.[40,41] If replicated, our results suggest that at least some children with ADHD and irritability may benefit from continuous MPH treatment or re-initiation of treatment prior to the commencement of the next academic year. Further studies on irritability and its response to MPH treatment among children with ADHD may evaluate the roles of teacher/peer relationships, academic competence, and subthreshold symptoms of depression/anxiety, and may also employ teachers as informants.

To date, studies have reported that ADHD may be impaired in various domains of the ER, including recognition, reactivity, impulsivity, arousal, expression, lability and salience of negative stimuli.[11-13,32-39]

Studies evaluating cognitive emotion regulation among those with ADHD found that these patients used maladaptive strategies such as rumination, self-blame, and catastrophizing significantly more frequently, while adaptive strategies such as reappraisal were rarely used.[42-44] The use of maladaptive strategies has been associated with academic- social problems as well as internalizing symptoms used.[42-44] Emotion control training may also improve the use of reappraisal among patients with ADHD symptoms.[45] Our results are partially in accordance with those previously reported. There were no significant correlations between parent reported affective reactivity and child emotion regulation strategies while child reported affective reactivity correlated positively with catastrophizing and rumination, at baseline and after initiation of MPH respectively. The participants with ADHD in our study increased their use of self-blame after the initiation of treatment and continued to use it even after drug holidays. Their use of planning increased significantly with MPH treatment although this returned to baseline after drug holidays. Finally, they used catastrophizing significantly more frequently during the last evaluation. The increase in self-blame in our sample may reflect elevated internalized stigmatization, perhaps through parental reactions[46,47] or cognitive maturation. Methylphenidate may increase planning as a cognitive ER strategy even in the absence of ER training, although its effects may be temporary. Finally, the increased use of catastrophizing in the last evaluation may reflect the effects of cognitive maturation. Correlation analyses (Supplementary Tables 1-3) suggest that affective reactivity in children with ADHD may correlate with differing facets of cognitive emotion regulation before and after MPH treatment. Sensitivity analyses suggested that children with ADHD who use adaptive strategies, such as putting into perspective and positive reappraisal, may be more likely to continue MPH treatment. Future studies on cognitive emotion regulation and its response to treatment among children with ADHD may evaluate the effects of ER training and non-stimulant agents on more diverse and larger samples and follow participants for longer durations.

Finally, MPH treatment in our sample significantly reduced clinician-rated disorder severity, although it increased after drug holidays. This supports our results in a previous study and suggests that prolonged drug holidays may increase clinician-rated disorder severity.[19]

The results of this study should be evaluated based on their limitations. First, it i's possible that our findings are unique to the research center and cannot be applied to other centers, samples from the community or those with hyperactive/impulsive presentations of ADHD. Second, the results might have been impacted by the small sample size which was predominantly from lower socio-economic status and high attrition rate. The significantly lower use of adaptive cognitive emotion regulation strategies among patients lost to follow-up may support selective attrition, although other sociodemographic and clinical variables were similar between the groups. Therefore, our results may have been affected by the selective attrition. Fourth, the inclusion of additional treatment modalities with weekend drug holidays, continuous MPH treatments or ER training in addition to MPH may have enriched the results. Fifth, rather than using static emotional/ facial stimuli with limited real-world validity we may have used dynamic stimuli tapping various domains of emotion recognition (e.g., MASC, movie for the assessment of social cognition).[48] Reading the mind in the eyes test and FT had low levels of reliability in our sample affecting our results. Sixth, the improvement in RMET performance may not continue in the longer term, and future studies may use longer follow-up durations to evaluate treatment gains. Seventh, along with parent and child reports of affective reactivity/irritability, we may have employed teachers as informants or used neuropsychological tasks that focused on irritability/frustration tolerance. Eighth, dependence on children's reports for affective reactivity, emotion regulation strategies and emotion recognition tests may have introduced shared method variance as well as recall and reporting bias. Lastly, the high rate of comorbidity might have had an impact on our findings, although we tried to control this with secondary analyses controlling for family wise error rates. Notwithstanding these limitations, our study is the first to use a prospective design to assess the impact of prolonged drug holidays on ER/irritability in children with ADHD.

Although there are studies in the literature that have examined the effects of drug holidays on

ADHD symptomatology, disorder severity, adverse effects, tolerance, anthropometric measures, and neuropsychological evaluations, our study is the first to examine the effects of drugs on ER. Our results suggest that MPH treatment improves child- and parent-reported irritability, clinician-rated disorder severity, RMET performance, and the use of planning as a cognitive ER strategy, although only the improvement in RMET performance continued after drug holidays. The use of self-blame increased after the treatment, which may reflect the effects of internalized stigmatization or the effects of confounders. It would be appropriate for the clinician to adopt a personalized approach to the decision-making process, outlining the risks, benefits, and alternate coping techniques for each patient, as advised by the AACAP, CADDRA, and NICE guidelines. Our results may support the importance of continuing treatment over the holidays for most children with ADHD unless necessitated by adverse events, growth problems, or development of tolerance.

Data Availability Statement: The work was conducted in Bolu Abant İzzet Baysal University Child and Adolescent Psychiatry Department, Bolu, Türkiye as part of the dissertation of Dr. Merve Taşkan, MD.

Ethics Committee Approval: This study was approved by the Ethics Committee of Bolu Abant Izzet Baysal University University (Approval no.: 2021/286, Date: 07.12.2021).

Informed Consent: Verbal and written informed consent was obtained from the parents, along with the children's verbal or written assent to participate in the study.

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