Parent and Teacher Ratings of Attention during a Year-Long Methylphenidate Trial in Children Treated for Cancer*

Kelli L. Netson,1 PhD, Heather M. Conklin,1 PhD, Jason M. Ashford,1 MS, Lisa S. Kahalley,2 PhD, Shengie Wu,3 MS, and Xiaoping Xiong,3 PhD

1Department of Psychology, St. Jude Children’s Research Hospital, 2Section of Psychology, Department of Pediatrics, Baylor College of Medicine, and 3Department of Biostatistics, St. Jude Children’s Research Hospital

All correspondence concerning this article should be addressed to Heather M. Conklin, PhD, St. Jude Children’s Research Hospital, 262 Danny Thomas Place, Mail Stop 740, Memphis, TN 38105. E-mail: heather.conklin@stjude.org

*The methods for this study are based on those first reported on in Mulhern et al., 2004.

Objective Longitudinally examine attention performance in childhood cancer survivors prescribed methylphenidate (MPH) to ameliorate cognitive late effects, comparing measures for inter-rater and inter-method discrepancies. Methods Survivors of acute lymphoblastic leukemia (n = 33) or brain tumor (n = 35), mean age 11.11 ± 0.37 years, completed a 12-month, open-label trial of MPH. Conners’ Parent and Teacher Rating Scales were completed at baseline, 1, 3, 6, and 12 months. The Conners’ Continuous Performance Test (CPT) was completed at baseline and 12 months. Results Improved attention was reported after 1 month of MPH (p < .05), with relative stability throughout the trial. Inter-rater agreement was low-to-moderate (ICC = –.06 to .46). Observer ratings correlated with select CPT indices at baseline (p < .05), but not at 12 months. Conclusions Childhood cancer survivors’ attention improved after 1 month on MPH. Modest agreement between parents and teachers, and low-to-moderate correlations between behavior ratings and performance-based attention measures highlight a need for multimodal assessment.

Key words attention; cancer; intervention outcome.

Introduction

Children who receive central nervous system (CNS) targeted therapy for acute lymphoblastic leukemia (ALL) or brain tumor (BT) are at risk for cognitive late effects of disease and treatment. Cognitive late effects are thought to be directly related to the impact of disease and treatment (e.g., chemotherapy, radiation therapy), and typically include gradual declines in global intellectual functioning and decreased academic achievement (Moleski, 2000; Palmer et al., 2003; Ris & Noll, 1994; Walter et al., 1999). More distal outcomes associated with cognitive late effects include reduced rates of high school graduation, lower job satisfaction, and reduced overall quality of life (Armstrong et al., 2009; Mirby et al., 2003; Mody et al., 2008). Prior investigations have suggested that global declines may be due to deficits in underlying processes of attention and working memory (Mulhern et al., 1998; Rodgers, Horrocks, Britton, & Kernahan, 1999; Schatz, Kramer, Ablin, & Matthy, 2000), likely mediated by reduced cerebral white matter volumes thought to result from CNS-directed chemotherapy and/or radiation therapy (Mulhern, White et al., 2004; Reddick et al., 2003). The identification of these proximal causes of cognitive late effects has provided clues regarding etiology and informed avenues for intervention.
Studies aimed at the amelioration of attention deficits in childhood cancer survivors have emerged, hypothesizing that the attention deficits seen in this population would respond to stimulant medications in a similar fashion to those seen in attention-deficit/hyperactivity disorder (ADHD). It has been postulated that atypical dopaminergic function, particularly in the frontal–striatal circuitry, is responsible for difficulty with attention regulation and reward response in children with ADHD (for a review, see Sonuga-Barke, 2003). Methylphenidate (MPH), a piperidine derivative, increases presynaptic dopamine availability in the prefrontal cortex by inhibiting dopamine transport away from that region (Nelson, 1995). Although it is most frequently used to treat ADHD, MPH has been shown to improve attention acutely in childhood cancer survivors (Conklin et al., 2007; Thompson et al., 2001). These survivors also experienced sustained benefit after week-long administrations of MPH during a placebo-controlled home crossover trial, with symptom improvement demonstrated on parent- and teacher-report measures (Mulhern, Khan et al., 2004). Evidence from a 1-year efficacy trial of MPH in childhood cancer survivors experiencing cognitive late effects has recently emerged, suggesting long-term cognitive and behavioral benefits of stimulant treatment in this population (Conklin, Reddick et al., 2010). While the ADHD literature suggests that children experience stable, sustained benefit during year-long stimulant trials (Abikoff et al., 2004; Wiblen et al., 2003), it remains unknown whether childhood cancer survivors follow a similar pattern of response, as longitudinal intervention studies have only emerged recently in this population.

Parent- and teacher-report measures have been used to document MPH treatment response in childhood cancer survivors. Although both sources report improved attention, discrepancies were found between parent and teacher ratings (Mulhern, Khan et al., 2004). Disagreement between parent and teacher reports of attention deficits has been well documented in the ADHD literature across a number of measurement instruments. Typical inter-rater agreement falls in the low-to-moderate range (Collett, Ohan, & Myers, 2003; DuPaul, Power, McGoe, Ikeda, & Anastopoulos, 1998; Hartman, Rhee, Willcut, & Pennington, 2007; Tripp, Schaughency, & Clarke, 2006), despite findings that both parents and teachers provide useful diagnostic information (Pelham, Fabiano, & Massetti, 2003; Weiler, Bellinger, Marmor, Rancier, & Weber, 1999). Explanations for these discrepancies include the possibility that parents and teachers are observing different behaviors or phenotypes (Hartman et al., 2007; Mitsis, McKay, Schulz, Newcorn, & Halperin, 2000; Soma, Nakamura, Oyama, Tsuchiya, & Yamamoto, 2009), particularly given the more structured demands of school settings versus relatively less organized home activities (Polanczyk & Jensen, 2008). Further, it has been proposed that parents and teachers observe different therapeutic phases of short-acting pharmacologic agents, such that medication benefits have subsided by the afternoon and evening hours in which parents observe behaviors. Accordingly, inter-rater agreement improves with the use of long-acting treatment formulations (Biederman, Faraone, Montueaux, & Grossbard, 2004; Biederman, Gao, Rogers, & Spencer, 2006).

