FLORIDA INTERNATIONAL UNIVERSITY

Miami, Florida

TOLERANCE TO PSYCHOSTIMULANT MEDICATION AMONG CHILDREN WITH ADHD: A SCHOOL-YEAR STUDY

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in

PSYCHOLOGY

by

Marcela C. Ramos

2023

To: Dean Michael R. Heithaus
College of Arts, Sciences and Education

This dissertation, written by Marcela C. Ramos, and entitled Tolerance to Psychostimulant Medication Among Children with ADHD: A School-Year Study, having been approved in respect to style and intellectual content, is referred to you for judgment.

We have read this dissertation and recommend that it be approved.

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Date of Defense: June 26, 2023

The dissertation of Marcela C. Ramos is approved.

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Dean Michael R. Heithaus
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Florida International University, 2023

ABSTRACT OF THE DISSERTATION

TOLERANCE TO PSYCHOSTIMULANT MEDICATION AMONG CHILDREN WITH ADHD: A SCHOOL-YEAR STUDY

by

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Florida International University, 2023

Miami, Florida

Professor William Pelham, Jr., Major Professor

The current investigation represents the first study designed to evaluate tolerance to stimulant medication among children with Attention-Deficit Hyperactivity Disorder (ADHD) in a school setting. Participants included two-hundred and thirty-seven elementary-aged children (aged 5-12; M_{age}= 8.1 *SD*= 1.8). Participants were randomly assigned to receive extended-release methylphenidate (OROS-MPH) either 5-days per week or 7-days per week for the duration of a school year. Monthly teacher ratings of child functioning were used to assess children's treatment response to pharmacological treatment, and insufficient responders received increased dose adjustments as necessary. The study aimed to investigate (1) whether tolerance developed over the course of the school year (Aim 1); (2) whether randomization to drug holidays (weekend holidays) mitigated the need for dose escalations compared to continuous dosing (7-day-a-week) (Aim 2), and (3) potential individual characteristics as moderators of dose escalation (Aim 3). Tolerance to stimulant medication was observed, as children's prescribed doses doubled on average by study endpoint. In addition, the group assigned to weekend holidays required fewer dose escalations. Furthermore, children with ADHD and

comorbid diagnoses were at an increased risk for requiring higher doses of medication over the school year. These findings support the clinical practice of recommending drug holidays to mitigate tolerance to stimulant medication.

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CHAPTER I. INTRODUCTION TO PORFOLIO OF RESEARCH

Organization of the Thesis

The overarching aim of this body of work is to provide a comprehensive evaluation of different interventions for children with attention-deficit/hyperactivity disorder (ADHD). In the subsequent chapters, each devoted to specific research aims, findings derived from empirical evaluation will be presented in detail. Chapter 2 focuses on the impact of long-term use of psychostimulant medication, in a randomized-controlled study, within a naturalistic school setting. Furthermore, findings reporting on the impact of medication breaks as well as the role of individual characteristics in response to pharmacological treatment will be discussed in turn. Chapter 3 explores complementary and alternative treatments for ADHD that are commonly used in clinical practice and school settings. Specifically, the study utilizes a multi-level model analytic approach to investigate the effect of a mindfulness-based intervention as an adjunct to behavioral treatment. The setting in which this study was conducted was within an analogue classroom setting. Thus, the research conducted in both Chapter 2 and 3 focuses on investigating the impact of commonly employed non-pharmacological and pharmacological interventions on children's behavior in classroom settings. This area of research is critical as school functioning is a domain in which children with ADHD routinely show marked deficits. Last, Chapter 4 explores the combination of pharmacological and behavioral intervention for the treatment of complex ADHD with comorbid Tourette's Disorder (TD). The methodology in Chapter 4, which entailed using an intensive repeated-intervention design, was adapted from an intensive behavioral

intervention treatment program for children with ADHD and related disorders, which I have been responsible for leading for nearly a decade. Thus, in line with my interest in investigating the single and combined effects of interventions, Chapter 4 couples this interest with investigating the impact of intensive doses of behavioral intervention to improve clinical outcomes for children with ADHD and comorbid TD.

Significance and Contribution

The objective of this program of research has been two-fold. First, I have trained to conduct research at the highest level of rigor, including submission to peer-reviewed journals, to ensure a meaningful contribution to this area of research. Secondly, and more importantly, the research I have conducted and contributed to over the past six years has focused on advancing clinical practice and improving the lives of children with ADHD and their caregivers, including parents and teachers. The findings from the empirical studies conducted in this body of work have direct implications for clinical practice guidelines that in turn inform treatment recommendations for children with ADHD. It is my hope that my area of research and clinical work provides a meaningful impact on the hundreds of families I have had the privilege to meet in the last decade.

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in childhood, occurring in approximately 10% of the population (Danielson et al., 2018), and is characterized by inappropriate levels of inattention, hyperactivity, and/or impulsivity (American Psychiatric Association, 2013). The presence of these symptoms may lead to functional impairment across settings, including, but not limited to, conflicts with parents, teachers, and other adults, often leading to marked caregiver strain (Anastopoulos et al., 2009; Babinski et al., 2020), problems with peers (e.g., peer rejection; Hoza et al., 2005; Pelham & Bender, 1982), difficulties in school performance (e.g., academic achievement; Arnold et al., 2020; Loe & Feldman, 2007), and school disciplinary acts due to misbehavior (Robb et al., 2011). It is well-established that evidence-based treatments for ADHD include (1) medication with central-nervous system (CNS) psychostimulants (Med; Conners, 2002), (2) behavioral interventions (Beh; Evans, Owens & Bunford, 2014; Fabiano et al., 2009; Pelham & Fabiano, 2008), and the combination of (1) and (2) (Comb; Pelham & Altszuler, 2020). Although each of these three interventions produce acute beneficial effects in the short term, no intervention has been found to have any residual benefit once discontinued. Thus, despite having well-established interventions that produce short-term benefits, it is unclear why these benefits fail to translate to long-term improvements in adolescence and later adulthood (Arnold et al., 2020; Molina et al., 2009).

In the last two decades, pharmacological treatment of ADHD has increased substantially (Kazda et al 2021), such that 90% of children with ADHD will be prescribed stimulant medication in their lifetime (Danielson et al., 2018). Though

combined treatment is the most commonly recommended and preferred treatment for elementary-aged children with ADHD (e.g., Wolraich et al, 2019; Society for Developmental and Behavioral Pediatrics, 2020), stimulant medication as monotherapy remains the most common treatment regimen (Hoagwood et al., 2016). Indeed, stimulant medications have long been the most researched and prescribed pharmacological treatment for ADHD (Swanson et al., 1993, 2003). Among youth who receive pharmacological treatment, elementary-aged children account for the highest percentage (68.6%) of stimulant use (Danielson et al., 2018). Stimulant treatment for these children has been found to produce acute beneficial effects in ADHD-related symptom reduction and improvement in domains of functioning, including improvement in parent-child relationship (Chronis et al., 2003), peer interactions (Pelham & Bender, 1982), and academic productivity and rule following behaviors in the school setting (Fabiano et al., 2007). Nevertheless, the literature on long-term beneficial effects is scant, such that existing ADHD treatment guidelines describe long-term benefits as uncertain, thus warranting further investigation (NICE guidelines, 2018; Wolraich et al., 2019).

The Multimodal Treatment Study of ADHD (MTA), the largest and most comprehensive longitudinal treatment study of ADHD to date (MTA, 1999), provides a clear example of this effect. At the end of a 14-month treatment-by-protocol phase, treatment conditions with stimulant medication as a component (Med, Comb) were superior to treatment conditions without CNS medication as a component (Beh). However, during the naturalistic follow-up phase of the MTA, prior advantage of treatment conditions with a medication component (Med, Comb) dissipated by 50% by the 24-month assessment and completely by the 36-month assessment (Jensen et al., 2007).

In the MTA (Pappadopulos et al., 2009), as in other studies (e.g., Marcus & Durkin, 2011), treatment nonadherence is routinely observed, suggesting that the absence of long-term effects may be due to there being no residual benefit of stimulant treatment once it is discontinued. However, even individuals who used medication consistently for 10 years in the MTA did not show significantly better outcomes compared to subgroups that remained untreated or discontinued treatment early (Molina et al., 2009). Therefore, it is unlikely that the absence of long-term benefit of stimulant use is uniquely accounted for by nonadherence.

Another possibility is that the initial effects of medication dissipate over time, thereby reducing the long-term effectiveness of stimulant medication (Swanson, 2019). This concept, herein referred to as tolerance, refers to a decrease in dose sensitivity or effectiveness in response to sustained exposure to a medication (Cappell & LeBlanc, 1981). Tolerance to CNS stimulant medication was first observed within the context of a clinical practice setting, in which Swanson (1986) observed the need for a continuous increase in medication dose to maintain comparable beneficial effects over across a short period of time. Indeed, acute tolerance to stimulant medication has been observed in a laboratory setting for some children (Swanson et al., 1998) and has since led to the clinical development of timed release-dose preparations – one of the greatest advancements in ADHD pharmacology (e.g., OROS-MPH; Pliszka, 2007).

A perceived loss of efficacy has been reported in both clinical practice (Safer & Allen, 1989; Swanson et al., 1986) and empirical studies (Vitiello et al., 2001) and across stimulant classes. This phenomenon, often described as tolerance, is often observed in clinical practice as the need for recurrent dose escalations to achieve the same therapeutic

effect over time. However, despite the existence of post-hoc evidence, a systematic study of tolerance to stimulant medication in a school setting over the course of a school year has yet to be conducted.

For example, in the MTA study, in which most children who received CNS stimulant alone or in combination with behavioral treatment (Comb) required subsequent dose increases over the 14 months of treatment (Vitiello et al., 2001), despite having been titrated to their highest tolerable dose at the start of the study (Greenhill et al., 2002). Moreover, in the 12-year follow up of the MTA, 56% of participants reported they stopped medication due to a perceived lack of effectiveness (Brinkman et al., 2018). Similar results were found in an extension study for the amphetamine-based stimulant medication (Adderall XR®) (McGough et al., 2005). Following a three-week titration to reach the optimal dose, the mean dose was 16 mg/day. During the 24-month follow-up, the average dose increased by over a third, reaching 20.2 mg at 6 months. However, this observed clinical need for dose increases was observed only for a subset of children participating in the study. Similar results are found in the two-year extension study of OROS-MPH (Concerta®), whereby dose increases were frequently observed within the first year, but not thereafter, resulting in an average dose increase of 26% (Wilens et al., 2005). Like the MTA, these dose increases were needed despite subjects having been previously titrated to their optimal dose. As in the MTA and other extended trials of CNS stimulants, an increase in medication dose by 25% or more was required to maintain therapeutic effects over the course of a year (Wigal et al., 2006).

Indeed, dose escalations are commonly observed in the ADHD treatment literature (Weiss et al., 2018). However, it is unclear whether these increases are due to

tolerance, as previous findings have been observational and without a priori hypothesis testing. It has been posited that scheduled medication breaks, also known as drug holidays, may be prescribed to improve the tolerability of CNS stimulants. Drug holidays may vary from short breaks (e.g., not taking medication during weekends) to longer breaks (e.g., school holidays). For example, Matthijssen and colleagues (2019) conducted a randomized placebo-controlled trial in a sample of children and adolescents receiving regular clinical care. The study found a beneficial effect of continuous methylphenidate use after 24 months. However, over time, the acute between-group differences based on investigator ratings between participants randomized to methylphenidate versus placebo dissipated, resulting in a reduction of the effect size by one-third (from d= -0.71 to d=-0.23). It is important to note that the study did not account for between-subject holiday schedules (i.e., weekend off versus weekend on) in the methylphenidate group, which could account for a moderating effect.

While some studies offer support initial support for drug holidays (Cortese et al., 2021), others discourage this practice (Coghill et al., 2014). Nevertheless, stimulant drug holidays are often prescribed (Ibrahim et al., 2015), despite any clear guidance on its utility. To our knowledge, only one prior study has been designed specifically to investigate whether tolerance to stimulant medication occurs among elementary-aged children with ADHD. The largest study of acute tolerance was recently completed, in which participants received either placebo or their optimal stimulant medication dose for 3 weeks, including weekends, and then crossed over to the other condition. Using a well-validated measure of response to medication (i.e., PERMP; Swanson et al., 2002), the acute effects of tolerance to medication were measured following 3 weeks of placebo or

following 3 weeks of steady medication. No effect of acute tolerance was detected. While the study by Macphee et al., (in preparation) has considerable strengths, including a large and comprehensively diagnosed ADHD sample, one notable limitation is that the study was only designed to evaluate acute tolerance over a period of three weeks in a well-controlled analog setting. Furthermore, although the measurement of acute tolerance was based on children's performance on a school-based measure (i.e., PERMP), the analog setting did not allow for the measurement of school-based tolerance. Thus, it is unclear whether findings generalize to a naturalistic setting. Lastly, no study has systematically evaluated whether medication increases are due to the development of long-term tolerance over the course of a year. Given that stimulant medications are the most commonly prescribed treatment for ADHD, with most children being medicated during the school-hours, this phenomenon warrants further investigation.

Current Study

The current investigation represents the first study designed specifically to evaluate tolerance to CNS stimulant use among children with ADHD in a school setting. Using the same sample from the recently completed study investigating acute tolerance in an analog controlled setting (Macphee et al., in preparation), the present study builds upon prior work by investigating whether tolerance occurs over the course of a school year within the context of a naturalistic setting. Within this design examined three important clinical questions/aims: First (Aim 1), to what degree did tolerance occur over the course of the school-year? Second (Aim 2), do drug holidays (weekend holidays) mitigate the need for dose escalations compared to continuous dosing (7-day-a-week)? Third (Aim 3), what other individual indices can moderate differences in dose escalation,

average dose and endpoint treatment, and time until dose increase is needed?

Method

Participants

Table 1 lists diagnostic and descriptive information. Participants included two hundred and thirty-seven children between the ages of 5 and 12 (M = 8.08 SD = 1.83) diagnosed with ADHD per *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994). Participants were recruited in four annual cohorts and participated in the Summer Treatment Program (STP) – (described in Macphee et al., in preparation) prior to participation in the school year follow up.

Study participants were required to (a) meet formal DSM-IV diagnostic criteria for ADHD, (b) be between the ages of 5 and 12, (c) have an estimated IQ of 80 or above, (d) not meet DSM-IV criteria for autism spectrum disorder, and (e) not be receiving psychotropic medication for conditions other than ADHD or active medical or psychiatric conditions that could be worsened by stimulants (e.g., seizures, pregnancy, arrhythmias, hypertension, Tourette's Disorder, psychoses, mania).

Exclusionary criteria included the following: presence of any medical condition that would contraindicate the use of stimulant medication; presence of any physical condition or severe learning difficulty that would interfere with participation in the laboratory classroom assessment (e.g., IQ below 80 as determined by the Wechsler Intelligence Scale for Children at screening); receiving additional medication (beyond OROS-MPH) for ADHD; receiving any medication having CNS effects, anticonvulsants, or investigational medications; having reached menarche; and having blood pressure at or above the 95th percentile for age and height. Further, study medical staff gathered

medical history and confirmed with participants' primary care physicians that it was medically appropriate for subjects to be prescribed stimulant medication. Diagnosis of ADHD was assessed by two PhD/MD-level clinicians. Each clinician completed an independent review of the following: teacher- and parent- report on the Disruptive Behavior Disorders Rating Scale (Pelham et al., 1992), teacher- and parent-report of cross-situational impairment on the Impairment Rating Scale (IRS; Fabiano et al., 2006), and a structured parent interview (NIMH Diagnostic Interview Schedule for Children IV, computerized version: Shaffer et al., 2000), as is the standard and recommended practice in the field (Pelham, Fabiano & Massetti, 2005; Wolraich et al., 2005). Additionally, parent report on the Child Behavior Checklist (CBCL; Achenbach, 1991) was used as a broadband measure of externalizing problems. If there was a discrepancy in diagnostic impressions between the two clinicians, a third clinician completed an independent review to resolve the discrepancy. Lastly, children completed a brief intelligence test (WASI-II; Wechsler, 1999) and achievement testing (select subtests of the WIAT-III; Wechsler, 2011).

