Long-Term Efficacy of Methylphenidate in Enhancing Attention Regulation, Social Skills, and Academic Abilities of Childhood Cancer Survivors

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ABSTRACT

Purpose

Methylphenidate (MPH) ameliorates attention problems experienced by some cancer survivors in the short term, but its long-term efficacy is unproven.

Patients and Methods

This study investigates the long-term effectiveness of maintenance doses of MPH in survivors of childhood brain tumors ($n = 35$) and acute lymphoblastic leukemia ($n = 33$) participating in a 12-month MPH trial. Measures of attention (Conners' Continuous Performance Test [CPT], Conners' Rating Scales [CRS]), academic abilities (Wechsler Individual Achievement Test [WIAT]), social skills (Social Skills Rating System [SSRS]), and behavioral problems (Child Behavior Checklist [CBCL]) were administered at premedication baseline and at the end of the MPH trial while on medication. A cancer control group composed of patients who were not administered MPH (brain tumor = 31 and acute lymphoblastic leukemia = 23) was assessed on the same measures 2 months apart.

Results

For the MPH group, repeated measures analysis of variance revealed significant improvement in performance on a measure of sustained attention (CPT indices, $P < .05$); parent, teacher, and self-report ratings of attention (CRS indices, $P < .05$), and parent ratings of social skills or behavioral problems (SSRS and CBCL indices; $P < .05$). In contrast, the cancer control group only showed improvement on parent ratings of attention (Conners' Parent Rating Scale indices; $P < .05$) and social skills (SSRS and CBCL indices; $P < .05$). There was no significant improvement on the academic measure (WIAT) in either group.

Conclusion

Attention and behavioral benefits of MPH for childhood cancer survivors are maintained across settings over the course of a year. Although academic gains were not identified, MPH may offer benefits in academic areas not assessed.

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INTRODUCTION

Children treated with CNS-directed therapy for malignant brain tumors (BTs) or acute lymphoblastic leukemia (ALL) are at significant risk for cognitive impairments¹⁻³ that have been associated with a reduced quality of life.⁴⁻⁵ Recent findings suggest impairments in attention and/or working memory underlie well-established global cognitive declines,⁶⁻⁸ including declines in intellectual functioning and academic skills.^{2,9} Despite this growing body of research, there have been few attempts to develop interventions that target impairments emerging secondary to childhood cancer and its treatment.

Stimulant medications have been used for decades to treat healthy children diagnosed with atten-

tion deficit hyperactivity disorder (ADHD).¹⁰⁻¹¹ The most commonly prescribed medication for ADHD is methylphenidate (MPH), a piperidine derivative that acts by releasing dopamine from presynaptic vesicles, reducing dopamine reuptake and inhibiting monoamine oxidase.¹² For people diagnosed with ADHD, MPH has consistently been associated with improvements on measures of attention and concentration as well as observable classroom and social behavior.¹⁰ Findings from the ADHD literature may not generalize to childhood cancer survivors; children who are neurologically compromised may have lower response rates or medication tolerance.¹³

There is emerging evidence to support the short-term efficacy of MPH for addressing attention

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problems experienced by some childhood cancer survivors. Two randomized, double-blind, placebo-controlled trials demonstrated improvement on performance-based measures of attention after a single MPH dose.¹⁴⁻¹⁵ Findings from a 3-week, placebo-controlled, crossover study revealed significant improvement on parent and teacher ratings of attention and teacher ratings of social skills.¹⁶ None of these studies evaluated MPH benefits extending beyond a 1-week trial.

In this study, we investigated the long-term efficacy of MPH in childhood cancer survivors when compared with cancer survivors not taking MPH. We included performance-based and rater-based measures that assessed skills in both home and school settings. On the basis of the existing literature, we predicted MPH would enhance and maintain attention regulation and social skills among childhood cancer survivors who had identified attention and learning problems. Evaluation of academic outcomes was exploratory given lack of previous empiric support.

PATIENTS AND METHODS

Patients

This investigation represents the final phase of a multiphase, multisite trial investigating the benefits of MPH for survivors of childhood cancer experiencing attention and learning difficulties. Participant selection criteria have been previously described.^{14,16,17} In short, participants were treated for a malignant BT or ALL with chemotherapy and/or CNS-directed radiation therapy and completed treatment at least 12 months before study enrollment without evidence of recurrent disease. Participants were primary English speakers between 6 and 18 years of age. Exclusion criteria included a premorbid ADHD diagnosis, uncontrolled seizures, severe sensory loss, uncorrected hypothyroidism, patient or family history of Tourette syndrome, glaucoma, substance abuse history, or current use of psychotropic medication. Written informed consent was obtained from a legal guardian before participation. The protocol was approved by the institutional review boards of participating sites (ie, St Jude Children's Research Hospital, Duke University Medical Center, and the Medical University of South Carolina). Data collection occurred between January of 2000 and July of 2008.