Inter-rater discrepancies have been documented when parents and teachers rate attention problems in children with intellectual impairment and borderline intelligence, with intra-class correlations ranging from $r = .07$ to $.46$ (Deb, Dhaliwal, & Roy, 2008). The authors suggest that raters may have difficulty distinguishing symptoms of inattention from symptoms of low intellectual functioning or may attribute inattentive and hyperactive behaviors to other developmental causes. They proposed that parents might attenuate their ratings based on lowered behavioral expectations or, in contrast, could endorse greater distress due to parenting “burnout” (Deb et al., 2008). These findings may be particularly salient for childhood cancer survivors who are at risk for global intellectual decline as a result of their disease and treatment, highlighting a need to consider the expectations placed on children by various environments and raters.

Despite established discrepancies between these two sources of information in the ADHD literature, parent and teacher questionnaires remain the most efficient tools for assessing changes in attention and other behaviors. The need for information about functioning across multiple settings, and thus multiple informants, has been well established in the ADHD literature (Biederman, Faraone, Milberger, & Doyle, 1993; Mitsis et al., 2000; Polanczyk & Jensen, 2008). Likewise, obtaining both parent and teacher reports of attention dysfunction is critical in understanding the effectiveness of interventions for the attention dysfunction that results from childhood cancer treatment. Alternative methods for assessing attention include performance-based measures (e.g., continuous performance tasks; CPTs), which require specialized equipment and usually entail a clinic visit. In children with ADHD, CPTs tend to correlate poorly to moderately with parent and teacher ratings and demonstrate relatively low sensitivity and consistency when diagnosing subtypes of ADHD (Barky, 1991; Edwards et al., 2007). Thus, despite the added investment, these tests have limited ecological validity and provide only a brief snapshot of a child’s attentional
capacity in a controlled environment. In vivo behavioral observations maximize the ecological validity of the assessment, but require even more extensive investment in professional training and time. Given the reliance of intervention studies on parent and teacher reports of behavior change, it is important to characterize and understand the response patterns of these two groups of informants, the rate of agreement across raters, and the relationship to performance-based measures of attention.

This report is one in a series resulting from a multi-site, multi-phase investigation of the efficacy of MPH for addressing attention deficits associated with late effects of childhood cancer treatment. This series of reports currently comprises the largest investigation of intervention for late effects in childhood cancer survivors to date. The series began with a 2-day, in-clinic, placebo-controlled crossover design that demonstrated positive response to MPH among cancer survivors, particularly in the areas of processing speed and response tendency (Conklin et al., 2007). Children who acutely tolerated MPH went on to participate in a 3-week, randomized, double-blind, placebo-controlled home crossover trial, in which placebo, low dose MPH, and moderate dose MPH were administered in the home setting in randomized order during 3 consecutive weeks with washout periods during the weekends (Mulhern, Khan et al., 2004). Findings indicated positive clinical response to MPH relative to placebo, with improvements in cognitive performance and inattentive behaviors reported on behavior rating scales. A separate investigation of drug tolerability during the 3-week crossover trial revealed that cancer survivors tolerated low to moderate doses of MPH well, although girls, children with a BT diagnosis, and those with lower baseline IQ were at greater risk for experiencing side effects (Conklin et al., 2009).

The final phase of this trial comprised a 12-month, open-label MPH trial investigating the long-term effectiveness of individually titrated maintenance doses of MPH. Significant improvement was noted between medication baseline and 1-year follow-up on performance-based measures of sustained attention as well as parent-, teacher-, and self-reported measures (Conklin, Reddick et al., 2010). A year-long investigation of growth deceleration during this phase revealed that childhood cancer survivors experienced a significant, but modest deceleration in weight and BMI (Jasper et al., 2009). In summary, this series of studies has provided support for the efficacy, safety, and tolerability of MPH in childhood cancer survivors acutely and over the course of 1 year. Some questions remain, however, with regard to the pattern of symptom change throughout the year of treatment. Long-term investigations examining the trajectory and stability of symptom change in childhood cancer survivors are absent from the literature, and agreement between parent and teacher ratings of inattentive symptoms remains unexamined in this population. Finally, the relation between observer ratings and performance-based measures of attention requires further elucidation to determine whether childhood cancer survivors’ performance on these measures mimics that of other clinical populations (e.g., children with ADHD).

Based on the current literature regarding pharmacologic intervention for cognitive late effects of childhood cancer, this study aimed to address specific knowledge gaps by investigating parent and teacher ratings of attention during a 12-month, open-label trial of MPH in childhood cancer survivors. Objectives were as follows: (1) characterize the longitudinal pattern of MPH response based on both parent and teacher ratings of attention; (2) compare parent and teacher ratings of attention and behavior for inter-rater agreement and discrepancies; and (3) compare parent and teacher ratings with performance-based measures of attention. It was hypothesized that survivors of childhood cancer would demonstrate an initial response to MPH and maintain stable improvement across the year-long trial. It was further predicted that parent and teacher ratings would be in general agreement, approximating the levels of correlation found in the ADHD literature. Finally, agreement between observer ratings and a performance-based measure of attention was expected to be modest based on prior findings.