Caregivers were required to give signed informed consent, and children aged 7 years or older were also required to give written assent. The consent and assent forms, study protocol, and any advertisements for subjects were reviewed and approved by the Western Institutional Review Board and the study was registered at clinicaltrials.gov (NCT02039908).

Table 1

Sample Characteristics at Study Entry

Variable	Full Sample	Study Weekend Randomization

	(N =237)	Medication	Placebo
	Mean (SD)	Mean (SD)	Mean (SD)
Age in years	8.1 (1.8)	8.1 (1.9)	8.1 (1.8)
Female	23 %	16 %	19 %
White	88%	88%	87%
Black	11 %	11 %	13 %
Asian	0.8%	1.7%	0.0%
Hispanic	85 %	87 %	80 %
Estimated full-scale IQ	96.7 (12.7)	96.0 (12.7)	97.4 (12.8)
Previously Medicated	69.6%	72.9%	66.4%
Diagnosed with ADHD	100%	100%	100%
Combined Subtype	78.1 %	77.1%	79.7
Predominantly Impulsive/Hyperactive Subtype	3.8 %	4.0 %	2.4 %
Predominantly Inattentive Subtype	18.1 %	18.9 %	17.9 %
Diagnosed with comorbid ODD	63.3 %	67.2 %	59.3 %
Diagnosed with comorbid CD	10.3 %	10.8 %	9.8 %
Number of ADHD impulsivity/hyperactivity symptoms endorsed on DBD-RS	7.4 (2.2)	7.4 (1.9)	7.5 (2.4)
Number of ADHD inattention symptoms endorsed on DBD-RS	8.4 (1.3)	8.4 (1.2)	8.3 (1.4)
Number of ODD symptoms endorsed on DBD-RS	4.7 (2.7)	4.9 (2.8)	4.5 (2.6)
Number of CD symptoms endorsed on DBD-RS	1.0 (1.5)	1.13 (1.5)	0.9 (1.4)

Note. IQ = intelligence quotient, ADHD = Attention Deficit Hyperactivity Disorder, ODD = Oppositional Defiant Disorder, CD = Conduct Disorder, DBD-RS = Disruptive Behavior Disorders Rating Scale. Values are means with standard deviations in parentheses, or proportions (%) for binary variables. Estimated full-scale IQ based on Wechsler Abbreviated Scale of Intelligence (Wechsler, 2011). Diagnoses were made at study entry as described in text. For symptom counts, symptom was counted as endorsed when either parent or teacher rated the symptom as occurring "pretty often" or "very often" on the DBD-RS (Pelham et al., 1992).

Procedures

Each month, the child's classroom teacher reported on the child's behavior and academic functioning using a modified version of the Impairment Rating Scale, which has been used in previous school-based trials (e.g., Pelham et al., 2016). The rating assessed several typical domains of functioning, including relationships with peers and teachers,

and academic progress. The ratings from the modified Impairment Rating Scale were used to evaluate any changes in the child's behavior and performance each month. If the child was experiencing impairment in domains related to ADHD (not primarily due to learning problems), the investigators recommended an increase in medication dose at monthly case review meetings. Parents were consulted before any dose increases, and the medication dose was increased only with parent consent. If the child reached the maximum recommended daily dose of OROS-MPH, the study protocol was to recommend switching to amphetamine-based compounds, such as mixed amphetamine salts XR, as switching stimulant classes is the recommended treatment when an initial stimulant trial is not successful (Pliszka, 2007).

Medication Procedures

Optimum Dose Titration. Medication management began with a 10-day double-blind daily-switch titration of sustained release methylphenidate (OROS-MPH). During the medication titration trial conducted during the Summer Treatment Program prior to the school year, children were unmedicated on the first day and then received medication in a specific pattern, including three randomly ordered repeats of 18 mg (3 days), 27 mg (3 days), and 36 mg (3 days) for young children and ordered repeats of 27 mg, 36 mg, and 54 mg for older children. Each dose was given before 8 am, and a team of PhD/MD-level clinicians reviewed behavioral response graphs for each dose. By consensus, the study investigators selected the optimal dose for each child and that dose was used as the medication dose for the remainder of the STP acute trial. At the start of the academic school year, parents and staff were informed, and the child's optimal dose from the titration trial became their starting dose. Out of the 237 children who participated in the study, 78%

were assigned a starting dose of 18 mg/day, 18% were assigned 27 mg/day, and 4.1% were assigned 36 mg/day for the school year.

Weekend Group Allocation. At the start of the school year, participants were randomly assigned to one of two groups with equal probability: (1) receive medication either 5-days per week or (2) 7-days per week for the duration of the school year. Medication was dispensed in dated blister packets separated by weekday and weekends. Parents, teachers, and study staff were masked to weekend medication status by using a coated capsule to enclose active stimulant medication (allocated for 7 days per week) or placebo (allocated for weekend for one group) in the weekend blister packet.

Children began the school year on the optimal dose determined by a titration trial in an analog setting (Macphee et al., in preparation). Two prior placebo-controlled trials have demonstrated that stimulant dose in the STP/analogue classroom settings was comparably effective during the child's regular school setting (Pelham et al., 2001, 2002), so dose adjustments were not necessary during the transition from STP to school.

Assessing Need for Medication Increase. Each month, parents and teachers completed ratings on a study-specific version of the Impairment Rating Scale (IRS; Fabiano et al., 2006). The IRS was modified to ask whether, given the treatment currently in place, the child needed additional treatment, with responses ranging from 1 (definitely not) to 5 (definitely yes) (see Appendix). If the child was rated as needing additional treatment (indicating (4) probably (5) definitely needing additional treatment in any domain), study staff followed up to determine if the rating reflected true need for additional treatment and ruled out alternative explanations, such as a significant adverse life event or comorbid learning problems causing impairment in academic progress

domain. This procedure has been successfully implemented in other studies (e.g., Coles et al., 2020; Pelham et al., 2016).

Medication Management. If a child was determined to need additional treatment, their dose could be increased in 18-mg increments during monthly clinic visits. However, the dose increase was limited to the US Food and Drug Administration (FDA) age maximum or 2 mg/kg/day of MPH, whichever was lower. In a few cases, OROS-methylphenidate was not effective or well-tolerated, or the child had difficulty swallowing pills, so alternative medications such as extended release (ER) methylphenidate stored in capsules or amphetamine products (ER mixed amphetamine salts) were prescribed.

Adverse Events. The Pittsburgh Side Effects Rating Scale, a questionnaire consisting of 13 items, was completed by parents to rate the most common side effects of stimulant medication. The ratings were on a scale of None, Mild, Moderate, or Severe. Adverse events were counted if the side effect was rated as Moderate or Severe on at least one occasion by parents and was deemed possibly or probably related to the study medication. At the end of the study, 88 (35.9%) families reported no side effects, 122 (49.8%) reported mild side effects, 28 (11.4%) reported moderate side effects, and 7 (2.9%) reported severe side effects.

In addition, height, weight, blood pressure, and pulse were recorded at monthly medication visits. Any child who developed persistent systolic or diastolic blood pressure ≥95th percentile for age or gender or who had a blood pressure measurement ≥150 mm Hg (systolic) or ≥100 mm Hg (diastolic) was withdrawn from the study.

Measures

Monthly Dose

Children's monthly dose was calculated by dividing the prescribed dose for each month, measured in milligrams (mg), by the child's monthly weight, measured in kilograms (kg) to produce a mg/kg variable for each month of treatment.

Teacher- and parent-rated ODD/CD symptoms

To predict the need for medication increases during the school year, symptoms of comorbid Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) were evaluated using the Disruptive Behavior Disorders Rating Scale (DBD; Pelham et al., 1992). Parents and teachers rated the symptoms on a Likert scale of 0 (not at all) to 3 (very much) prior to the analogue summer study. The symptoms of ODD and CD were aggregated to create an externalizing conduct problem variable, which was then used as a covariate variable, and has been shown to have acceptable reliability and validity (Pelham et al., 1992).

Internalizing symptoms

The parent-reported Child Behavior Checklist (ages 6-18) was administered as a broadband psychopathology scale (CBCL; Achenbach, 1991). The CBCL is a standardized 118-item schedule that assesses both problem behaviors and social competencies of children, as reported by their caregivers. The broadband internalizing subscale of the CBCL consists of 32 items each of which is evaluated using a three-point Likert scale with the following anchors: Not true (0); Somewhat or Sometimes True (1); and Very True or Often True (3). Raw scores for each scale were converted to norm-referenced *T*-scores ($M = 50$, $SD = 10$). Separate norms are provided for each gender within the age ranges. The internalizing subscale on the CBCL was included as a

moderator variable in analyses given that prior work has shown that ADHD children with comorbid anxiety symptoms show differential response to MPH (DuPaul, 1994).

Prior Stimulant Use

At the intake assessment, parents were interviewed by a member of the medical staff to gather information on their child's prior stimulant treatment, including the duration, type, and medication dose. To calculate the baseline dose variable, the lifetime daily dose across various psychostimulant preparations was standardized using a well-established method in the literature (Swanson et al., 2017). Children who had never received stimulant treatment were assigned a value of zero for this variable. Previous research has demonstrated high levels of reliability (>80%) and accurate reporting of prior stimulant use by parents when compared to physician medication histories (Kuriyan et al., 2014).

Age

The child's age in years was calculated at the start of the study.

Analytic Plan

The R statistical programming environment (R Core Team, 2022) was used for the analyses. Prior to conducting the analyses, the distributions of all dependent measures were examined. The ggplot2 package (Wickham, 2009) was utilized in R to generate longitudinal trajectories plots. These plots were created to evaluate potential model time metrics, address measurement issues, and identify any miscoding or outliers. Moreover, longitudinal plots were created for each participant to evaluate individual change trajectories. All outcomes were found to be normally distributed, and no outliers were detected.

Specification of Multilevel Models

To analyze the monthly mg/kg data, a series of mixed-effects regression models were fitted using the lme4 package (Bates, Machler, Bolker, & Walker, 2015). Each child contributed 8 rows to the dataset, reflecting each month of the study, and time was represented as a one-unit change per month. The data were structured in long format, and time was centered to baseline by subtracting time – 1. Statistical inference was conducted using the lmerTest package (Kuznetsova, Brockhoff, & Christensen, 2017).

Within each regression model, the continuous dependent variable, child's medication dose in mg/kg, was first regressed on the predictor of interest, weekend medication schedule, followed by a higher-order interaction term between the predictor and time. Next, this model was estimated while controlling for covariates that have been shown to predict differences in patterns of medication use, including externalizing symptomatology and internalizing symptomatology.

During the analysis, additional fixed effects for cohort, child's biological sex, child's age, adherence to medication regimen, and duration of previous stimulant medication use were explored. However, these effects were not found to be statistically significant and did not have a significant impact on the estimates and standard errors of the parameters of interest. Therefore, these fixed effects were not included in the final model.

Last, a t-test was performed to obtain between group values for total methylphenidate use over the school year based on group allocation to weekend medication schedule.

Handling of missing data

Missing data was handled using Maximum Likelihood (ML) (Arbuckle, 1996) in all estimated models, which uses all available observations for each subject to generate estimates. Missing data for outcome was assumed to be missing at random and related to other variables in the model and to their values at previous time points (Schafer & Graham, 2002).

Results

The aim of this study was to examine the effects of medication, time, and behavioral symptoms on OROS-MPH dose trajectories throughout the school year using generalized linear mixed models. Table 3 shows the results of the fitted models. A series of mixed-effects model were fitted to the data, with subject (i.e., each child participant) as a random intercept and time as a within-subjects factor. Next, a linear mixed-effects model was estimated to investigate the relationship between the dependent variable (mg/kg) and a set of predictor variables (Time, Weekend Holiday, Internalizing symptoms, ODD/CD symptoms, and their interactions). The residuals were found to be approximately normally distributed. See Table 2 for results.

Aim 1: Effect of Time on School Year Dose Trajectory

Model 1 included only the main effect of time and served as the baseline model. The results showed a significant positive effect of time on OROS-MPH dose, indicating that the dose increased over the course of the school year ($b = 0.06$, $SE = 0.01$, $p < 0.001$).

Aim 2: Effect of Weekend Medication Schedule on School Year Dose Trajectory

According to Model 2, which included the main effect of weekend medication assignment (placebo vs. OROS-MPH) and its interaction with time, there was no

significant main effect of weekend medication assignment on OROS-MPH dose (b = 0.04, SE = 0.05, p = 0.411). However, there was a significant interaction between time and weekend medication assignment (b = 0.01, SE = 0.00, *p* = 0.012), such that the increase in OROS-MPH dose over time was greater for those randomly assigned to OROS-MPH on weekends compared to those assigned to placebo (See Figure 1).

Simple slope analyses revealed that the rate of change in medication dosage (as measured in mg/kg) over time was greater for children randomized to continuous 7-day-week stimulant medication use (M = 1.012, SE = 0.034) compared to children randomized to weekend holidays (5 days per week) (M = 0.931, SE = 0.033), t(470) = 2.67, p = 0.008. This represents an 35% higher mg/kg dose for the 7-day group (continuous medication) compared to the 5-day (weekend holiday) group at endpoint.

Figure 1

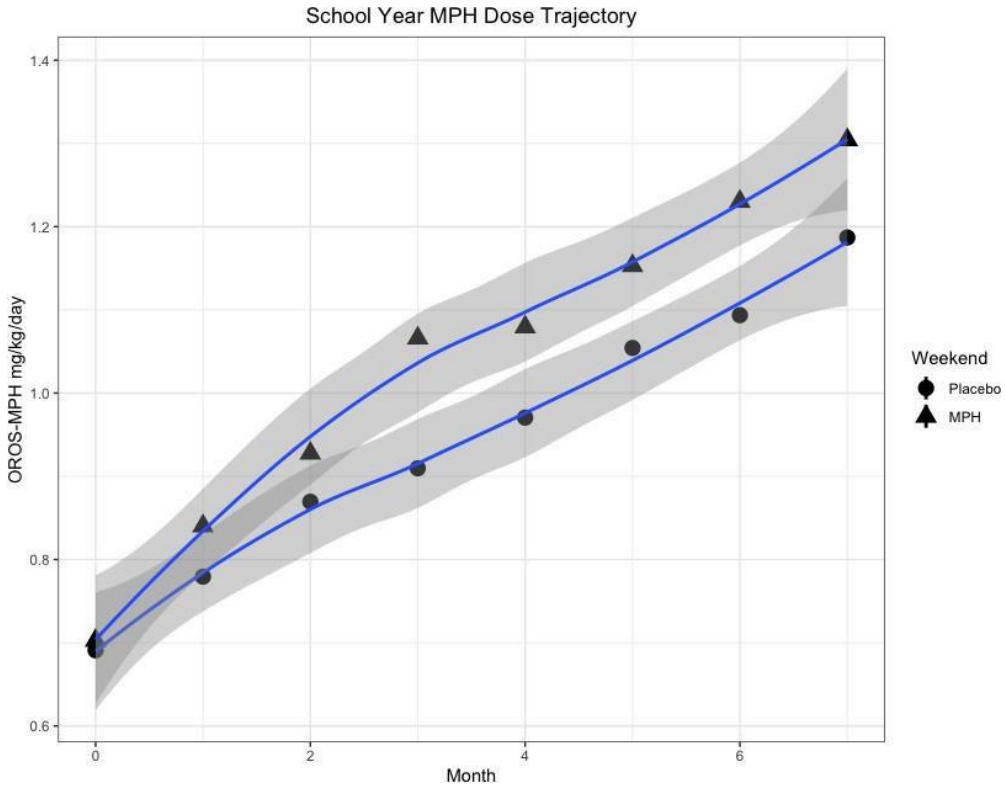


Table 2

Generalized Linear Mixed Models of School-Year OROS-MPH Dose Trajectories

	Model 1			Model 2			Model 3		
Predictors	*B*	*SE*	*p-value*	*B*	*SE*	*p-value*	*B*	*SE*	*p-value*
Time	0.06	0.01	**<0.001**	0.02	0.01	0.159	-0.14	0.05	**0.002**
Weekend	0.04	0.05	0.411	0.02	0.09	0.852	0.13	0.32	0.687
Time*Weekend	0.01	0.00	**0.012**	0.02	0.01	**0.006**	0.08	0.03	**0.009**
Conduct Problems				0.01	0.02	0.631	0.01	0.02	0.767
Time*Conduct Problems				0.01	0.00	**0.001**	0.01	0.00	**0.010**
Weekend*Conduct Problems				0.00	0.01	0.853	0.00	0.01	0.883
Time*Weekend*Conduct Problems				-0.00	0.00	**0.041**	-0.00	0.00	0.190
Internalizing							0.00	0.01	0.832
Time *Internalizing							0.00	0.00	**<0.001**
Weekend*Internalizing							-0.00	0.01	0.692
Time*Weekend*Internalizing							-0.00	0.00	**0.044**

Note. Time = Month of school year; Weekend = Medication assignment on weekends (Placebo = 0 vs. OROS-MPH = 1); Conduct = ODD + and CD symptoms at baseline; Internalizing = CBCL Internalizing T Score at baseline.