**Methods**

**Participants**

Participants were survivors of ALL or BT, recruited from three academic medical centers (St. Jude Children’s Research Hospital, Duke University, and Medical University of South Carolina), who completed the final phase of a multi-site, multi-phase, controlled efficacy trial of MPH in childhood cancer survivors with attention and academic problems. Participant selection for other phases of the trial has been described previously (Conklin et al., 2007; Conklin et al., 2009; Conklin, Helton et al., 2010; Conklin, Reddick et al., 2010; Jasper et al., 2009; Mulhern, Khan et al., 2004). Inclusion criteria required treatment for ALL or BT with chemotherapy and/or CNS-directed radiation therapy. Treatment was completed at least 1 year prior to participation and there was no evidence of disease recurrence. Participants were native English speakers between 6 and 18 years of age who demonstrated weaknesses on measures of attention and academic achievement (defined below). Children with a pre-cancer diagnosis of
ADHD identified by parent report or notation in the medical record were excluded. Additionally, children with uncontrolled seizures, severe sensory loss, untreated hypothyroidism, personal or family history of Tourette syndrome, glaucoma, substance abuse history, or current use of psychotropic medications were excluded.

Initial screening for the multi-phase investigation resulted in 470 individuals initially screened, 211 who met eligibility criteria, and 135 who provided consent for the initial phase of the study. These participants completed a 2-day, in-clinic, double-blind crossover trial in which they received MPH and placebo in a randomly assigned order (Conklin et al., 2007). Of these, 2 children discontinued due to side effects and 15 declined further stimulant medication. Children who continued on to the next phase included 118 participants who initiated a 3-week home crossover trial in which placebo, low dose MPH (0.3 mg/kg; maximum dose 10 mg b.i.d.), and moderate dose MPH (0.6 mg/kg; maximum dose 20 mg b.i.d.) were administered in the home setting during 3 consecutive weeks with washout periods during the weekends (Mulhern, Khan et al., 2004). During this phase, “clinical response” was defined a priori as improvement of at least 3 raw score points on any index (Cognitive Problems/Inattention, Hyperactivity, or ADHD) from the parent- or teacher-report form of the Conners Rating Scale, Revised (CRS-R; Conners, 2000). Of these 118 participants, 16 were considered non-responders, 4 discontinued due to side effects, and 7 withdrew from the study.

The remaining 91 children were offered enrollment in the 12-month, open-label MPH trial. A total of 23 participants failed to complete the trial (Side effects n = 8; Medical problems unrelated to MPH n = 6; Patient/Parent request n = 6; Lost to follow-up n = 3). These 23 participants did not differ from the 68 who completed the trial on any demographic or treatment-related variables. The group that discontinued scored higher at baseline than those who completed the trial on the CPRS Cognitive Problems/Inattention Index (p = .044) and the CTRS ADHD Index (p = .035), suggesting more significant attention dysfunction. There were no statistical differences in performance-based measures of attention. Given that more severe ratings at baseline predict better MPH response (Conklin, Helton et al., 2010), it is unlikely that this baseline discrepancy systematically skewed these findings in favor of detecting treatment response.

The 68 participants who completed the year-long trial were, on average, 5 years of age at diagnosis, 11 years of age at study entry, and completed treatment 4 years prior to study entry. The sample was balanced with respect to sex, diagnosis (ALL or BT), and age at treatment (≤4 years or >4 years). Mean estimated IQ (±SE) was 89.39 ± 1.89 at baseline (Conklin, Reddick et al., 2010). Clinical and demographic characteristics for the study cohort are reported in Table I.

Table I. Demographic and Clinical Characteristics of the Sample

<table>
<thead>
<tr>
<th>Mean (SE)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years at diagnosis</td>
<td>5.21 (0.36)</td>
</tr>
<tr>
<td>Time since diagnosis</td>
<td>4.25 (0.32)</td>
</tr>
<tr>
<td>Age in years at study entry</td>
<td>11.11 (0.37)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
</tr>
<tr>
<td>Female</td>
<td>31</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>57</td>
</tr>
<tr>
<td>African American</td>
<td>10</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
</tr>
<tr>
<td>Father’s education</td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>6</td>
</tr>
<tr>
<td>High school or some college</td>
<td>39</td>
</tr>
<tr>
<td>Bachelor’s or graduate degree</td>
<td>20</td>
</tr>
<tr>
<td>Mother’s education</td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>3</td>
</tr>
<tr>
<td>High school or some college</td>
<td>47</td>
</tr>
<tr>
<td>Bachelor’s or graduate degree</td>
<td>18</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Brain tumor</td>
<td>35</td>
</tr>
<tr>
<td>ALL</td>
<td>33</td>
</tr>
<tr>
<td>Treatment age (in years)</td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>29</td>
</tr>
<tr>
<td>&gt;4</td>
<td>39</td>
</tr>
<tr>
<td>RT</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25</td>
</tr>
<tr>
<td>Yes</td>
<td>43</td>
</tr>
<tr>
<td>Whole brain</td>
<td>10</td>
</tr>
<tr>
<td>Focal</td>
<td>20</td>
</tr>
<tr>
<td>Whole brain plus focal</td>
<td>13</td>
</tr>
<tr>
<td>Age in years at RT</td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>11</td>
</tr>
<tr>
<td>&gt;4</td>
<td>32</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>57</td>
</tr>
<tr>
<td>Age in years at chemotherapy</td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>26</td>
</tr>
<tr>
<td>&gt;4</td>
<td>31</td>
</tr>
<tr>
<td>Treatment intensity*</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>25</td>
</tr>
<tr>
<td>Moderate</td>
<td>8</td>
</tr>
<tr>
<td>High</td>
<td>35</td>
</tr>
</tbody>
</table>

Note. ALL = acute lymphoblastic leukemia; RT = radiation therapy.