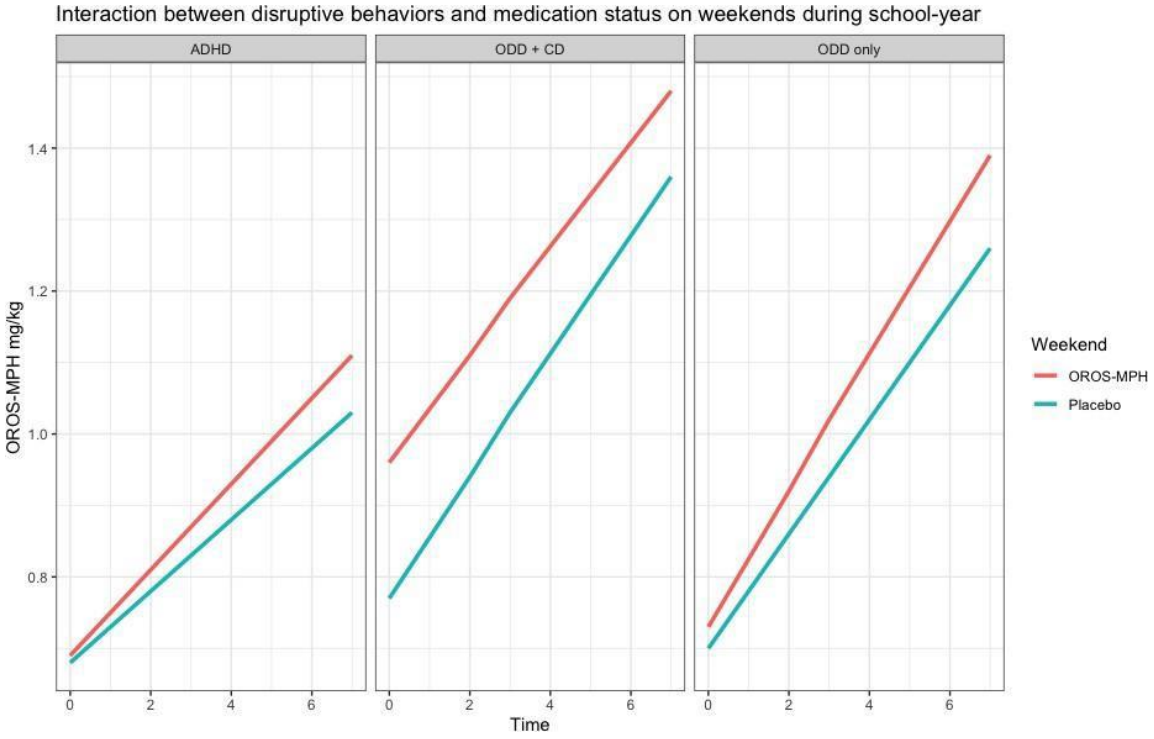
Aim 3: Effect of Individual Participant Characteristics on School Year Dose Trajectory

Model 2 added the main effects and interactions of conduct problems (ODD and CD symptoms) and Model 3 included internalizing symptoms (CBCL Internalizing T Score) at baseline. The results showed no significant main effects of conduct problems (p = 0.631) or internalizing symptoms (p = 0.832) on OROS-MPH dose. However, there were significant interactions between time and conduct problems (b = 0.01, SE = 0.00, p = 0.001), time and internalizing symptoms (b = 0.00, SE = 0.00, $p < 0.001$). In Model 2, the three-way interaction between time, weekend medication assignment, and conduct problems was significant ($p < 0.5$). However, in Model 3, there was a significant three-way interaction between time, weekend medication assignment, and internalizing symptoms (b = -0.00, SE = 0.00, p = 0.044) but not for conduct problems when accounting for internalizing symptoms (p = .190).

Simple slopes analyses were then conducted to examine diagnostic subgroups with co-occurring Oppositional Defiant Disorder (ODD) and (Conduct Disorder) based on Model 2 (see Figure 2). As previously mentioned, the predicted amount (total mg/kg) at endpoint for the OROS-MPH subgroup was higher than that of the Placebo subgroup for all three groups (ADHD, ODD only, and ODD + CD). Therefore, the group with the higher predicted amount (total mg/kg) at endpoint is the one that received OROS-MPH on weekend, regardless of the diagnosis group. Subgroup analyses revealed diagnostic subgroup differences (ADHD, ODD only, and ODD + CDD) for total mg/kg. First, the predicted amount (total mg/kg) at end point for the OROS-MPH group was approximately 8% higher than that of the Placebo group for the ADHD only subgroup.

Second, for the ODD subgroup, the predicted amount (total mg/kg) at end point for the OROS-MPH was approximately 10% higher than that of the Placebo group for the ODD only subgroup. Third, for the ODD + CD subgroup, the predicted amount (total mg/kg) at endpoint was approximately 9% higher than that of the Placebo group for the ODD + CD subgroup.

Figure 2



Total Methylphenidate Intake

Over the full duration of the school year, children randomized to MPH 7-days per week consumed 38% more MPH than those who did not receive MPH on weekends and holidays. The mean exposure was 57,504 mg for the former group and 39,393 mg for the latter group ($p < .001$). Table 3 reports on mean dose of methylphenidate per month.

Table 3

Raw Means and Standard Deviations for School-Year Dose Trajectory

	Weekend Medication Randomization

Outcome	Placebo M (*SD*)	OROS-MPH M (*SD*)
Month 1	0.69 (0.21)	0.7 (0.23)
Month 2	0.78 (0.30)	0.84 (0.32)
Month 3	0.87 (0.34)	0.93 (0.40)
Month 4	0.91 (0.39)	1.07 (0.49)
Month 5	0.97 (0.41)	1.08 (0.47)
Month 6	1.05 (0.44)	1.15 (0.49)
Month 7	1.09 (0.49)	1.23 (0.51)
Month 8	1.19 (0.56)	1.31 (0.56)

Note. Based on available data from N = 237 children. Values were calculated using OROS-MPH mg/kg/month. OROS-MPH = osmotic-release oral system methylphenidate See Figure 1 for visualization of between group differences in OROS-MPH dose trajectory.

Discussion

The use of medication holidays is a common clinical practice in the treatment of ADHD, but there is a lack of research on the effectiveness of this approach. To our knowledge, this is the first study to compare the clinical utility of short medication holidays (i.e., weekends) for preventing tolerance over the course of a school year. Following a titration trial to determine optimal dosage, two hundred and thirty-seven children with ADHD were randomly assigned to a 7-day per week (continuous) or a 5-day per week (weekend placebo medication) OROS-MPH dosing schedule at the start of the academic school year. Monthly teacher and parent ratings of each child's functioning across domains of impairment were collected to evaluate treatment response. Children's response to treatment was evaluated and monthly adjustments were made as indicated for 8 months. Using a repeated measures design, the present study aimed to three key questions: Do children require dose increases over a school year? Do weekend holidays mitigate the need for dose increases? And are there individual participant characteristics

that explain dose trajectory over an 8-month school-year period? The findings of this study have important implications for clinical practice and highlight the need for more research on the optimal use of medication holidays to mitigate the development of tolerance to psychostimulant medication over time. The following sections discuss the findings of the study, addressing each of the three aims in turn and ultimately addressing how the present findings impact future clinical practice guidelines and subsequent research aimed at optimizing psychostimulant treatment for children with ADHD.

Aim 1: Effect of Time on School Year Dose Trajectory

Throughout the eight-month school year period, the prescribed dose, on average, doubled among study participants, as measured by prescribed OROS-MPH milligrams per weight in kilograms (mg/kg). Thus, a perceived loss of effectiveness, measured as a need for dose increases, was observed over the school year. Moreover, dose increase patterns were variable, with approximately two-thirds of participants accounting for moderate (2–3) to high (>5) rates of dose escalations. These results replicate previous findings in clinical trials and naturalistic longitudinal studies that have reported on a perceived loss of effectiveness in the pharmacological treatment, here defined as tolerance (e.g., Molina et al., 2009; Swanson et al., 1999).

In contrast to previous studies that found on average a 20-30% increase in the starting dose over time (e.g., Vitiello et al., 2001; McGough, et al., 2005; Wigal et al., 2006), the higher percentage of dose increase in the present study may be explained by the protocol used to determine children's optimized dose. Specifically, the optimal OROS-MPH dose was determined by choosing the lowest dose that produced a clinical improvement in behavioral functioning. In contrast to the MTA, in which stimulant doses

were titrated to their highest tolerable dose. As such, it is possible that starting at higher doses would have resulted in tolerance effects comparable to prior studies. On the other hand, approximately one-third of children reached the maximum approved dose per FDA regulation, resulting in a ceiling effect for a subset of children. Present findings add to the psychopharmacological literature on stimulant medication use among children with ADHD by illustrating the routine clinical observation of needing higher doses of stimulant medication to maintain its initial therapeutic effectiveness.

Aim 2: Effect of Weekend Medication Schedule on School Year Dose Trajectory

The current study also investigated the clinical utility of medication holidays in mitigating observed tolerance. Children were randomly assigned to receive continuous OROS-MPH 7 days per week (continuous) or 5 days per week (placebo on weekends). Results clearly support recommending weekend drug holidays to reduce the potential of tolerance.

Aim 3: Effect of Individual Participant Characteristics on School Year Dose Trajectory

The final aim of the study was to investigate whether individual characteristics moderated response to medication over the course of the school year. Children with ADHD and comorbid internalizing symptoms required significantly more increases in medication dose than children without comorbid symptoms of anxiety. Present findings replicate prior investigations that have similarly found that children with comorbid internalizing disorders are less responsive to methylphenidate treatment (DuPaul et al., 1994).

Lastly, approximately two-thirds of children in the current study met criteria for comorbid diagnosis of Oppositional Defiant Disorder (ODD) and/or Conduct Disorder

(CD). As has been reported routinely in the treatment literature for children with ADHD, comorbid disruptive behaviors were predictive of higher endpoint dose. Assignment to the 5 days per week medication schedule (weekend holidays) mitigated these increases across all diagnostic groups, suggesting that brief weekend holidays may be especially useful for children with ADHD alone or in combination with disruptive behaviors.

Limitations

Limitations should be considered when interpreting the findings of this study. First, the sample was not medication-naive, meaning that some participants had prior exposure to ADHD medications, which could impact the generalizability of the results to medication-naive populations. Nevertheless, stimulant medication use prior to study entry was controlled for in the analyses and was not found to predict an increase in dose over the school year. Next, a ceiling effect was observed in some participants, as they were not able to continue increasing their dose due to FDA regulations or were required to switch to a different stimulant class (Adderall XR) per study protocol. Thus, switching stimulant types may have limited the ability to observe further evidence of long-term tolerance over the eight months of the school year. Furthermore, switching to a different stimulant class has been found to mitigate tolerance in clinical practice. It is, therefore, possible that children who switched stimulant class to mixed salts amphetamine per study protocol would have otherwise required subsequent dose escalation had they remained on methylphenidate-based stimulant class. Finally, a small percentage of participants were prescribed other methylphenidate-based stimulants (e.g., Metadate CD) due to difficulty with pill swallowing. Future studies could benefit from using medication-naive

participants, avoiding the FDA regulation ceiling effect by including more dose levels or titration schedules and limiting the use of different stimulants.

Conclusions

About one-third of children did not require medication dose increases, another third required minimal dose adjustment, and one-third required frequent dose adjustments. Increases in dose were observed across groups but occurred significantly more in children assigned to the continuous medication schedule. Children with ADHD who have co-occurring conduct problems and higher levels of internalizing symptoms may require increases in medication doses more medication over time to achieve the same therapeutic effectiveness compared to children with ADHD who do not present with comorbidities. It is also possible that because internalizing and/or conduct symptoms were not addressed by stimulant medication treatment, teachers and parents rated these children as needing additional treatment. In summary, the results suggest that OROS-MPH dose trajectories during the school year are influenced by time, weekend medication assignment, and the presence of co-occurring internalizing and/or conduct symptoms. These findings highlight the importance of considering individual differences in medication needs and the need for careful monitoring and adjustment of medication regimens over time.

Clinical Implications

Guidelines for assessing treatment response in children with ADHD synthesize decades of research and provide practical recommendations for the treatment of childhood ADHD. These guidelines acknowledge the acute beneficial effect of stimulant medication on reducing ADHD symptoms. For example, The American Academy of

Child and Adolescent Psychiatry (AACAP) ADHD Practice Parameter recognizes that "most children will need dose adjustment upwards as treatment progresses" (Pliska et al., 2007). However, less guidance is available for recognizing tolerance or how to address tolerance clinically when it occurs. Typically, increasing the medication dose, switching to a different class of stimulant, or taking brief medication breaks are recommended when tolerance develops to achieve comparable therapeutic effectiveness.

The present study found that children randomized to medication 7-days per week required higher doses of stimulant medication over the course of the school year compared to children randomized to weekend holidays has important clinical implications. It suggests that prescribers need to be aware of the potential for increased medication use when administering ADHD medication daily. Moreover, taking weekend breaks from medication may provide a potential benefit in mitigating the need for dose increases over time. It is possible that longer breaks, such as summer holidays, may also be an effective strategy to mitigate the tolerance effect that can occur with prolonged medication use.

Findings from the present study highlight the importance of regularly assessing medication efficacy and side effects and considering alternative dosing schedules that allow for regular medication free periods. As has been found in other medication trials, caregivers are amenable and often prefer a treatment protocol that allows for breaks from stimulant medication (Waxmonsky et al., 2020). Thus, medical staff should carefully weigh the benefits and risks of different medication schedules for each individual child and involve caregivers in shared decision-making regarding medication management. Future research should aim to investigate the optimal dosing schedules and duration of

medication breaks that support the acute benefits of stimulant treatment and minimize the potential for tolerance.

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III. CHAPTER 3.

MINDFULNESS AS AN ADJUNCT TO BEHAVIOR MODIFICATION FOR ELEMENTARY-AGED CHILDREN WITH ADHD.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD), characterized by inappropriate levels of inattention, hyperactivity and/or impulsivity, is one of the most common childhood mental health disorders, affecting between 8% and 12% of children and adolescents (Danielson et al., 2018). In addition, children with ADHD experience significant impairment across multiple domains of daily life functioning including, but not limited to, conflicts with parents, teachers, and other adults often leading to marked caregiver strain (Anastopoulos et al., 2009; Babinski et al., 2020), problems with peers including peer rejection (Hoza et al., 2005; Pelham & Bender, 1982), and low academic achievement and behavior problems in school (DuPaul & Jimerson, 2014; Loe & Feldman, 2007).