*Mild: Chemotherapy only; Moderate: ≤24 Gy RT with or without chemotherapy; High: >24 Gy RT with or without chemotherapy.
Cognitive and Behavioral Assessment

Participants completed a cognitive assessment at pre-medication baseline and after 12 months of treatment with MPH. This screening battery has been described in detail previously (Conklin et al., 2007) and is summarized here. Global intellectual functioning was estimated based on selected subtests from the Wechsler Intelligence Scale for Children, Third Edition (Wechsler, 1991) or Wechsler Adult Intelligence Scale, Third Edition (Wechsler, 1997), depending on the child’s age. Scaled scores from the Information, Similarities, and Block Design subtests were imputed into a formula provided by Sattler (1992) to obtain an estimate of the participant’s full-scale IQ score. Baseline IQ > 50 was required for participation in the current study based on empirical evidence of response to MPH in children with IQ scores ranging from 50 to 74 (Handen, Breaux, Gosling, Ploof, & Feldman, 1990). Furthermore, it was important to include children with low IQ to better reflect the cancer survivor population and enhance generalizability of findings.

Academic achievement was assessed with five subtests from the Wechsler Individual Achievement Test (Wechsler, 1992): Basic Reading, Reading Comprehension, Spelling, Numerical Operations, and Mathematics Reasoning. Scores at or below the 25th percentile on one or more of these subtests were required for inclusion in the study. This criterion was utilized to identify a weakness in academic achievement that might be amenable to treatment with MPH (Thompson et al., 2001). These criteria were selected to include those children with subtle weaknesses and enhance the generalizability of findings.

Attention problems were identified using both performance-based measures and observer ratings. The Conners’ CPT is a computerized, performance-based test that reliably identifies children demonstrating attention problems with ~87% sensitivity and 74% specificity, with negligible practice effects (Conners, 1995). Multiple indices are derived from each administration. Of particular interest in the current study were indices suggesting inattention (Errors of Omission), impulsivity (Errors of Commission), reaction time (Hit Reaction Time), vigilance or signal detection (d’), risk-taking (β), and a composite index score. A score at or above the 75th percentile on Errors of Omission (failure to respond to a target) was required for study entry.

Observer ratings of attention were obtained with the short form of the CRS-R (Conners, 2000). The Conners’ Parent Rating Scale, Revised, Short Form (CPRS) and the Conners’ Teacher Rating Scale, Revised, Short Form (CTRS) are 27-item questionnaires. CPRS and CTRS forms were administered to parents and teachers over the telephone. Parents rate a series of behaviors on a scale from 0 (not true at all) to 3 (very much true), yielding four indices for each form: Hyperactivity, Cognitive Problems/Inattention, Oppositional, and ADHD Index. The CPRS and CTRS have internal consistency ratings between .86 and .95 with appropriate test–retest reliability. Inter-rater reliability between parents and teachers ranges from r = .06 to .52 (Conners, 2000). Based on the phenotype associated with cognitive late effects of cancer treatment, the Oppositional Index was not of interest in this study and was excluded from analyses; accordingly, ratings at or above the 75th percentile on any of the remaining three indices (Cognitive Problems/Inattention, Hyperactivity, ADHD) were required for study eligibility. Parents completed the CPRS on-site during the baseline and Month 12 evaluations; remaining CPRS (at 1, 3, and 6 months) and all CTRS forms were administered to parents and teachers over the telephone.

Procedures

Procedures for other phases of the randomized, double-blind, placebo-controlled portion of the larger study have been described in detail elsewhere (Conklin, Helton et al., 2010; Conklin et al., 2009; Conklin, Reddick et al., 2010; Mulhern, Khan et al., 2004). In summary, potential participants were identified after review of medical records and were approached by clinically trained research assistants. Individuals meeting the eligibility requirements provided parental consent and patient assent for participation in this study. Initial screening was conducted to assess for adequate intellectual functioning and any attention and academic deficits that might be amenable to intervention with MPH as indicated in the description of the cognitive battery above. Participants demonstrating acute tolerance of MPH during the 2-day, in-clinic phase and clinical response relative to placebo during the 3-week crossover phase were offered participation in the current phase of the trial.

The 12-month open-label trial sought to maximize benefit from MPH and minimize side effects by individual dose titration. Dosing was managed by a research team including a neurologist, pharmacist, and registered nurse. Children weighing at least 30 kg were typically started on 18 mg of extended release MPH daily, with doses titrated to 27 mg/day or 36 mg/day as indicated based on response and report of side effects. Children weighing <30 kg typically began treatment at a dose of 5 mg once or twice per day, with titration upward based on clinical response and side effects as reported during monthly telephone interview with a research nurse. Once a favorable clinical
response was achieved (i.e., maximized parental perception of benefit with minimized side effects), dosage was maintained unless a change was indicated based on parent-reported symptom rebound. Extended release formulations were used whenever possible.