Decades of research support behavioral treatment (BT; behavioral classroom management (BCM), behavioral parent training (BPT), and peer interventions (BPI) as effective first line interventions for children with ADHD (Barbaresi et al., 2020; NICE, 2018). Psychostimulant medication (i.e., central nervous system [CNS] stimulants) as a unimodal treatment or in combination with BT is also considered an effective intervention for ADHD (AACAP, 2007; AAP, 2011, 2019; Evans et al., 2018; Pelham & Fabiano, 2008; Pelham, Wheeler & Chronis, 1998). Reviews of studies evaluating the incremental benefit of adding an adjunctive treatment – typically, methylphenidate to behavioral interventions – in classroom settings (Fabiano et al., 2007) and social-recreational settings (Pelham et al., 1990b, 2005, 2014) have shown routinely that children treated with adjunctive interventions (e.g., combined pharmacological and behavioral) show greater effects of acute intervention compared to unimodal treatment.

Unfortunately, as with unimodal treatments, there is no evidence to support the maintenance of these acute effects in the long-term (Merrill et al., 2020; Molina et al., 2009). A multitude of factors have been associated with the absence of long-term beneficial effects despite the documented short-term effectiveness of BT and CNS medication, including families' treatment preference for non- pharmacological interventions, ongoing implementation of interventions, barriers associated with families gaining access to treatment, and the perceived utility of an intervention by the parents and teachers tasked with its implementation – all of which result in the limited or inconsistent use of these treatment recommendations (Adler & Nierenberg, 2010; Chronis et al., 2004). Limitations of existing pharmacological, behavioral, and combined interventions have led to the implementation, but not-yet evidence-based, clinical practice of integrating complementary and alternative medicine (CAM) approaches into the delivery of well-established treatments (e.g., BT) in hopes of enhancing their overall effectiveness and impact (Pellow et al., 2011). A recent study by Wang and colleagues (2020) found that, "meditation (10.8 %), yoga (9.6 %), and deep breathing (7.3 %) were the most commonly used mind- body CAM modalities in ADHD children in 2017, with their use increased 468%, 433 %, and 192 %, respectively, since 2012". Mind-body CAM modalities are invariably interrelated and have been subject of study given their emerging therapeutic benefits for youth with ADHD. Systematic reviews and meta- analyses (see Chimiklis et al., 2018; Evans et al., 2018; Krisanaprakornit et al., 2010; Vekety et al., 2021) have included studies of meditation, mindfulness, and yoga for the treatment of ADHD in youth, all of which caution against definitive conclusions for a myriad of reasons, including heterogeneity in results across studies given the varied modalities of

treatment delivery between meditation, yoga, and mindfulness. Thus, for the present study, we focused on the efficacy of mindfulness as an adjunctive treatment to well-established BT, given that yoga or meditation as sole modalities, both of which similarly have mixed results in the ADHD literature, were beyond the scope of the present study. Albeit that the use of CAM is less commonly implemented than behavioral and medication approaches (Danielson et al., 2018), its gaining popularity warrants empirical investigation. Indeed, as interest in and use of third-wave therapies such as mindfulness increase, it is important to examine whether this emerging treatment in the child treatment literature is beneficial for children with ADHD when delivered in conjunction with the already well-established, first-line interventions.

Mindfulness Interventions

With origins in Buddhism, mindfulness is operationally defined as the awareness that emerges through purposefully and nonjudgmentally attending to the present moment (Kabat-Zinn, 2003). Mindfulness-based practice has been conceptualized as having two main components (Bishop et al., 2004). The first component involves self-regulation of attention, such that by attending to available thoughts, feelings and sensations, awareness of the present moment is increased. This attentional component includes focused, broad, and sustained attention and skills in switching attention from one stimulus to the other, both of which are known to be marked deficits in children with ADHD (Burke, 2010). The second component involves experiencing the present moment with openness and acceptance (Bishop et al., 2004). It is theorized that the practice of accepting one's emotions facilitates emotion regulation whereby individuals learn to observe the unfolding of present experiences regardless of their emotional valence (Lindsay &

Creswell, 2019) resulting in a reduction of maladaptive emotional reactivity (Teper et al., 2013). With repeated and sustained practice, it is hypothesized that these skills are internalized by the practicing individual and produce subsequently a downstream effect on behavior such as improvements in executive functions (EF) and behavioral self-regulation, which are also areas of significant impairment for children with ADHD (Meiklejohn et al., 2012).

One possible pathway that mindfulness-based therapies (MBT) may lead to beneficial outcomes for children with ADHD is that they may strengthen deficient EF processes through training and extended practice. Indeed, empirical studies of MBT among elementary-aged children have shown improvements in executive function (Crooks et al., 2020; Diamond, 2012; Diamond & Lee, 2011; Flook et al., 2010), self-regulated attention (Meiklejohn et al., 2012; Napoli et al., 2005), and effortful control (Zelazo & Lyons, 2012), with some studies showing that individuals who possess deficient EF skills at baseline stand to improve the most at post-test measures of EF after receiving MBT (Flook et al., 2010, 2015). While these findings among non-diagnosed samples are promising, no controlled study has directly investigated whether children with ADHD, who often present with EF deficits, will benefit from MBT.

Mindfulness-Based Therapies for Children

Leading organizations such as Mindful Schools, with a network of more than 60,000 educators who have received training to implement mindfulness, are estimated to have reached over three million children worldwide (mindfulschools.org). Current prevalence rates indicate roughly 10% of children have ADHD (Danielson et al., 2018), such that an estimated three-hundred thousand children who have received mindfulness

within the school setting likely have or qualify for an ADHD diagnosis. Of importance, the majority of studies that have evaluated mindfulness interventions and found improvements in emotion regulation (Semple et al., 2009), executive functioning (Crooks et al., 2020; Flook et al., 2010; Thierry et al., 2016), academic grades (Schonert-Reichl et al., 2015), and attention (Black & Fernando, 2014; Meiklejohn et al., 2012; Napoli et al., 2005; Schonert-Reichl & Lawlor, 2010) have been with non- diagnosed samples of children – as such, there is a gap in the research of whether children with ADHD benefit from MBTs that are increasingly being provided at the school-wide level and are being delivered, presumably, to youth with ADHD.

A study by Long and colleagues (2018) compared MBT to BT in a sample of 75 elementary-aged children placed in an alternative educational setting due to significant disciplinary problems and found moderate beneficial effects of MBT (d = .55) on externalizing symptoms. Of interest, the MBT condition used a behavior response-cost system in which children received a tally on the board when they exhibited inappropriate behaviors and conversely received specific praise when behaving appropriately. However, given that point- systems for behavior management are one of the most common components of BT for ADHD and related disorders, the MBT group in this study also received BT, and gains may have resulted from a combined MBT+BT intervention rather than MBT alone. As a result, we may extrapolate that children with externalizing symptoms may benefit from MBT as an adjunctive intervention to traditional BT, offering support for the design of an active control study that can evaluate the additive effect of MBT to commonly employed BT among youth presenting with externalizing behaviors. While the aforementioned school-wide studies have shown

sizeable effects across a range of domains that youth with ADHD are often impaired in, the nature of the study samples, which lack diagnostic information, precludes us from generalizing these findings to clinical ADHD samples.

Mindfulness-Based Therapies for Children with ADHD

Evidence that MBT leads to improved attentional, behavioral, and EF skills among non- diagnosed elementary-aged children suggests that MBT may address these deficits among children with ADHD. As such, MBTs offer a potential non-pharmacological approach to enhancing the effectiveness of BT for children with ADHD. There is limited research available on the separate evaluation of mindfulness for elementary-aged children with ADHD, with most studies evaluating MBT combined with BPT for ADHD youth and their parents concurrently (Bogels et al., 2008; Lo et al., 2020; Muratori et al., 2020; Van de Weijer-Bergsma et al., 2012; Van der Oord et al., 2012; Zylowska et al., 2008), with adolescents (Haydicky et al., 2012; Zylowska et al., 2008), or in direct comparison with other meditative practices (e.g., yoga, meditation; Cairncross & Miller, 2016; Chimiklis et al., 2020; Evans et al., 2017). More recently, Vekety and colleagues (2021) completed a meta-analysis of randomized controlled studies and found MBTs to have an overall small to moderate effect in reducing symptoms of inattentiveness ($g+ = 0.22$, $p = .03$) and hyperactivity-impulsivity ($g+ = 0.36$, $p < 0.001$); however, of the 21 studies included in the meta-analysis, only two implemented MBT with a diagnosed ADHD sample. Across those studies, significant effects were found for teacher-reported behavior but not for parent-reported or self-reported behavior. One important limitation, as noted by Vekety and colleagues, is that teachers were not masked to group allocation and assessment, given that they were themselves in charge of

delivering the intervention. This limitation underscores the need to include objective measurement of children's behavior to mitigate potential expectation bias.

Despite preliminary evidence from these studies suggesting potential benefits of mindfulness interventions for children with ADHD, a number of methodological limitations associated with the work reviewed in meta-analyses indicate that currently the risk of bias limits available findings due to a lack of the use of control groups or randomization to interventions (Chimiklis et al., 2018; Evans et al., 2018), variability in diagnostic criteria (Vekety et al., 2021), and in some instances a combination of the three. To date, only one study has evaluated the direct effect of MBT – that is, without the confounding effect of parallel interventions with caregivers (e.g., BT + MBT) – in a diagnosed sample of elementary-aged children with ADHD. Carboni and colleagues (2013) used a multiple baseline design to investigate whether MBT resulted in improvements in on-task behavior among four eight-year-old children with ADHD within a school setting. Behavioral observations, as well as parent and teacher ratings, showed that MBT resulted in an increase in on-task behavior and a decrease in hyperactive behavior, respectively. Notably, changes from pre- to post-intervention on attention, as measured by the BASC-2 Attention Scale, were not found. While this study provides an initial step towards evaluating the direct effect of MBT on children with ADHD, its small sample size limits us from generalizing these findings.

This review indicates the potential of using MBT for elementary-aged children with ADHD, but also brings to attention the many limitations of the present literature – small sample sizes (Carboni et al., 2013), uncontrolled studies (Zylowska et al., 2008), and lack of diagnostic information (Long et al., 2018). The inconsistent effects found

across informants (parents, teachers, direct observations) and measures (behavior, EF, mindful awareness) illustrate the shortcomings of the present literature and highlight the need for multimethod, multi-informant assessment in this area. As such, the present gap in the literature underscores the need for well- designed studies to address the efficacy of mindfulness interventions for children with ADHD. Further, available studies have not been designed to answer the question of whether MBTs have an incremental benefit on BT, therefore limiting our availability to isolate the effect of MBT on children with ADHD.

The present study aimed to add to the limited literature of MBT for children with ADHD within a highly controlled setting. Limitations from prior work were addressed in our study design through the use of random assignment, an active control condition, and having a multi- informant/multimethod design to measure multiple outcomes of interest. The study was conducted in a Summer Treatment Program (STP; Pelham et al., 2017) setting, which has been widely used to evaluate treatments among children with ADHD. The goals of the current study were to test the incremental value of MBT in the context of intensive behavioral treatment (BT) on (a) children's disruptive behavior (b) executive functioning (EF), (c) child self-reported mindful awareness, and (d) parent report of child's mindful awareness. Based on prior work (Long et al., 2018) we hypothesized that children in the MBT + BT (COMB) group would, on average, show fewer disruptive behaviors over time compared to BT only group. In addition, we hypothesized that children who received MBT would score higher on measures of EF (Flook et al., 2010, 2015) and mindful awareness at post-treatment.

Method

Participants

Fifty-eight children with ADHD ages 7 to 12 (M = 9.2 years, SD = 1.4, grades 3 - 6) who were treated in the STP participated in the current study (Table 1). Parents of children participating in an STP were approached at the start of STP by the study staff for recruitment. Children were permitted to attend the STP and enroll in the study regardless of medication status. Consistent with past STPs, families were asked to keep medication status stable and to notify clinical supervisors of any changes in medication status. Study participants were required to: (a) meet formal DSM-5 diagnostic criteria for ADHD (American Psychiatric Association, 2013) and/or have a previous diagnosis of ADHD, (b) be between the ages of 7 and 12, (c) have an estimated IQ of 70 or higher as measured by the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II; Wechsler, 2011), and (d) have no history of autism spectrum disorder according to parent report of diagnostic history. ADHD diagnoses were made using evidence- based assessment procedures (Pelham et al., 2005). Specifically, a clinical interview was conducted to obtain relevant clinical history and a summary of presenting problems. DSM-5 symptoms of ADHD, ODD, and CD were assessed using parent and teacher ratings on the Disruptive Behavior Disorder (DBD) rating scale (Pelham et al., 1992), and symptoms rated as “pretty much” or “very much” by either the parent or teacher were counted as being present.

Cross-situational impairment was assessed using parent and teacher ratings on the Impairment Rating Scale (IRS; Fabiano et al., 2006), with ratings of “3” or higher (“0” = no problem, “6” = extreme problem) reflecting clinically significant impairment.

Conferral of diagnoses of ADHD, ODD, and CD were made according to DSM-5 diagnostic guidelines by a Ph.D. level clinician prior to enrolling in the study. The Institutional Review Board of the University where the study was conducted approved the study. Parents of all the participants provided consent and the child participants provided assent prior to the initiation of the study.

Setting

The STP is an 8-week intensive summer treatment program for children with ADHD and related disorders that focuses on teaching appropriate behaviors across recreational and classroom settings (Pelham et al., 2017). Children attended the program from 8:00 AM to 5:00 PM on weekdays and participated in 2-hour academic lessons, 1-hour art lessons, and the rest of the day was spent in recreational activities. Children were placed in age-matched groups of 12- 15 children who were supervised by one lead counselor and five undergraduate counselors who were supervised by permanent Ph.D.-level staff members during recreational activities or a teacher and an aide during classroom activities. Staff members were trained intensively to provide treatment with fidelity and to record behavioral data reliably. As a result, a benefit of the STP is that it provides the opportunity to conduct studies in a highly controlled environment – and thus, an ideal setting in which to examine the added benefit of a mindfulness intervention when combined with BT.

Design

The current investigation consisted of a single between-group factor. Following a 2-week adjustment period, participating children were randomly assigned to receive one of the two following conditions for the last 6 weeks of the STP – either the mindfulness

intervention in combination with BT (COMB) or the standard intensive STP BT. Children randomly assigned to the COMB group received a 20-minute mindfulness intervention in a separate room at the beginning of the art class period while children who were not assigned to receive the mindfulness intervention (i.e., BT group) participated in art class as usual during this time.

Mindfulness sessions occurred three to four times per week for six weeks and were led by 1 teacher with support from 2 classroom aides. Children assigned to the BT group received all the same standard STP behavioral interventions that the mindfulness group (COMB) received.

Accordingly, the only difference between the control (BT) and intervention (COMB) group was that the BT group did not receive the mindfulness intervention. Following the 20 minutes of the assigned intervention, both groups reconvened in the art classroom and participated in an art activity for the remaining 40 minutes of art class.

Intervention

Mindfulness. When searching for an appropriate mindfulness intervention, we considered MBTs that (a) had prior empirical evaluation showing promising effects on associated symptoms of ADHD, (b) had been delivered to elementary-aged children in a classroom setting, and (c) were manualized to minimize the potential for variability in its delivery. The mindfulness intervention utilized herein was a modified version of the MindUP program as it is one of the most widely studied school-based programs to date that has been submitted to empirical evaluation. MindUP is a manualized mindfulness and social and emotional learning program that has been shown to produce improvement in multiple domains of impairment associated with ADHD, including self- regulation,

behavior, and attention among non-diagnosed elementary aged children (Crooks et al., 2020; Foundation, 2011; Schonert-Reichl et al., 2015). The MindUP curriculum is manualized, such that it provides detailed guidelines and procedures for teachers to conduct mindfulness training within a classroom setting. The curriculum is tailored to elementary-aged children (grades 3-6) and includes exercises and activities intended to promote mindful awareness through sensory awareness (visual, auditory, kinetic, tactile, gustatory) and mindful movement. Each lesson is designed to be brief and sequential, such that there is repetitive practice of each mindfulness skill taught. The program also emphasizes mindful breathing through exercises that are guided to direct children's attention to their breathing or to the sensation of the belly as they breathe in and out. Social-emotional learning lessons from the MindUP curriculum were removed from the intervention to allow for the investigation of the effects of mindfulness practice alone on the functioning of children with ADHD. Thus, the present study included only MindUP lessons uniquely pertaining to mindfulness, as socio- emotional learning practices are beyond the scope of this study.

Behavioral Management. Behavioral treatment was implemented within all contexts of the STP, whereby children's behavior was modified using a response-cost and reward system (Kazdin & Weisz, 2018, p.215-232; Pelham et al., 2014). The behavioral program includes a number of evidence-based components of treatment for ADHD (e.g., a point system in which children earn points, rewards, and praise) for positive behavior (e.g., compliance, following rules, school-work completion), and also receive consequences (e.g., point loss, time out) for negative behaviors (e.g., violating rules, noncompliance). Within the art and academic classroom settings, classroom rules

resembled those found in typical classrooms (e.g., obey adults, stay in assigned seat, be respectful of others). Children started each class with a "bank" of 100 points and lost points if they did not follow the rules. Praise and social reinforcement for appropriate behaviors was provided frequently, as is common practice in general classrooms (Hart et al., 2017). During recreational activities, STP counselors monitored children's behavior and awarded or removed points continually throughout the day (Pelham et al, 2017).

Fidelity.

Fidelity checklists were created for each session based on the session content outlined in the MindUp Program Curriculum (Goldie Hawn Foundation, 2011). Observers coded all MindUp sessions in-vivo to evaluate session length, adherence to the manual, and the duration and quality of the teacher-guided MindUp core practices (i.e., mindful breathing). For each lesson, observers completed a Post-Observation Global Rating of Fidelity, a five-item scale that assessed facilitators' ability to be nonjudgmental, use of appropriate communication and reinforcement, and ability to respond to contributions with questions to elicit further responses in a nonjudgmental way. Overall participant engagement was assessed by the degree to which participants "appeared to be on the same page, working towards the lesson goals, working in a collaborative manner". Lastly, the overall environment set by the lesson facilitator was assessed on a 7-point Likert-type scale, with higher scores indicating a more positive global rating. Post-Observation Global Rating of Fidelity showed that, on average, facilitators were rated positively across categories, and student engagement was routinely high (supplement). Similarly, adherence to the study protocol was monitored via direct observation whereby independent observers completed a checklist measuring adherence to designated

activities and to ensure no cross- contamination across conditions. Each facilitator was observed for each MindUP lesson, and fidelity checklists indicated that, on average, 98.6% of content from the MindUP lesson was implemented (Fidelity Checklist is available in supplement).

Measures

Observed behavior. Frequency counts of point system behaviors (as recorded by staff) and classroom behavior were compared across each treatment condition (COMB, BT). Objective observation of child behavior is considered the gold standard in the assessment of treatment response for children with ADHD as it has been shown to be sensitive to experimental manipulations in numerous controlled studies (Fabiano, 2007; Pelham et al., 2016), and possesses excellent inter-observer reliability for on-task behavior (kappa = .79) as well as for disruptive behaviors (kappa = .77) (Pelham et al., 2002).

Teacher Recorded Point System Behavior. Child behavior in the classroom was measured daily by the total number of classroom rule violations via teacher-recorded frequencies of classroom behavior using a well-established coding system (Atkins et al., 1985; Fabiano et al., 2007). Classroom rules included: (a) be respectful of others, (b) obey adults, (c) work quietly, (d) use materials appropriately, (e) remain in assigned seat or area, (f) raise hand to speak and ask for help, and (g) stay on task. Teachers recorded rule violations using a standard protocol (Pelham, Gnagy, & Greiner, 1998) consistent with procedures that have demonstrated the ability to produce reliable and valid data in past studies (Atkins et al., 1985; Fabiano et al., 2007; Macphee et al., 2019).

Counselor Recorded Point System Behavior. Indices of peer- and staff-directed social behavior were frequency counts derived from the STP response-cost point system observation code. Consistent with past research conducted within the STP (Chronis et al., 2004; Pelham et al., 2005, 2014), the following behavioral categories were derived from the point system: (a) rule violations (e.g., follow the rules of the sport, use materials and possessions appropriately), (b) verbal abuse to staff, (c) name-calling/ teasing peers, and (d) cursing/swearing. Also consistent with several past STP studies (e.g., Pelham et al., 2000, 2005, 2014), one of the dependent variables in the recreational setting, *negative verbalizations*, was derived from the following negative point system behaviors: verbal abuse to staff, name calling/teasing peers, and cursing/swearing.

Executive Functioning. To evaluate executive functioning (EF), children completed three tasks from the NIH Cognitive Toolbox (NIH-TB; Weintraub et al., 2013; Zelazo & Lyons, 2012) at baseline (week 2 of STP) and post-treatment (week 8 of STP). All participants completed the NIH-TB tasks on an iPad. Data were collected by graduate students and trained research assistants who ensured participants' compliance and understanding of tasks. The administration of the NIH-TB tasks were counterbalanced to minimize potential order effects. Tasks included the NIH-TB Dimensional Change Card Sort, Flanker Inhibitory Control and Attention Test, and List Sorting Working Memory Test that provide estimates of task-based EF functioning in the areas of cognitive flexibility, working memory, and inhibitory control (Zelazo & Lyons, 2012). Furthermore, all tasks have shown high test-retest reliability (DCCS, ICC = .95; Flanker, ICC = 0.95; WM, ICC = .87; Weintraub et al., 2013). As previously mentioned, deficits in EF have been linked to ADHD, with some evidence suggesting that it can be improved via mindfulness training (Weintraub et al., 2013).

NIH-TB Dimensional Change Card Sort (Executive/Shifting). This task is purported to evaluate children's cognitive flexibility, known as task switching or set shifting. In each trial, children were presented with a visual stimulus and were required to match the stimuli (e.g., yellow ball, blue trucks) to one of the two presented target images according to shape or color. The task had 40 trials and a total administration time of 4 minutes. Scores were calculated based on raw scores of accuracy and reaction time, with higher scores indicating greater accuracy and shorter reaction time.

NIH-TB List Sorting Working Memory Test (Working Memory). This task is purported to evaluate children's working memory. Following a practice trial, children were presented with a series of pictures of different sizes that were either animals or food. Each stimulus presented was accompanied by an auditory description of each item. After the presentation of a set of items, children were asked to repeat the items from smallest to largest to the experimenter, who then scored the trial as either correct or incorrect (1 or 0). Subsequent trials increased in difficulty, such that trials increased in length and complexity (e.g., interleaved categories of animals and food). To proceed to the next trial, children were required to provide a correct response in one of the two opportunities provided for each trial. If a correct response was not provided within the two opportunities given for a trial, the task was terminated. The List Sorting task took approximately 7 minutes. Test scores were calculated using raw scores, with higher number of total correct trials indicating better performance.

NIH-TB Flanker Inhibitory Control and Attention Test (Executive/Attention). This task was adapted from the Attention Network Task (Fan et

al., 2002; Rueda et al., 2004) and is intended to assess children's ability to inhibit visual attention to irrelevant task dimensions.

Children first completed a practice block that consisted of four trials and were required to answer correctly in three of the four practice trials to pass onto the next testing block. Children who successfully completed the practice block were then presented with 25 trials (16 congruent and 9 incongruent). In both the practice and testing block, children were presented with age- appropriate stimuli (e.g., fish, arrows) pointing to the left or the right and had to determine whether the stimuli presented in each trial was congruent or incongruent with the surrounding stimuli (e.g., some trials the surrounding stimuli pointed in the opposite direction of the given target stimuli). This task was timed to terminate at 3 minutes or upon completion of the trials, whichever criterion was met first. Scoring was calculated using raw scores and was based on both speed and accuracy, with higher scores indicating greater accuracy and shorter reaction time.

Reported Mindful Awareness. Mindful awareness is typically measured using self-report. However, given that children with ADHD demonstrate poor insight regarding their own behavior and cognitions (Hoza, 2007; Owens et al., 2007; Sibley et al., 2019), the current study utilized parent ratings in addition to child self-report to measure mindful awareness. Thus, parent-report of mindful awareness in the present study was exploratory. However, present effort to include parents as informants is consistent with recommendations by Frank and colleagues (2003) urging for improvements in measurement design when assessing for changes in this internal construct by including multiple informants.

Parent-report. Parents completed an adapted version of the Mindful Attention Awareness Scale (MAAS) at baseline (STP Week 2) and at post-intervention (STP Week 8) based on their perception of their child's behavior. The MAAS is a 15-item scale designed to assess a core characteristic of dispositional mindfulness, namely, open or receptive awareness of and attention to what is taking place in the present. The MAAS has been used extensively and has been shown to have high internal consistency ($\alpha = .82$) (MAAS; Black et al., 2012; Brown & Ryan, 2003). All 15 items from the self-report MAAS (e.g., "I find it hard to stay focused…") were modified for parent report of children's trait mindful awareness (e.g., "Your child finds it hard to stay focused…"). Responses were recorded using a 6-point Likert-type scale, with higher scores purported to reflect higher levels of mindful awareness (1 = almost always, 6 = almost never). In the present study, these items displayed strong reliability ($\alpha = .93$).

Child-report. Children were asked to complete the Mindful Attention Awareness Scale – Children (MAAS-C). Adapted by Lawlor and colleagues (2014) from the MAAS, the MAAS-C has been shown to have high internal consistency ($\alpha = .84$) for both boys and girls. The MAAS-C includes 15 items that assess for trait mindfulness (e.g., "I could be feeling a certain way and not realize it until later") and uses a six-point Likert-type response format (1 = almost never, 6 = almost always). Items were reverse-scored with higher scores indicating higher levels of mindfulness. Given the possibility that children's reading level may have resulted in difficulty reading some of the items, the research staff read each item aloud to groups of 3 to 5 children.This scale was previously validated for use with children up to fourth grade (Lawlor et al., 2014).

Analytic Plan

Data analyses were performed in *R* (v 3.6.3, R Core Team, 2020) and Mplus (v6, Muthén and Muthén, 2010). Several analytic methods were used for each of the three domains of measurement: 1) observed behavior (e.g., rule violations, negative verbalizations), 2) executive functioning, and 3) parent and child report of mindful awareness and are reported in order below.

Observed behavior. We used *R* (R Core Team, 2020) with gmler function in lme4 (Bates et al., 2018) to fit generalized linear mixed-effects models (GLMM) and sjPlot package for data visualization (Ludecke, 2021). To accommodate for the zero-inflated non-normal distribution of our count data, estimated models were specified to reflect a Poisson distribution ("family = poisson"). GLMM were fit separately to answer the question of whether the accumulation of mindfulness skills through repeated practice over time was associated with behavioral improvements as measured by teacher-recorded behavior (e.g., classroom rule violations) and counselor-recorded behavior (e.g., negative verbalizations). Behavioral data were collected daily over the six-week period of the study, such that repeated measurements of behavioral data were nested within each child. Therefore, in our two-level model, each child was at the highest level (level-2) and the series of repeated measurements (i.e., behavioral data) at the lowest level (level- 1). As the observed outcome variables were nested within each child, each outcome variable of interest was regressed on a random factor for child, and the following variables for fixed effects: (a) time (i.e., day of measurement occasion), (b) medication status, (c) ADHD symptoms at baseline, (d) intervention group, and (e) the interaction between intervention group and time. Intervention group was coded with BT only as the reference group (BT =

0, COMB = 1). Total number of ADHD symptoms as measured by baseline parent and teacher-rated DBD and medication status were included as covariates.

Executive functioning. We ran a multiple regression path model analysis to investigate whether the mindfulness intervention had an effect on EF at post treatment using baseline performance on the cognitive tasks as a covariate. Full information maximum likelihood was used to address missing data. All results were standardized for interpretability (Figure S1).

Mindful awareness. Confirmatory factor analyses (CFA) were performed separately for the parent and child-adapted versions of the Mindful Attention Awareness Scale. A theory-driven unidimensional factor structure was estimated given previous evidence supporting this model in adults, adolescents, and elementary-aged children (Brown & Ryan, 2003; Lawlor et al., 2014). Additionally, Cronbach's alpha was calculated to measure internal reliability. Next, we conducted two separate full structural regressions with group assignment (i.e., COMB vs. BT) predicting mindful awareness at post-treatment while controlling for baseline scores of mindful awareness. A probit link function was used in both the parent and child structural regressions given that both dependent outcomes were ordinal. Models were assessed using fit indices, including the chi-square test (χ^2), goodness of fit indices (i.e., comparative fit index [CFI], Tucker-Lewis Index [TLI]), root mean-square error of approximation [RMSEA], and standardized root mean square residual [SRMR]), as is recommended (Bollen, 1990).

Power Analysis. We conducted post-hoc power analyses using the SIMR package (Green & MacLeod, 2016a, 2016b) in R statistical software (R Core Team, 2013). The function powerSim() was used to estimate the power to detect the effect of the

intervention (COMB, BT) using fitted models for each outcome of interest. Post-hoc power analyses indicated that the power to detect an effect of the intervention over time in the current study was 44.00% lower than recommended. Due to being underpowered, we used the function powerCurve() to estimate the power required to detect an effect of the intervention at different sample sizes at level-2 (participants) and retaining number of occasions (mindfulness days) based on 1000 simulations. Last, we used the plot() function to examine power estimates at each sample size (Figure S2). It was determined that a sample size of approximately $N = 150$ would provide 80% power to detect a small-to-medium effect size. This value is comparable to rule-of-thumb cutoffs for two-level GLMM (Arend & Schäfer, 2019).

Results

Observed Behavior. GLMM results indicated nonsignificant main effects between group assignment (COMB, BT only) on rule violations in the academic classroom ($b = -0.02$, SE = 0.20, $p = 0.923$), art classroom ($b = 0.24$, SE = 0.31, $p = 0.459$), and negative verbalizations in the recreational setting ($b = -0.24$, SE = 0.37, $p = 0.511$) (see Figure 1, Table 2). Similarly, the interaction between treatment group assignment and time was nonsignificant across all outcome variables (*ns*). Examination of group difference effect sizes (see Table 3) indicated small acute effects in the academic ($d = 0.166$) and art classroom ($d = 0.198$) in favor of BT only, and a small acute effect in the recreational setting ($d = -.305$) in favor of the COMB group. Similarly, Figure 1 depicts a positive trend in favor of mindfulness (COMB) for negative verbalizations in the recreational setting. There is perhaps, however, an adverse effect of mindfulness on rule violations in the art classroom. Lastly, there appears to be no

observable effect in either direction for rule violations in the academic classroom. In summary, while there is perhaps a positive trend in the recreational setting, there is a trend in the opposite direction in the art classroom, and no apparent effect for the academic classroom. Notably, the bars in Figure 1 indicate standard error around the marginal means. Given that the bars for the BT and COMB group have observable overlap, these trends may be due to measurement error.

ADHD symptoms. There was a main effect of baseline ADHD symptoms on classroom behavior in both the academic classroom (b = 0.49, SE = 0. 0.18, p = 0.006) and art classroom (b = 0.46, SE = 0.14, p = 0.001) where, on average, a 1-unit increase in ADHD symptoms were associated with a 0.49 and 0.46-unit increase in rule violations in the academic and art classroom setting. This main effect was not found in the recreational peer setting (b = 0.14, SE = 0.18, p = 0.420).