Patient response to MPH was monitored during the titration phase by a weekly telephone call from a research nurse. Parents reported on general response to MPH (no benefit, mild benefit, significant benefit) and experience of side effects (no side effects or side effects impacting daily functioning) to provide an efficacy rubric. Once optimal dosing was achieved based on this efficacy rubric, telephone calls were conducted monthly to assess side effects and adherence through parent-reported pill count, resulting in high adherence levels. At the identified time points, the research nurse administered the CPRS to parents and the CTRS to teachers in individual telephone calls. No additional education was provided regarding the benefits of MPH during these telephone calls.

**Analyses**

Descriptive analyses were calculated to characterize the demographic and clinical aspects of the sample. The first aim of the study, the characterization of longitudinal response to MPH over 12 months by both parent- and teacher-report, was addressed with linear mixed models. To compare parent and teacher ratings for agreement and discrepancies, intraclass correlations (ICCs) were employed. The Shrout–Fleiss ICC was selected to adjust for multiple raters rating the same child across time, treating the possibility of different raters at various time points as a random effect (Shrout & Fleiss, 1979). Finally, agreement between observer ratings and performance-based measures of attention was assessed with Pearson correlations between selected indices from the CPRS, CTRS, and Conners’ CPT at pre-medication baseline and Month 12.

Indices of interest from the observer rating scales included the Cognitive Problems/Inattention and ADHD scales. Scales selected from the Conners’ CPT included Errors of Omission, Errors of Commission, Hit Reaction Time, Vigilance (d’), Risk Taking (β), and the overall Index score. These index scores were selected based on the cognitive phenotype of attention deficits in childhood cancer survivors, suggesting a pattern predominantly of inattention, rather than externalizing behaviors (Mulhern, Khan et al., 2004; Patel, Lai-Yates, Anderson, & Katz, 2007). A significance criterion of \( p < .05 \) was used for all analyses. Corrections for family-wise error inflation were not conducted, as they have been identified as too restrictive when employed in hypothesis-driven investigations (Garcia, 2004; Perneger, 1998).

**Results**

Several demographic and treatment-related variables were found to impact parent and teacher ratings of attention in the linear mixed models. Parental education impacted ratings on the CPRS Hyperactivity Index, where children with mothers \( (p = .02) \) and fathers \( (p = .01) \) with a bachelor’s or graduate degree were rated as less hyperactive than children whose parents had less education. Teacher ratings were impacted by sex, where girls received higher sex-adjusted ratings than boys on the CTRS Hyperactivity Index \( (p = .04) \). Children who received chemotherapy received lower CPRS Hyperactivity Index scores \( (p = .04) \).

Clinical and demographic factors including diagnosis, age, race, treatment intensity, and age at treatment did not impact parent or teacher ratings of attention problems.

Linear mixed models were used to characterize the pattern of observer ratings over time. Results revealed that both parents and teachers reported significant \( (p < .05) \) improvement on the Cognitive Problems/Inattention, Hyperactivity, and overall ADHD Indices on their respective Conners’ Rating Scales after 1 month of MPH treatment (See Figure 1). Stability in ratings between Month 1 and Month 12 was noted on Hyperactivity and ADHD indices; however, there was a statistically significant rebound in symptoms on the Cognitive Problems/Inattention index reported by both parents and teachers. Parent ratings of cognitive problems and inattention remained stable from Month 1 to Month 6. At Month 12, ratings rebounded and were significantly higher than Month 1 (2.26 points; \( p = .03 \)) and Month 3 (2.74 points; \( p = .01 \)) ratings. A trend was noted for symptom rebound between Month 6 and Month 12 (2.03 points; \( p = .06 \)). Teachers reported a...
rebound in symptoms relative to Month 1 at Month 6 (2.45 points; \( p = .038 \)) and Month 12 (3.87 points; \( p = .001 \)). Despite this rebound in ratings, scores at Month 12 remained significantly better relative to Baseline per both parent (\( p < .0001 \)) and teacher (\( p = .009 \)) report.

Agreement between parent and teacher ratings was assessed using ICCs that accounted for the random effects of multiple raters assessing the same child (Shrout & Fleiss, 1979). ICCs were calculated for each parent–teacher pair at each time point. Mean ICCs for all indices are reported in Table II. Many ICCs revealed statistically significant inter-rater agreement (\( p < .05 \)); however, the magnitude of agreement was moderate at best (e.g., Baseline Hyperactivity Index ICC = .46; \( p < .001 \)). The relationship between observer ratings and performance-based measures of attention was assessed using Pearson correlations for selected indices (identified above) from the CPRS, CTRS, and CPT, with all correlations reported in Table III. As reported previously (Conklin, Reddick et al., 2010), all indices of interest on the CPT demonstrated significant (\( p < .05 \)) improvement between baseline and Month 12. Current results reveal that the overall Index from the CPT was poorly associated with Cognitive Problems/Inattention and ADHD indices from the CPRS and CTRS at both Baseline and Month 12. The CPT Vigilance Index (\( d' \)) correlated most strongly with observer ratings at baseline. Significant correlations (\( p < .05 \)) in the expected direction were found with CPRS Cognitive Problems and ADHD indices as well as the CTRS ADHD Index. A trend toward significance was noted between \( d' \) and the CTRS Cognitive Problems Index (\( r = .24; p = .073 \)). Also at baseline, parent ratings correlated significantly with a measure of impulsivity (Errors of Commission; \( p = .001 \)), while teacher ratings correlated with a measure of risk taking (\( \beta; p < .05 \)). After 1 year of MPH treatment, only one significant correlation was found between performance-based measures and observer ratings. Hit Reaction Time correlated negatively with teacher-rated cognitive problems (\( r = -.32; p = .013 \)) and trended toward correlation with teacher-rated ADHD symptoms (\( r = -.23; p = .081 \)). Despite this trend in the expected direction (i.e., children with slower reaction time have more cognitive problems and ADHD symptoms), there was a trend toward an opposite relationship between reaction time and parent-rated ADHD symptoms (\( r = .21; p = .081 \)).