Executive functioning. The direct effect of group assignment (COMB, BT only) on the cognitive tasks was not statistically significant (Figure S1). Specifically, group assignment did not predict changes in the change card sort task (b = -0.2, p = 0.06, 95% CI [-3.37, 0.52]), working memory task (b = -0.13, p = 0.21, 95% CI [-2.90, 0.99], or flanker task (b = -0.14, p = 0.13, 95% CI [-4.99, 1.29]). Examination of group difference effect sizes (see Table 3) indicated negligible effects in the working memory task (d = 0.079), and a small acute effect for the change card sort task (d = -0.289) and working memory task (d = -0.308) favoring the BT only condition.

Mindful awareness. Similarly, group assignment (COMB, BT only) did not predict changes in parent- (b = -0.03, p = 0.881) or child-reported (b = -0.02, p = 0.957) mindful awareness. Examination of group difference effect sizes (see Table 3) indicated

negligible effects in parent (d = -0.071) or child-reported (d = 0.002) mindful awareness. Nevertheless, results from both parent and child CFA confirmed previously validated one factor structure for both the adults and child self-report scale of mindful awareness (MAAS; Brown & Ryan, 2003), suggesting that mindful awareness can be represented under one factor (Table S1-S3).

Discussion

The goal of the present study was to evaluate the effectiveness of mindfulness as an adjunctive intervention to a well-validated behavioral intervention in the context of an ongoing summer program for children with ADHD. To the authors' knowledge, this is the first study to evaluate the effects of mindfulness as an adjunct to behavioral treatment among elementary-aged children with ADHD using a multimethod and multi-informant approach. A multi-method approach was used to evaluate the effects of the mindfulness intervention including direct observation of behavior in classroom and recreational settings, parent- and self-report of mindful awareness, and cognitive tasks designed to measure EF (Weintraub et al., 2013). Results indicate that across outcome measures, the mindfulness intervention did not produce any significant benefit beyond the standard behavioral treatment implemented in the summer treatment program. Of note, post-hoc power analyses indicated that the present study was not sufficiently powered to detect the effect of MBT as an adjunct to intensive BT. As such, results should be interpreted within the context of this limitation.

Observed Behavior

A core component of mindfulness interventions is the facilitation of the development of self-regulatory skills (Bishop et al., 2004). One potential explanation for

the failure to find an effect of the mindfulness intervention implemented in this study is that children with ADHD- related deficits lack the metacognitive ability to self-direct their attention. Indeed, studies that have examined the meta-cognitive ability of youth with ADHD have found significant age effects on indicators of meta-cognitive awareness with older children reporting higher accuracy for some (i.e., breath-monitoring), but not all indicators (i.e., thought awareness), leading one to conclude that abstract meta-cognitive abilities (i.e., thought awareness) are still underdeveloped even among elementary-aged children (Satlof-Bedrick & Johnson, 2015). This deficit may be even more evident in children with ADHD, who are typically thought to be two to three years developmentally behind their peers (Berger et al., 2013). Other interventions that have relied heavily on meta-cognitive awareness include cognitive training, including self-instructional training, cognitive modeling, self-reinforcement, and interpersonal problem solving, with decades of research concluding they are not efficacious interventions for children with ADHD on objective measures of behavior in natural settings (Abikoff, 1991; Waschbusch & Hill, 2003).

EF Task Outcome

We were also unable to detect statistically significant differences in task-based executive functioning among children with ADHD who received mindfulness as an adjunct intervention compared to controls. Our findings are consistent with other studies that have examined intervention effects of MBT on task-based EF among non-clinical samples of children, in that the MBT did not selectively improve task-based EF (Flook et al., 2015; Schonert-Reichl et al., 2015). Further, existing support for improvement of EF among children who receive MBT is based on scant literature, which has pooled together

findings from yoga, mindfulness, and exercise interventions (Diamond & Lee, 2011), and thus, limits our ability to determine the treatments through which beneficial effects of EF improvement are produced.

MAAS Parent Report / Child Report

Our results showed no significant changes in parent-report and children's self-report of their trait mindfulness. Notably, parents were masked to their child's intervention condition (COMB vs. BT only) but were aware that their child was receiving behavioral treatment in the STP. It is possible that failure to find a significant intervention effect of parent-report of their children's trait mindfulness may be due to parent's perception that their children were improving at the STP regardless of whether they received the mindfulness intervention. Indeed, the absence of parent-reported benefit is unsurprising given that parent-report in previous STP studies (Pelham & Hoza, 1996; Pelham et al., 2014) has routinely been overwhelmingly positive – such that there may have been little room for improvement following the addition of mindfulness to the intensive behavioral treatment already provided in the summer program.

Lastly, children's self-report of trait mindfulness based on MAAS-C did not differ across conditions. Individuals with ADHD routinely exhibit positive illusory bias and therefore are typically inaccurate reporters of their own behavior and cognitions (Hoza, 2007; Owens et al., 2007; Sibley et al., 2019). This presents a particular challenge, as changes in mindfulness and its associated benefits (e.g., improvement in self-regulation, attention) have generally been documented through self-report measures (Brown & Ryan, 2003; Lawlor et al., 2014). As such, it is possible that positive illusory bias among our ADHD sample may have interfered with our ability to find an effect of our intervention

on self-reported trait mindfulness. Evidence for such an effect is reflected in the small, yet statistically significant, discrepancy in scores between child self-reported mindfulness (M=4.09, *SD* = 1.32) and parent reported scores (M=3.79, *SD* =1.02), where child self-report indicates higher levels of reported mindfulness on the MAAS-C.

In the development of the Mindful Attention Awareness Scale, Brown and Bryan (2003) found that statements reflecting mindless states (e.g., "I break or spill things because of carelessness, not paying attention, or thinking of something else") to be more accessible than mindful states (Lawlor et al., 2014). Interestingly, parent ratings of their child's 'mindlessness' (e.g., fails to give close attention to details or makes careless mistakes; Pelham et al., 1992) are used routinely in research and clinical practice to assess for ADHD symptomatology given caregiver's accuracy in the reporting of observable behaviors such as those listed in the MAAS- C rating scale. Given the similarity between items from the MAAS-C and those found in ADHD- rating scales (e.g., DBD), we suggest the possibility that we failed to detect an effect due to there being no observable change between groups.

Taken together, findings from our study using a multimethod and multi-informant approach do not support the use of mindfulness training as an adjunct to an intensive evidence-based behavioral treatment. We hypothesize that our failure to find an effect of our intervention may have been due to several factors. One factor may be that our mindfulness intervention did not produce any clinically meaningful changes in the domains of measurement we were interested in (e.g., observable behavior, EF, mindful awareness). However, post-hoc analysis indicated that a sample of approximately 150 subjects is needed to detect the effect of MBT as an adjunctive intervention to intensive

BT. Thus, it is recommended that future studies of MBT for children with ADHD approximate the recommended sample size. Alternatively, other factors such as our sample's level of meta-cognitive awareness, a ceiling effect on parent-reported ratings of improvement being overwhelmingly positive due to treatment expectancy of the STP, as well as the role of positive illusory bias for children's self-report may have prevented us from finding effects. It is also possible that our MBT intervention itself, such as the techniques used and the dosage of our intervention (e.g., frequency, duration), was insufficient to produce a therapeutic change in our sample. While MBT techniques employed in sessions relied on sensory activities to promote mindful awareness, participants were also expected to participate in guided breathing. Although the MindUP curriculum included both external sensory awareness (e.g., focusing on different sounds) and internal awareness (e.g., core breathing exercises), we did not systematically assess whether one particular activity (external versus internal) was more amenable to our sample participants. It is possible that different components are more likely to engage children with ADHD, such as mindful movement. Similarly, it is possible that other MBT curriculums, developed specifically for adults and adolescents with ADHD (e.g., Zylowska et al., 2008) or for children with ADHD and their parents (e.g., van der Oord, Bögels, & Peijnenburg, 2012), may have led to more beneficial effects. Indeed, while MindUP is among the most widely implemented and researched MBT for elementary-aged children, it is not representative of all MBT appropriate for youth.Furthermore, while our study closely mirrored session length and frequency from MindUP program (see http://thehawnfoundation.org) – that is, brief and frequent sessions as opposed to longer and less frequent sessions –it is possible that the dose of our intervention was

insufficient to produce a desirable change in children's ADHD symptoms. Indeed, others have argued that it is unlikely that the commonly employed dosages of mindfulness training are sufficient to lead to normalization of domains of impairment associated with ADHD (Barkley, 2014, p. 659). Recent meta-analyses (e.g, Chimiklis et al., 2018; Vekety et al., 2021) investigating dosage of mindfulness have found it to be varied (between 3-4 hr) with a median of 6 hr and 10-12 sessions in total, suggesting that the dose delivered in our study (7 hr 30 min and 21 sessions in total) is comparable to other studies examining mindfulness for youth at risk for or diagnosed with ADHD. Nonetheless, the MindUP curriculum traditionally includes a social and emotional learning (SEL) component and is taught across 15 lessons lasting 45 minutes, a 33% increase in dosage. Of note, we excluded SEL lessons as we intended to isolate the effect of mindfulness as a complementary intervention to BT.

However, there are currently no empirical guidelines available to determine the optimal frequency and duration of MBT, particularly for ADHD children who present with attentional and behavioral difficulties. Consequently, achieving sustained changes in the observed behavior, EF, and mindful awareness of children with ADHD may require more intensive long-term interventions. Determining the appropriate dosage of MBT as well as the therapeutic mechanism of change (e.g., core breathing, sensory awareness) necessary to produce a therapeutic change among children with ADHD is an empirical question and should be further evaluated.

Limitations

It is possible that the behavioral intervention delivered as part of the STP may have been too effective in reducing disruptive behaviors, such that that little room was left for

mindfulness to produce an incremental benefit. As in most studies of clinical interventions for children with ADHD, samples sizes are relatively small, and dependent on resources available. Given our sample size, the present study was statistically underpowered to detect the incremental benefit of mindfulness and should be interpreted in the context of this limitation. Future studies might consider evaluating the addition of MBT to less intensive BT than was used in the current study. It is also possible that the concurrent BT allowed the MBT interventions to take place, as without BT, children's behavior may have been too disruptive.

Further, although parents of participants were asked to keep the medication status of their child constant throughout the eight weeks of the STP, we are unable to ascertain the degree of fidelity with which families adhered to this request. Thus, although medication was not manipulated as part of this study, including both medicated and unmedicated children may have prevented us from assessing a unique incremental effect of mindfulness practice as an adjunct treatment for ADHD (Fabiano et al., 2007; Pelham et al., 2014).

Clinical Implications

The results of the current study add to the limited literature on the efficacy of MBT for children with ADHD. An advantage of exploring the use of MBT as an adjunctive treatment for ADHD rather than as the first line of treatment is that it is arguably a more accurate representation of what is likely to occur in clinical practice. It is estimated that three-fourths of children with ADHD have been prescribed psychostimulant medication (Danielson et al., 2018) for school behavior, and almost all (> 90%) of general education teachers report using some type of behavioral support for

elementary-aged students with ADHD (Hart et al., 2017; Schatz et al., 2021). Arguably, most children with ADHD are already receiving well-established behavioral and/or pharmacological interventions and are exposed to complementary treatments such as mindfulness in an attempt to enhance the effectiveness of evidence-based treatments in school. Our results fail to support the use of mindfulness as a complementary treatment to BT in classroom settings.

One area that mindfulness-training interventions may be effective in reducing child and adolescent symptoms of ADHD is when parents of these children receive training. A handful of studies have investigated mindfulness-training interventions targeting parents and their children in parallel and have found reductions in child and adolescent symptoms of ADHD (Muratori et al., 2020; Zylowska, 2008; Van de Weijer-Bergsma et al., 2012; van der Oord et al., 2012).

However, findings from these studies are limited by the absence of a comparison group and thus warrant further empirical investigation.

Given the host of impairments associated with ADHD across the span of development, it is unsurprising that interventions for ADHD have been at the forefront of child and adolescent mental health research. Of concern is the public consumption of complementary practices and their perceived efficacy in clinical populations despite a lack of evidence or warranted empirical investigation (Briggs & Killen, 2013). Further, many complementary treatments such as MBT are costly and may require caregivers (e.g., parents, teachers) to learn a specific skill set that is, unfortunately, not as therapeutically advantageous for addressing ADHD symptoms among children when compared to robust therapeutic effects of well-established behavioral management

strategies. As such, efforts should be placed on disseminating and implementing with fidelity evidence-based behavioral treatments for ADHD within the appropriate settings (Pelham & Altszuler, 2020; Pelham & Fabiano, 2008).

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IV. CHAPTER 4.

INTENSIVE BEHAVIOR THERAPY FOR TICS AND CO-OCCURRING ADHD: A CASE REPORT.

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Introduction

Tic disorders (TDs) are neurodevelopmental disorders characterized by sudden and involuntary motor (i.e., arm jerking, shoulder shrugging) and phonic (i.e., throat clearing, animal sounds) tics. TDs broadly encompass a number of current DSM-5 diagnoses, such as Tourette's disorder, persistent or chronic motor or vocal tic disorder, and provisional tic disorder (American Psychiatric Association [APA], 2013). Importantly, TDs have a significant impact on youths' overall daily functioning. Specifically, they can have deleterious effects on youth's social, familial, and academic functioning (Kurlan et al., 2001; Roessner et al., 2011; Specht et al., 2011) and are demonstrated to impair their quality of life (Storch et al., 2007). Further, parents of children with TDs are likely to experience increased stress and caregiver burden (Cooper et al., 2003). As a result, TDs can impact the entire family's overall wellbeing.

A majority of children with a TD also meet criteria for at least one co-occurring disorder. In particular, over 60% of children with a TD also meet criteria for attention-deficit/hyperactivity disorder (ADHD) (Center for Disease Control and Prevention, 2009), a chronic neurodevelopmental disorder characterized by inappropriate levels of inattention, hyperactivity, and impulsivity (APA, 2013). Research suggests that co-occurring TDs and ADHD in childhood often lead to greater impairment than TDs alone (i.e., Lebowitz et al., 2012), including pronounced difficulties across familial and social domains (Sukhodolsky et al., 2003).

Numerous randomized controlled trials have suggested that Comprehensive Behavioral Intervention for Tics (CBIT) is effective in reducing tic symptom severity, intensity, frequency, and duration among children (e.g., Piacentini et al., 2010; Himle et

al., 2012). McGuire and colleagues' (2014) recent meta-analysis found that individuals with a TD who engaged in a behavioral intervention, such as CBIT, were more likely to benefit from treatment (i.e., reduction in tic symptoms), as compared to control interventions, and experienced comparable treatment effects to those found with alpha-adrenergic agonist (a-agonists) medication use. As such, the American Academy of Neurology (AAN; Pringsheim et al., 2019) recommends CBIT as the first line of treatment for individuals experiencing TDs, given its minimal risk (i.e., side effects) and equivalent efficacy when compared to alternative treatments (i.e., a-agonists, antipsychotics) (Pringsheim et al., 2019). These recommendations also include support for services provided via teleconference or video conference, should in-person services be unavailable or inaccessible.

Traditionally, CBIT was designed to be an eight to ten-week, one-hour, individual and in-person treatment, during which functional assessments, relaxation, habit reversal training, and relapse prevention are taught to and practiced with children and parents, with the goal of reducing children's tic symptom frequency, severity, duration and intensity (Piacentini et al., 2010). However, despite substantial support for CBIT for improving TD symptoms, highly comorbid disorders, such as ADHD, are not explicitly address in the standard treatment protocol (Coffey, 2015). As a result of this important limitation, an alternative intervention modality that provides treatment strategies to address both TDs and equally impairing comorbidities is warranted.