**Discussion**

This study is the first to report on the trajectory of observer ratings of attention problems associated with late effects

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**Table II. Intraclass Correlations between Parent and Teacher Ratings**

<table>
<thead>
<tr>
<th></th>
<th>CPRS, n</th>
<th>CTRS, n</th>
<th>ICC</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Problems Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-MPH baseline</td>
<td>68</td>
<td>55</td>
<td>.09</td>
<td>.257</td>
</tr>
<tr>
<td>Month 1</td>
<td>66</td>
<td>63</td>
<td>.10</td>
<td>.206</td>
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<tr>
<td>Month 3</td>
<td>63</td>
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<td>Month 6</td>
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<td>Hyperactivity Index</td>
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<tr>
<td>Pre-MPH baseline</td>
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<td>55</td>
<td>.46</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Month 1</td>
<td>66</td>
<td>63</td>
<td>.33</td>
<td>.004*</td>
</tr>
<tr>
<td>Month 3</td>
<td>63</td>
<td>58</td>
<td>.34</td>
<td>.006*</td>
</tr>
<tr>
<td>Month 6</td>
<td>68</td>
<td>63</td>
<td>.17</td>
<td>.088**</td>
</tr>
<tr>
<td>Month 12</td>
<td>68</td>
<td>59</td>
<td>.26</td>
<td>.024*</td>
</tr>
<tr>
<td>ADHD Index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-MPH baseline</td>
<td>68</td>
<td>55</td>
<td>.46</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Month 1</td>
<td>66</td>
<td>63</td>
<td>.35</td>
<td>.003*</td>
</tr>
<tr>
<td>Month 3</td>
<td>63</td>
<td>58</td>
<td>.21</td>
<td>.063**</td>
</tr>
<tr>
<td>Month 6</td>
<td>67</td>
<td>63</td>
<td>.38</td>
<td>.001*</td>
</tr>
<tr>
<td>Month 12</td>
<td>68</td>
<td>59</td>
<td>.36</td>
<td>.002*</td>
</tr>
</tbody>
</table>

*Note. CPRS = Conners’ Parent Rating Scale; CTRS = Conners’ Teacher Rating Scale; ICC = intraclass correlation; MPH = methylphenidate.*

*p < .05; **p < .10.*

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**Table III. Pearson Correlations (\( r \)-values) between Performance-based and Rater-based Measures of Attention**

| CPT indices                | Baseline | Month 12
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CPRS</td>
<td>CPRS</td>
</tr>
<tr>
<td>Cognitive problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Errors of omission</td>
<td>-.07 (.547)</td>
<td>-.06 (.642)</td>
</tr>
<tr>
<td>Errors of commission</td>
<td>.40 (.001)*</td>
<td>.03 (.816)</td>
</tr>
<tr>
<td>Hit reaction time</td>
<td>.14 (.257)</td>
<td>.18 (.152)</td>
</tr>
<tr>
<td>Vigilance (( d' ))</td>
<td>.37 (.002)*</td>
<td>-.01 (.991)</td>
</tr>
<tr>
<td>Risk-taking (( \beta ))</td>
<td>.08 (.503)</td>
<td>-.10 (.414)</td>
</tr>
<tr>
<td>Overall index</td>
<td>-.17 (.163)</td>
<td>-.09 (.460)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ADHD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Month 12</td>
</tr>
<tr>
<td>Cognitive problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Errors of omission</td>
<td>-.13 (.279)</td>
<td>-.03 (.826)</td>
</tr>
<tr>
<td>Errors of commission</td>
<td>.38 (.001)*</td>
<td>.09 (.454)</td>
</tr>
<tr>
<td>Hit reaction time</td>
<td>.19 (.120)</td>
<td>.21 (.081)**</td>
</tr>
<tr>
<td>Vigilance (( d' ))</td>
<td>.38 (.001)*</td>
<td>.08 (.514)</td>
</tr>
<tr>
<td>Risk-taking (( \beta ))</td>
<td>.13 (.296)</td>
<td>.05 (.685)</td>
</tr>
<tr>
<td>Overall index</td>
<td>-.11 (.370)</td>
<td>.01 (.969)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive problems</td>
<td>.19 (.165)</td>
<td>.07 (.631)</td>
</tr>
<tr>
<td>Errors of omission</td>
<td>.10 (.451)</td>
<td>-.06 (.652)</td>
</tr>
<tr>
<td>Errors of commission</td>
<td>.22 (.113)</td>
<td>-.32 (.013)*</td>
</tr>
<tr>
<td>Hit reaction time</td>
<td>.24 (.073)**</td>
<td>.04 (.757)</td>
</tr>
<tr>
<td>Vigilance (( d' ))</td>
<td>.28 (.038)*</td>
<td>.07 (.621)</td>
</tr>
<tr>
<td>Risk-taking (( \beta ))</td>
<td>.25 (.064)**</td>
<td>.11 (.420)</td>
</tr>
</tbody>
</table>

*\( p < .05; **p < .10.*
of childhood cancer during a year-long MPH efficacy trial. As predicted based on acute laboratory response (Conklin et al., 2007; Thompson et al., 2001) and a 3-week home crossover trial (Mulhern, Khan et al., 2004), both parents and teachers rated fewer problems in the areas of attention/cognitive problems, hyperactivity, and ADHD symptoms 1 month after initiating MPH, relative to pre-medication baseline ratings. Parent and teacher ratings of hyperactivity and ADHD symptoms remained stable between Month 1 and Month 12, suggesting sustained benefit of MPH in some specific symptom domains. This finding is consistent with the ADHD literature (Abikoff et al., 2004; Wilens et al., 2003), which suggests that children with ADHD experience stable, sustained benefit during year-long stimulant trials.

Contrary to expected stability in symptoms during the year-long trial, both parent and teacher ratings suggested a potential mild rebound in symptoms comprising the Cognitive Problems/Inattention subscale of the CRS-R. Parents reported stability in these symptoms for the first 6 months of treatment, but reported a significant increase in symptoms at 12 months of treatment. Teachers reported symptom rebound earlier, indicating that cognitive and inattentive symptoms increased at 6 months of treatment. After a year of treatment, teachers reported symptom rebound rising to the a priori threshold for “clinical significance” (i.e., ≥3 raw score points). It is notable that this threshold for “clinical significance” was fairly liberal. Prior efficacy studies have revealed raw score changes of approximately 3 or more points on CRS-R Hyperactivity and Cognitive Problems indices in children with ADHD (Wilens, Kratochvil, Newcorn, & Gao, 2006), although changes of this magnitude have variable translation to standardized T-score changes, ranging from 3 to 15 T-score points depending on the age and sex of the child. The CRS-R manual suggests a 5-point T-score change to identify clinical significance (Conners, 2000). Our criterion is variable with regard to meeting this standard, and it is possible that less profound score changes reflect normal variability, regression toward the mean, or diminishing placebo effects, rather than a clinically relevant behavior change. In addition, the lack of a placebo control group renders this a speculative finding that should be further investigated to clarify these issues.

It is also important to note that the criterion of improvement on any one of the six CPRS/CTRS indices suggests that some children may have been identified as “responders” when there was simply normal variability in their scores across time. Prior investigations have revealed more pronounced response to MPH in children with more severe attentional and behavioral symptoms (Conklin, Helton et al., 2010); thus, the inclusion of children with less severe symptoms and potentially less pronounced “clinical response” suggests that the current findings may have been stronger if these children had been excluded. Despite this, the current results are more generalizable to the population of cancer survivors, who experience weaknesses in their attention and concentration that, in some cases, may be less severe than those experienced by children with ADHD.

Some longitudinal investigations employing parent and teacher ratings in the ADHD literature have found greater symptom stability across the duration trials (Wilens et al., 2003), while the current findings suggest a potential mild rebound in cognitive symptoms/inattention based on both parent- and teacher-report. The significance of this potential rebound is unclear, given the lack of a control group; however, it suggests a need for replication of findings. One possible explanation is that Wilens and colleagues’ (2003) findings are based on data with an attrition rate approaching 60% for parent ratings and 75% for teacher ratings at the end of 1 year, leaving the true trajectory of symptom change for the entire sample unclear. The high response rate in the current study suggests better reliability of these findings; however, longer term follow-up will be needed to elucidate this possible rebound effect further. If symptom rebound is replicated in childhood cancer survivors treated with MPH, it would highlight a need to consider more aggressive MPH titration, as well as identify additional pharmacologic and non-pharmacologic interventions that provide generalizable and stable benefits.

Because of the difficulty in securing complete longitudinal data from multiple observers, it is important to examine the agreement between sources to determine if a single source might provide sufficient information. ICCs comparing parent and teacher ratings on the CRS-R revealed several significant correlations, yet these were in the low-to-moderate range across index scores and across time points throughout the study. Although these ratings were not strongly related, their level of agreement was similar to that seen in the ADHD literature (Collett et al., 2003) and the CRS-R normative sample (Conners, 2000). Hypotheses regarding this limited level of agreement have been posed in prior studies of stimulant efficacy with other child and adolescent populations, and these theories are plausible for this group of cancer survivors as well. The environmental structure and behavioral expectations in school tend to be more rigorous than those in the home, placing different demands on children depending on the setting (Hartman et al., 2007; Soma et al., 2009). Thus, parent and teacher ratings vary because the
fundamental behaviors they observe are different, high-
lighting a need to obtain reports from both observers
(Biederman et al., 1993; Mitsis et al., 2000; Polanczyk &
Jensen, 2008). As a group, parents uniformly reported
greater magnitude of symptom improvement than did
teachers. There may be some susceptibility to placebo
effect as noted above, or an expectation bias based
on the parental decision to enroll their child in a pharma-
ceutical trial. Teachers, in contrast, may employ more ac-
curate peer referencing, using a group of presumably
typically developing peers against which to rate the
cancer survivor’s behavior (Hartman et al., 2007; Soma
et al., 2009). Given these known discrepancies and their
emergence across multiple studies and multiple underlying
diagnoses, it is important to employ multimodal assess-
ment of attention dysfunction in studies of intervention
efficacy.