An important next step in treatment development for TDs is to evaluate alternative treatment modalities that modify CBIT to be capable of treating co-occurring ADHD. Indeed, non-traditional delivery formats, such as intensive interventions, as

opposed to standard weekly sessions, are well-established for the treatment of related and comorbid disorders and have been shown to be an efficacious and cost-efficient modality for delivering multimodal interventions (Fabiano, Schatz, & Pelham, 2014; Ehrenreich & Santucci, 2009). Intensive treatment delivery formats provide the opportunity for families to gain access to treatment for a limited period of time without the extended burden often associated with weekly treatment sessions. Recently, there has been emerging evidence to support intensive, group-based treatment, particularly for diagnoses that are less common or are known to require specialized interventions that are not widely accessible. For example, Cornacchio and colleagues (2019) found that an intensive, group-based format for children with selective mutism was associated with minimal perceived barriers from caregivers, high treatment satisfaction, and clinically significant reductions in symptoms eight weeks post-treatment. Additionally, Graziano and colleagues (2020) evaluated an intensive model for behavioral parent training (BPT), an evidence-based treatment for ADHD and disruptive behavior disorders (for reviews, see Evans, Owens, Wymbs & Ray 2018; Fabiano et al., 2009; Pelham & Fabiano, 2008). Similarly, results from this study found that BPT delivered in an intensive format was equally efficacious compared to standard weekly BPT and that parents who experience high levels of stress were more likely to benefit from the intensive formats than standard BPT. Overall, intensive intervention modalities are effective across a number of childhood mental health illnesses, and this treatment delivery method has begun to be extended to CBIT to address TDs.

While initial support for an intensive form of CBIT has begun to emerge, the literature is limited. Flancbaum and colleagues (2011) adapted standard CBIT into a two-

week intensive format for a 25-year-old male exhibiting motor and vocal tics. Findings suggest reductions in the participant's subjective units of distress (SUDs), however, no post-assessment Yale Global Tic Severity Scale (YGTSS; Leckman, 1989), the gold-standard TD assessment, was conducted to assess changes in overall tic frequency, severity, intensity, duration, and impairment post-intervention. The authors also reported that the patient did not participate in all agreed-upon booster sessions following the end of treatment and, upon meeting with the patient 5-months following the end of treatment, the patient noted difficulty implementing CBIT strategies. Further, the authors note the importance of booster sessions in aiding the generalizability of skills into an at-home setting. Blount and colleagues (2018) conducted a four-day intensive program (N=5), which resulted in improvements following the end of treatment for 4 out of 5 primarily adult participants. To our knowledge, only three studies to date have evaluated intensive CBIT in an exclusively pediatric population. Blount and colleagues (2014) conducted a preliminary case series utilizing a four-day intensive approach, predominately focused on preadolescents (N=2), providing support for the utility of intensive CBIT for reducing tic symptoms rapidly. Kennedy and colleagues (2016) provided eight sessions over the course of two consecutive weeks to 10 children (M_{age} = 13.7) and found significant treatment-induced improvements in YGTSS-assessed total tic severity. In addition, Heijerman-Holtgrefe and colleagues (2020) evaluated the use of a group-based intensive exposure with response prevention (ERP) protocol for 14 children (M_{age} = 11.69 years) and found a 16% reduction in total tic scores. While improvements were noted, the reduction reported in this study is significantly lower when compared to studies utilizing CBIT. Taken together, preliminary evidence for the utilization of intensive CBIT for

children and adults is promising. However, none of the interventions described above included components targeting ADHD explicitly, despite the high incidence among individuals with TD.

One of the most well-studied psychosocial interventions for ADHD is the delivery of BPT to the parents of children with ADHD. Grounded in social learning theory principles (e.g., Patterson, 1982; Patterson & Fisher, 2002), BPT seeks to modify parenting behaviors that may inadvertently maintain disruptive behaviors. BPT programs largely share a core set of common principles, including positive parenting (e.g., praise, positive attending), effective commands and consequences, as well as the development of an incentive system to shape target behaviors through positive reinforcement. Taken together, these core set of principles have been shown to be successful in reducing maladaptive parenting practices and improving child externalizing behaviors (Chronis et al., 2004; Kaminski et al., 2008; Pelham & Fabiano, 2008). Given the chronic nature of ADHD and its associated impairments across domains of functioning, the active engagement of caregivers of children with ADHD is considered essential in the management of the disorder (Sibley et al., 2012). In doing so, caregivers can serve as agents of change for ADHD-related impairment.

Over 60% of children with a TD also meet criteria for ADHD and treatments for TDs, such as CBIT, and ADHD, such as BPT, have been shown to be effective. An integral next step is to evaluate a combined approach of CBIT and BPT provided in an intensive modality, as intensive CBIT may be utilized as a mechanism to target proximal (e.g., tics, disruptive behaviors) as well as distal (e.g., parental stress) outcomes. As such,

we used a case study design approach to evaluate the utility of an intensive and combined intervention for the treatment of a TD and co-occurring ADHD.

Method

The following case study functions as a preliminary test of the acceptability, feasibility, and effectiveness of the treatment described below. Jacob's parents sought services outside of their geographic region, as there are no trained CBIT providers locally. Further, the family was restricted to a two-week window for the intervention. As such, the intervention described below was deemed to adequately suit the family's needs and time-restriction. A total of six intensive CBIT sessions (spanning across two weeks) were provided at a university-based outpatient clinic specializing in the treatment of TDs and ADHD.

Relevant Background and Context

At the time of intake, Jacob was an 11-year, 9-month old biracial male who traveled with his biological parents to receive treatment for both motor and vocal tics. His parents reported that Jacob's first motor and vocal tics appeared when he was 8 and 9 years old, respectively. Presenting problems at the time of intake included frequent vocal tics, namely, cursing/swearing (coprolalia). Furthermore, Jacob's parents reported that his vocal tics had become more impairing and intense due to an accompanying increase in voice-level volume coupled with higher rates and more complex coprolalia (e.g., a string of cursing/swearing as opposed to a single curse/swear word). Furthermore, his parents reported that both vocal and motor tics were a source of significant impairment across home and school settings, as well as with peers. Jacob was enrolled in a standard school setting, however, given the increased volume and frequency of his vocal tic, which

caused disruptions in the classroom, he often left school prior to standard dismissal time. Additionally, Jacob's parents were concerned about his self-esteem as he reported feelings of embarrassment and anger due to vocal tics within the school setting and in front of peers. As a result of the numerous domains of impairment at school, his parents reported switching his educational setting to home. Upon intake, Jacob was receiving a home school education. At home, in addition to vocal tics, Jacob presented with both simple and complex motor tics, varying in the degree of impairment.

Jacob also presented to treatment with a prior diagnosis of ADHD, combined presentation, which was given at the age of five. Before intake, Jacob had been prescribed Clonidine extended-release for his ADHD-related symptoms and TD. Despite subsequent adjustments in medication dosage over the course of a year, Jacob's parents reported that they chose to discontinue the medication due to a perceived lack of improvement in both ADHD and TD-related symptoms. At the time of Jacob's clinical intake, he was not taking medication.

Treatment Design and Assessment

Treatment Development. To address ADHD and TD symptoms simultaneously, the protocol by Woods and colleagues (2008) as well as standard BPT core constructs were adapted to meet the unique needs of families presenting with TDs and co-occurring diagnoses. First, overlapping strategies across both protocols were evaluated and selected based on their utility and appropriateness for children. For instance, the use of a reinforcement system through which specific behaviors and utilization of competing responses (CRs) can be rewarded was considered clinically useful for the simultaneous treatment of TDs and management of ADHD-related behaviors. Further, additional

strategies that incorporate differential attention, such as planned ignoring for reducing inappropriate behaviors, and positive reinforcement, such as labeled praise for increasing positive and/or desirable behaviors (e.g., practicing CRs for tics), were deemed most useful. Next, key elements from diagnosis-specific interventions, such as awareness training for detection of premonitory urges and strategies to evaluate and understand tics more thoroughly, and the use of effective behavioral management strategies (e.g., using short, clear, and direct commands), to address ADHD-related impairment were added to the treatment plan. Finally, the set of core skills selected were strategically adapted into an abbreviated format.

Assessment and Diagnosis. See Figure 2 for a timeline of assessment and intervention sessions. Tic assessments were conducted at three time points: (1) psychoeducational evaluation, completed 8-months prior to treatment by providers not affiliated with the current study, (2) pre-treatment clinical intake assessment, completed by the first and third authors, and (3) a post-assessment, conducted four months following the end of treatment, conducted by the second author. The post-assessment was conducted at this time to align with the booster session, as well as evaluate long-term treatment outcomes. An immediate post-treatment assessment was not conducted given the family's time restraint.

Assessment one: Psychoeducational evaluation. Approximately eight months prior to the initial clinical assessment, Jacob received a full psychoeducational evaluation. The results of the psychoeducational evaluation included clinical diagnoses of Tourette Disorder and confirmation of ADHD, combined presentation. The Yale Global Tic Severity Scale (YGTSS; Leckman, 1989) Global Tic Severity Scale Score from the

psychoeducational evaluation was 66/100, indicating significant elevations in tic severity and tic-related impairment.

Assessment two: Pre-treatment. Jacob's parents provided consent before intake procedures occurred, which included consent to use data collected throughout treatment for research purposes. A thorough assessment of symptoms prior to treatment included a semi-structured clinical interview with Jacob's mother and father and a separate interview with Jacob, to evaluate tic-related and ADHD symptoms. The Disruptive Behavior Rating Scale (DBD-RS; Pelham et al., 1992) was administered to Jacob's parents to assess for ADHD-symptoms, whereby Jacob's parents endorsed 7/9 inattention (i.e., *is often distracted by extraneous stimuli*) and 6/9 hyperactive/impulsive (i.e., *often leaves seat in classroom or other situations in which remaining seated is* expected) symptoms. During the evaluation, Jacob required significant redirection, repetition of instructions, and was observed fidgeting and squirming in his chair that was unrelated to his tics. Jacob and his parents completed the YGTSS, obtaining a Global Tic Severity Scale Score 66/100 for patient-and parent-reported assessments. Clinicians met to discuss parent and child severity ratings and used a multi-informant approach (i.e., evaluated parent and child reports) to determine a global severity score. Overall, parent and child reports were within ±1 point on total tic severity scores; therefore, no significant differences were noted in either informants' YGTSS scores.

Assessment three: Post-treatment assessment. The YGTSS was re-administered four months following the end of treatment, at the same time as booster session two, in order to reduce the burden of additional assessment appointments. Further, the assessor

collected anecdotal evidence from Jacob's parents regarding his ADHD symptoms and their impairment (see *Treatment Outcomes* for the results of this assessment).

Treatment

Intensive Course of Treatment

A complete outline of session content, duration, frequency, and format (i.e., the entire family together or concurrent sessions) is provided in Table 1. Sessions were conducted across three unique phases. Phase one consisted of skill-building, phase two of practicing and reinforcing, and phase three of review and telehealth-based booster sessions. Within each phase, parent- and child-specific strategies, as well as combined strategies were employed. All sessions were conducted with at least one of two primary clinicians. At times, sessions were conducted concurrently, with one clinician involved in each session; however, each session concluded with both Jacob's parents and Jacob together to ensure that all parties involved were aware of and understood the content of each session.

Phase 1: Skill Building. Treatment began with the clinicians separately providing Jacob and his parents psychoeducation about tics (i.e, symptoms, genetics/heritability, information about the progression of tic disorders, treatment options, an overview of CBIT and resources). Given that Jacob's parents received psychoeducation for ADHD prior to enrollment in CBIT, a brief review was conducted with Jacob's parents (i.e., how behavioral interventions can help manage behavioral problems and reduce impairment associated with ADHD). Jacob also created a hierarchical list of current tics, as well as learned awareness training and relaxation strategies (deep breathing and progressive muscle relaxation). Procedures for determining and utilizing CRs were also introduced to

Jacob. Parents were taught basic awareness training and CR development procedures and how to create and implement a reward system. In order to address ADHD symptoms, parents were provided with skills to utilize differential attention (e.g., ignoring inappropriate and praising appropriate behavior) and effective instruction (e.g., direct commands). Behavioral management strategies intended to address more serious behaviors such as non-compliance and aggression (e.g., time-out) were not taught, as Jacob readily followed directions with limited prompting and did not exhibit aggressive behavior toward others. With guidance from the clinicians, Jacob and his parents collaboratively developed a reward system in which Jacob actively participated by selecting prizes that he deemed rewarding and were subsequently used to reinforce appropriate behavior and skill use throughout the course of treatment. This final step was importantly established prior to phase 2 (practicing and reinforcing) in order to ensure that Jacob was familiar with the procedures and was adequately reinforced by the selected prizes. During phase 2, sessions lasted 1.5 hours and were conducted simultaneously but separately with Jacob and a clinician, as well as Jacob's parents and a separate clinician.

Phase 2: Practicing and Reinforcing. During this phase, the clinician met with Jacob alone and practiced awareness training and created a CR for two current and impairing tics (one motor and one vocal tic). A CR was deemed appropriate if it met the following criteria: (1) the CR behavior was physically incompatible with the tic; (2) the CR could be maintained for at least 1 minute or until the urge to tic subsided, whichever came first; and, (3) the CR was less noticeable that the tic itself. For Jacob's motor tic, a CR was created to impede the first tic behavior from occurring. For the vocal tic, Jacob

was instructed to engage in controlled breathing (e.g., slowly breathing in and out) through the nose while keeping lips closed, as this CR impeded Jacob from engaging in the vocal tic. Once the CRs were created, sessions consisted of repeated practice using the CRs, as well as implementing and modifying in-session and at-home behavioral charts and reward systems. Specifically, a behavioral chart for the two-week intensive intervention was created to increase the frequency and duration of out-of-session practice. At the end of treatment, an at-home behavioral chart was created to help address behaviors that occur in a more naturalistic setting. As practice with CRs continued, necessary modifications were made as needed in order to ensure that the most effective CR was utilized. During this phase, session 4 took place 2 days following session 3 to allow for extended practice time. In order to meet Jacob and his family's unique needs, additional time was spent on awareness training, which utilized immediate rewards in conjunction with practice. For example, a minimum of 45 minutes in sessions 1 and 2 was spent on awareness training and CR practice. Each time Jacob was engaged in awareness training (i.e., identifying an urge, or utilizing a CR), he earned points towards a larger reward. Further, sessions 2-6 also utilized this strategy to help Jacob engage in awareness training and CR practice. Outside of session practice (homework) was emphasized throughout treatment and Jacob was successful in completing a large majority of practice between sessions with some support from his mother. Awareness and/or CR practice was suggested between each session for a minimum of one-hour with parent and child together. Once the behavioral chart was created, Jacob's parents implemented this chart on a daily basis as part of their out-of-session homework. Finally, practice using relaxation strategies (i.e., deep breathing, progressive muscle relaxation)

was incorporated into out-of-session practice once these strategies were introduced in session. Throughout out-of-session practice, Jacob's parents were encouraged to implement parent-based strategies (i.e., praise for practice, ignoring negative behaviors) as needed.

To address Jacob's ADHD-related impairment, CBIT sessions were modified. For example, CBIT sessions are traditionally held in 1-hour weekly sessions where both the provider and patient sit in chairs and only stand-up when it is required of them (e.g., to practice a CR). In contrast, Jacob and his family met with clinicians for a total of 6 days, for approximately 1 to 1.5 hours each day (see Table 1). As previously noted, Jacob experienced high levels of hyperactivity, making it particularly difficult for him to sit for more than a few minutes at a time. In response to his hyperactivity impairment, session formats allowed for movement in an assigned area, while simultaneously practicing identifying urges and utilizing CRs. This modification was coupled with positive reinforcement, frequent breaks, and fun activities which were contingent upon Jacob's participation in the therapeutic session component. In addition, Jacob was easily distracted by extraneous stimuli. To address his distractibility and overall engagement, an intensive token-reward system was used to increase target behaviors, namely recognizing the urge to tic and the use of CRs. Points were awarded immediately after Jacob exhibited either behavior as prior studies have shown that immediate feedback is necessary to obtain clinically meaningful improvement for children with ADHD (Abramowitz et al., 1992; Fabiano & Pelham, 2003). At the end of each day, Jacob was able to exchange the points earned in-session for a tangible reward. Of note, ADHD-related impairment was addressed in-session to facilitate the delivery and practice of the CBIT treatment

components. The goal of using immediate reinforcement (e.g., awarding points) was to help increase Jacob's awareness of premonitory urges and/or tics, as well as reinforce the use of CRs.

Concurrently, Jacob's parents met with a clinician to discuss BPT strategies to address Jacob's ADHD symptoms. Specifically, over the course of six sessions, Jacob's parents were introduced to the following skills/strategies: (1) differential attention (praise and ignoring), (2) effective instructions, and (3) rewards and behavioral charts. During session reviews, at which time both Jacob's parents and Jacob were present in the same room, Jacob's parents were able to briefly practice utilizing the skills taught throughout sessions and receive live coaching during sessions (e.g., ignoring negative behaviors). While it is possible that ADHD symptoms (e.g., hyperactivity, distractibility) were reduced during the week-long intensive program, ADHD is a chronic disorder for which continued behavioral treatment is necessary to produce sustained behavioral improvements. As such, the BPT that was concurrently provided to Jacob's parents was intended to address ADHD-related impairment during and post-treatment, whereas in-session strategies used with Jacob were employed primarily to sufficiently manage his behavior for the purpose of providing CBIT treatment. Further, BPT skills review and brief live coaching were incorporated as a core component of booster sessions to ensure Jacob's parents were able to implement strategies effectively once they returned home.

Phase 3: Review and Telehealth-based Booster Sessions. The final in-person sessions consisted of relapse prevention, with particular emphasis placed on creating CRs for new tics that may appear in the future. Further, CRs for both tics and relaxation strategies were practiced. Lastly, the clinicians worked collaboratively with Jacob's

mother to establish a behavioral chart and reward system to ensure continued practice at home, such that Jacob would earn incentives when using CRs and relaxation techniques as well as when meeting behavioral expectations (e.g., staying on task during school assignments). Rewards were tiered into small, medium, and large rewards based on size, cost, and Jacob's indication of the degree of desirability, and included additional screen time (i.e., extra television, tablet, or videogame usage), time with friends, (i.e., playdates or sleepovers), toys and small desserts. Given the family's time restrictions on the last day, a post-treatment assessment was not conducted and, instead, the final session focused entirely on ensuring the family was familiar and comfortable with skills learned throughout the two weeks.

Telehealth-based booster sessions took place approximately three, four, and six months following the end of treatment and were individualized to meet the family's needs at each time point. The telehealth format was utilized given geographic barriers of the family, however, the use of telehealth as a treatment delivery platform has been shown to be efficacious (i.e., Comer et al., 2017). The first telehealth-based booster session (three months post-treatment) consisted of a review of progress since their last session and addressing any questions or difficulties they were experiencing with using the strategies learned throughout treatment. Specifically, Jacob's parents requested a review of each CR, as well as the steps to identifying premonitory urges and creating CRs. At the second telehealth-based (four months post-treatment) booster session skills associated with both disorders were discussed. Specifically, BPT skills (e.g., positive reinforcement, differential attention) were reviewed to ensure continued use of these strategies for ADHD-related symptoms. In addition, previous CRs were reviewed and modified if

necessary. Parents were receptive to the intervention strategies and were able to aid their child in the utilization of the skills at home. At this time, the YGTSS was conducted to evaluate long-term tic symptom severity. At the third telehealth-based booster session (six months post-treatment), a review of CRs, as well as a review of household rules, differential attention, and overall school progress. At this time, Jacob's parents reported an improvement in Jacob's academic performance and indicated no concerns about school.

Results

The YGTSS total score 4-months following the end of treatment was 40/100, indicating a 26-point decrease from the psychoeducational evaluation and pre-treatment assessments (see Figure 1). While Jacob was prescribed Clonidine extended-release to address TD and ADHD symptoms between the psychoeducational evaluation and his initial behavioral intervention intake, he was not taking any active medications during the behavioral intervention at the center of this case study. However, pre-treatment YGTSS scores indicated no change from the psychoeducational evaluation to the initial intake assessment, despite the use of medications for over one year prior to the initial intake assessment, but was not prescribed or being taken at the time of intake. This would suggest that the pharmacological treatment had no impact on parent-reported scores on the YGTSS prior to the start of CBIT treatment and was consistent with parent report on the reason for its discontinuation. In contrast, there was approximately a 23% reduction in the total tic severity score from pre- to post-treatment assessments following the combined CBIT + BPT intensive intervention, suggesting that improvements in YGTSS scores were a reflection of the psychosocial treatment provided. Further, these findings

support the combination of CBIT and BPT – two well-established psychosocial interventions – as non-pharmacological alternatives for the treatment of co-occurring TD and ADHD (Barbaresi et al., 2020). Programs designed to address tics or ADHD should consider utilizing a combined treatment approach that assesses for and provides individuals with the skills to reduce symptoms of either disorder.

During the booster sessions, Jacob's parents indicated significant improvements in tic severity, duration, and frequency. During booster session one, Jacob's parents indicated brief instances of "flare ups" occurred; however, these periods lasted approximately one day (as compared to pre-treatment, when such periods of time would have lasted up to three weeks). While his parents reported that their use of strategies had decreased following the end of treatment, they felt confident in their ability to reinstate any needed skills should tic symptoms reemerge significantly. During the final booster session, parents reported improvements in Jacob's behavior, particularly with his ability to remain on task during at-home school assignments with additional support from parents, as well as his use of CRs when needed. Jacob was also receptive to attending booster sessions and was able to collaboratively create and modify CRs with minimal support from the clinician.

Additionally, during the final booster session, the clinician received feedback from Jacob's parents regarding the format, structure, and content of the two-week intensive intervention they had received. Jacob's parents reported overwhelming support for the simultaneous CBIT and BPT approach, indicating that learning skills related specifically to TDs and ADHD within the same treatment format, and with the same treatment providers, was invaluable. His parents also reported that the use of CBIT strategies were helpful and necessary core skills; however, the additional parenting skills, such as

differential attention and praise were vital, as they provided strategies to promote positive interactions with Jacob, as well as improve his behavior. Overall, Jacob and his parents attended all sessions as indicated, and reported clinically meaningful improvements in TD and ADHD-symptom severity.

Discussion

The current case study provides preliminary support for combining CBIT and BPT and suggests that simultaneous implementation of strategies may be useful in treating TDs and co-occurring diagnoses, such as ADHD. Jacob exhibited significant improvements in tic symptomatology, as well as reductions in parent-reported impairment associated with ADHD. The findings in the current study are consistent with reductions in tic symptom severity following standard CBIT strategies (Dutta & Cavanna, 2013). Earlier case studies suggest that children with disruptive behaviors may not be suitable for intensive CBIT (Blount et al., 2014), however, these studies were limited to the standard CBIT protocol, which does not include strategies to manage such behaviors. By incorporating behavioral management strategies, such as a behavioral chart to target the most impairing behaviors and the utilization of reinforcement strategies, for example, a point system – through which Jacob earned points immediately after exhibiting appropriate behaviors – we were able to successfully address co-occurring ADHD symptoms and ultimately increase Jacob's active participation throughout sessions.

The evidence from the current study is promising and begins to fill an important gap in the TD treatment literature. Jacob's parent's qualitative feedback suggested overall acceptability of the intervention, as well as areas of improvement for treatment to further engage future families. Specifically, his parents indicated that more time in session

throughout the day, such as morning and afternoon sessions within the same day, would be beneficial to ensure proficiency with using each skill. Thus, this extended time within the same day may provide clinicians with the opportunity to incorporate additional strategies to address comorbid diagnoses, such as Cognitive Behavioral Therapy skills, or expand upon BPT skills learned within treatment, and also aid families in identifying associated triggers and/or stressors that may be limited to certain hours of the day. It was noted by Jacob's parents that a group-based format would have also been useful for children and parents to provide and gain social support and share their unique experiences with TDs and common comorbidities.

Given that access to trained providers in both CBIT and BPT is limited, the current study's format provides the opportunity for families to access treatment providers in an abbreviated manner, while also allowing for longer-term care through booster sessions conducted via telehealth (as needed). This study was conducted over the course of two weeks, however, the total number of intervention sessions, including the initial evaluation, was conducted over the course of seven days. Therefore, this intervention is likely amenable to further alterations to the treatment schedule to allow for accommodations associated with each family's differing schedules, such as occurring over one week of school vacation or the summer. While it is possible that there may be reductions in between-session CR practice, intensive formats could be more conducive to maximizing in-session practice as compared to a weekly format and may ensure that additional practice using CRs is accomplished during treatment. Overall, an intensive, combined intervention approach may be an acceptable alternative to traditional intervention modalities, as it may reduce several barriers to treatment.

Telehealth-based booster sessions also offer additional time spent practicing and modifying strategies that may be integral to maintaining gains seen throughout treatment and generalize these gains to the patient's naturalistic home environment. Booster sessions allow for individualized review and practice of skills that may reinforce their use after intensive treatment termination. Importantly, Flancbaum and colleagues (2011) noted that, while improvements were initially seen post-treatment, due, in part, to lack of participation in booster sessions, treatment gains were not maintained once the patient returned home. Therefore, these booster sessions likely provide additional and necessary support to families in order to ensure that skills learned throughout treatment are accurately and effectively implemented at home. Future studies should evaluate the utility of internet-based booster sessions and their effectiveness in maintaining treatment gains.

Preliminary evidence from the current case study suggests that combined CBIT and BPT can be a useful treatment modality for children experiencing TDs and co-occurring ADHD. The current treatment design provides an alternative to attending sessions with separate providers who specialize in TDs or ADHD and may facilitate increased access to care for families without providers within their community. Families and children experiencing significant distress and/or impairment from tics and who exhibit symptoms of co-occurring diagnoses are likely good candidates for the current treatment and may benefit from an intensive format in which presenting diagnoses can be targeted simultaneously.

This study is not without limitations. First, the results are based on a single patient and, therefore, the generalizability of the current findings are not known at this time. Second, specific patient and parent treatment satisfaction measures were not utilized;

instead, this information was collected via anecdotal evidence from parents. Future studies would benefit from utilizing standardized treatment satisfaction questionnaires to evaluate the family's overall perspectives of the treatment protocol. However, to avoid clinician bias, post-treatment assessments of tic symptoms were collected by a third-party clinician who was not involved in Jacob's treatment. Third, while immediate post-treatment assessments were not able to be collected, evaluations conducted four months following the end of treatment indicated long-term improvements, which may reflect a more important metric of the longevity of improvements and a possible underestimate of immediate post-treatment reductions in TD symptoms. Nonetheless, future studies should evaluate immediate post-treatment tic symptoms in addition to long-term changes. Fourth, future studies should evaluate the effectiveness and acceptability of combining CBIT and BPT in a larger sample to determine the generalizability of the current study's findings. Fifth, it is important to note that intensive outpatient treatment is sometimes not fully covered by all insurance types (i.e., private vs. government; i.e., Cook et al., 2014; James et al., 2014), therefore, intensive formats may not be amenable to all families. Policy and insurance companies should consider increasing coverage for intensive programs as a means to more efficiently treat comorbid disorders. Sixth, the current case presentation utilized two clinicians to provide treatment (i.e., one to meet with the child and one to meet with the parents) in order to provide treatment simultaneously and reduce the amount of time the family was required to spend in-clinic. The clinicians who participated in treatment had knowledge and experience in both CBIT and BPT, therefore, the family did not attend separate sessions in order to receive specialized treatment from either provider. However, the use of two clinicians may not be feasible

across all treatment providers and settings. Nonetheless, this treatment can easily be modified to be provided by one clinician to include parent-only sessions and child-only sessions at different time points throughout the day or may be modified to be conducted as one joint parent-child session. Seventh, post-treatment assessment of ADHD outcomes was limited to anecdotal parent feedback. As such, future studies would benefit from conducting standard ADHD post-treatment assessments to elucidate treatment-induced changes in ADHD symptoms. Finally, the utilization of an experimental design with an active treatment and control group would aid in elucidating clinically significant improvements from those associated with the natural passage of time (e.g., the child's symptoms may have improved, given the waxing and waning nature of tics).

Notwithstanding its limitations, the current study provides preliminary evidence for an abbreviated and combined intervention to address tic- and ADHD-related symptoms concurrently. Importantly, an intensive intervention format allows for families to exclusively focus on the acquisition and use of strategies without as many interferences from non-treatment related responsibilities. Additionally, a group-based version of this format would allow for treatment providers to offer services to a larger number of patients, particularly given the shortage of trained CBIT therapists nationally, while simultaneously reducing the geographic barrier often associated with finding a provider. Future studies are warranted to determine the efficacy of this treatment format, as well as the possibility of utilizing patient feedback provided in the current case study to evaluate a group-based combined intervention. Specifically, given that individual parent and child, as well as combined sessions, were conducted to address TD and ADHD symptoms simultaneously, group-based intensive interventions should consider

adopting this multimodal approach to provide general TD management strategies within a group setting, as well as individual patient-specific sessions to address their unique impairment due to co-occurring diagnoses strategies. This format likely alleviates many of the limitations indicated in the current case study (i.e., group-based social support, increased number of sessions per day, reduction in the total number of days spent in treatment) to improve overall outcomes for children experiencing TDs and ADHD and may also be more cost-effective for treatment providers.

TDs are prevalent throughout the United States and can lead to significant impairment in children's school and social functioning, as well as impact their family's overall well-being. Youth with TDs are also likely to experience a comorbidity, with ADHD as the most prevalent co-occurring diagnosis. Despite significant effort to train providers in CBIT nationally, access to providers still remains geographically limited. Currently, CBIT and BPT are both first-line non-pharmacological interventions to address TDs and ADHD and may drastically reduce impairment associated with these diagnoses. Therefore, the findings from the current study provide preliminary evidence for a cost- and time-efficient treatment alternative for families seeking behavioral interventions for TDs and ADHD that can simultaneously address common co-occurring diagnoses symptomatology.

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APPENDIX

Monthly Teacher Rating Scale

Check the column which best describes this child's behavior over the last 4 weeks.

	Not at all	Just a Little	Pretty Much	Very Much
Fidgeting	☐	☐	☐	☐
Hums and makes other odd noises	☐	☐	☐	☐
Excitable, Impulsive	☐	☐	☐	☐
Inattentive, easily distracted	☐	☐	☐	☐
Fails to finish things he or she starts (short attention span)	☐	☐	☐	☐
Quarrelsome	☐	☐	☐	☐
Acts "smart" (like a smart-aleck)	☐	☐	☐	☐
Temper outbursts-behavior explosive and unpredictable	☐	☐	☐	☐
Defiant	☐	☐	☐	☐
Uncooperative	☐	☐	☐	☐

For each area listed below, please circle the response that you believe reflects the degree to which the treatments in place **during the past 4 weeks** are working for the child**.**

1. How this child's behavior or attention affects his or her relationship with other children Choose an item.

2. How this child's behavior or attention affects his or her relationship with you Choose an item.

3. How this child's behavior or attention affects his or her academic progress Choose an item.

4. How this child's behavior or attention affects your classroom functioning Choose an item.

Do you think this child requires more intensive treatment (for example, an increase in medication dose)? Note that study doctors will make all final decisions regarding treatment; we ask your opinion only to help the study doctors determine how much of a problem the child is having at this time. Choose an item.

Please provide any additional information regarding your ratings above. Describe any progress or problems the child has made this month:

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PUBLICATIONS AND PRESENTATIONS

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