The final aim of this investigation was to examine
the relationship between observer ratings and objective,
in-laboratory, performance-based measures of attention
in this sample of childhood cancer survivors. As noted
above, CPT’s are routinely used to measure attention
dysfunction, but have limited ecological validity (Barkley,
1991). At the end of 1 year on MPH, this group of cancer
survivors demonstrated significant improvement on the
CPT as well as on parent and teacher ratings (Conklin,
Reddick et al., 2010). Despite these corresponding
findings, the association between overall indices on the
CRS-R and the CPT were low-to-moderate at baseline.
The CPT Vigilance Index proved to have the strongest
relationship with the parent- and teacher-rated Cognitive
Problems/Inattention index and parent-rated ADHD
index. The fact that a behavioral measure of vigilance has
the strongest relationship with both parent and teacher
ratings is not surprising, given the modal presentation in
cognitive late effects, with inattention but less difficulty
with hyperactivity or impulsivity (Mulhern, Khan et al.,
2004; Patel et al., 2007).

Despite the expectation that measures of impulsivity
would be less pronounced in this population, Errors of
Commission, or the tendency to respond when a response
is not warranted, was significantly correlated with parent-
reported symptoms. In contrast, Risk-taking (β) was asso-
ciated with teacher ratings for the same CRS-R indices such
that greater caution in responding was associated with higher teacher-reported symptoms. The tendency toward
more cautious responding on the CPT has been demon-
strated previously in a sample of medulloblastoma survi-
vors, although the impact of MPH was not examined
(Reeves et al., 2006). The dissociation between these indi-
ces on the CPT and observer ratings may point toward
the different behaviors being observed by parents and
teachers. Parents may very well find impulsive behaviors
more problematic in the home setting, while teachers view
excessive caution or hesitancy to respond as a detriment
in the classroom.

It is notable that significant relationships between ob-
server ratings and performance-based measures were largely
absent after 1 year of MPH treatment. Hit Reaction Time
demonstrated a moderate negative relationship with
teacher ratings of cognitive problems and ADHD symp-
toms, and this is generally consistent with the literature
that suggests improved processing speed and reaction
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ADHD (for a review, see Riccio, Waldrop, Reynolds, &
Lowe, 2001). That said, reaction time was related to
parent ratings in the opposite direction, such that slower
reaction time was related to fewer ADHD symptoms. The
variability in this relationship and the lack of other strong
correlations after a year of MPH treatment highlights a need
for further investigation. It is possible that the magnitude
of response achieved on performance-based measures
differs from that perceived by parents and teachers
(Mc Gee, Clark, & Symons, 2000). Parent and teacher rat-
ings might apply to a broader range of behaviors over more
extended periods of time, while in-clinic performance-
based measures provide only a brief sample of behavior
with limited generalizability (Barkley, 1991). Future inves-
tigations may increase the ecological validity of findings by
employing clinician observations or more “real-world”
tasks to identify symptom change in the naturalistic
environment.

The findings from this study are reported in full con-
sideration of some important study limitations. The use of
a cancer–control group against which to compare behavior
ratings throughout the course of the year would strengthen
these findings. Primarily, the identification of potential
rebound in cognitive symptoms near the end of the year
should be investigated relative to placebo controls to help
clarify whether this is indeed a real clinical finding, or
whether it represents factors such as regression to the
mean or diminishing rater bias. Further, the investigation of a dose–response pattern in attention ratings may be
helpful in determining whether childhood cancer survivors
require alternate dosing practices relative to children with
ADHD. Symptom improvement was measured throughout
the year solely by parent and teacher report, which is con-
sistent with the ADHD literature, but carries the potential
for bias. Additionally, due to the nature of the trial span-
nning 12 months, different teachers completed ratings on
the same child. While statistical analyses were selected to
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nning 12 months, different teachers completed ratings on
the same child. While statistical analyses were selected to
control for these inconsistencies, different raters introduce
variability in the data that may obscure important findings. Finally, this sample of participants was selected after they had already responded to a 3-week crossover trial of MPH, thus limiting the generalizability of findings to those children who may not have demonstrated as strong an initial response. Given that these children were identified as short-term responders to MPH and had already been identified as having learning and attention problems, it was considered unethical to randomize a subset of this sample to a 12-month placebo condition. This limits the ability for direct comparison of behavior ratings over time and the possibility of identifying frank placebo effects based on these data. It will be critical for future investigations to employ either placebo-controlled or alternative treatment control groups to better define the pattern of response to MPH in children experiencing the cognitive late effects of cancer treatment.

This study was the first to examine the trajectory of behavior change during a 12-month open-label trial of MPH in childhood cancer survivors experiencing cognitive late effects. Findings suggest that survivors experience initial benefit from MPH based on parent and teacher ratings with sustained symptom improvement after 1 year of treatment for many symptoms; however, there may be a mild rebound in cognitive problems and inattention after extended use. The clinical significance of this rebound remains unclear, although symptom rebound in cognitive late effects of childhood cancer treatment may highlight a need for different dosing practices or for non-pharmacologic interventions. The nature of this potential change warrants further scrutiny in studies employing a suitable control group, more stringent methods for measuring adherence, and mechanisms to more closely examine dose–response effects of MPH. Likewise, the potential for these improvements in attention to lead to enhanced academic performance and better grades should be explicitly examined. This study extended known findings from the ADHD literature to this sample of childhood cancer survivors, revealing low-to-moderate correlations between parent and teacher ratings of behavior, and between observer ratings and laboratory-based performance measures of attention. The lack of a strong relationship between these different sources of information suggests that a variety of behaviors is being assessed, demanding the use of multi-modal, multi-informant evaluations in intervention efficacy studies. Selecting outcome measures that highlight the unique symptoms of interest in these cancer survivors while maximizing the ecological validity of findings will be critical in future intervention studies.

Acknowledgments

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