Patients who met eligibility criteria were screened for adequate intellectual functioning as well as attention and academic difficulties that might be amenable to MPH therapy (described in the Cognitive and Behavioral Assessment section). Those patients who met screening criteria were offered participation in a 2-day, in-clinic, double-blind, crossover trial, during which they received MPH and placebo in a randomly assigned order.¹⁴ Patients who demonstrated adequate medication tolerance went on to participate in a 3 week, randomized, double-blind, placebo-controlled, home-based, crossover trial that consisted of placebo, low-dose MPH (0.3 mg/kg; maximum dose, 10 mg twice daily), and moderate-dose MPH (0.6 mg/kg; maximum dose, 20 mg twice daily).¹⁶ Patients in this study were selected for a 12-month open-label MPH trial if they demonstrated improvement (≥ 3 points on the parent and/or teacher Conners' Rating Scales [CRS]¹⁸) on MPH relative to placebo.

The 12-month, open-label trial included individually titrated MPH dosing to maximize clinical benefit and minimize toxicities. Dosing was determined by a research team that included a neurologist, pharmacist, and registered nurse. The starting dose was based on clinical response and adverse effects during the home-based crossover trial. In children who weighed at least 30 kg, the starting dose was typically MPH extended-release tablets 18 mg daily and was titrated upward to 27 mg/d, and possibly 36 mg/d, as indicated on the basis of clinical response and adverse effects. For children who weighed less than 30 kg, the starting dose was 5 mg MPH once or twice a day and was titrated upward on the basis of clinical response and adverse effects. If a good response was observed at any dose, dose was not increased any more. Extended-release formulations were used whenever possible. Baseline and post-trial assessments were conducted to investigate medication-related cognitive and behavioral changes.

We report on 68 cancer survivors who completed the 12-month, open-label, MPH trial as well as on 54 cancer survivors who served as a control group. Cancer survivors in the control group qualified for at least the first phase of the MPH study but did not participate in the 12-month, open-label trial for the following reasons: declined participation in any study medication phase ($n = 34$); completed the 2-day, in-clinic trial but refused additional participation ($n = 1$); discontinued the 3-week, home-based, crossover trial because of adverse effects ($n = 4$); completed the 3-week, home-based, crossover trial but refused additional participation ($n = 2$); or completed the 3-week, home-based, crossover trial but were classified as a nonresponder ($n = 13$). There were 23 survivors who began the 12-month MPH trial but did not complete because of adverse effects ($n = 8$), patient/parent request ($n = 6$), unrelated medical problems (eg, disease progression; $n = 6$), and loss to follow-up ($n = 3$).

Cognitive and Behavioral Assessment

The MPH group participated in testing at premedication baseline and again at the end of the 12-month MPH trial while still on medication. The control group completed testing at two time points, which were 12 months apart. The test battery completed by both groups, at both time points, was identical and is described in the next two paragraphs.

Intellectual functioning (ie, intelligence quotient [IQ]) was estimated on the basis of the information, similarities, and block design subtests from the age-appropriate Wechsler scale (Wechsler Intelligence Scale for Children, Third Edition [WISC-III]¹⁹ and Wechsler Adult Intelligence Scale, Third Edition [WAIS-III]²⁰) by using a formula provided by Sattler²¹ that produces an age-based score, which had a mean of 100 and standard deviation of 15. An estimated IQ ≥ 50 was required for study participation. Academic skills were assessed with the Wechsler Individual Achievement Test (WIAT).²² For study inclusion, participants were required to have an age standard score ≤ 25 th percentile in at least one academic area. Participants also were administered the Conners' Continuous Performance Test (CPT),²³ a computerized measure of sustained attention. The CPT provides scores for omission errors (ie, failing to respond to targets), commission errors (ie, responding to nontargets), reaction time (ie, processing speed), reaction time variability, d' (ie, vigilance), β (ie, risk taking) and a CPT Index (ie, weighted sum of all indices). Omission errors ≥ 75 th percentile for age and sex were required for study inclusion.

The Conners' Parent Rating Scale (CPRS), Conners' Teacher Rating Scale (CTRS), and Conners' Adolescent Self-Report Scale (CASS) are questionnaires designed to assess behaviors associated with ADHD.¹⁸ An ADHD Index, cognitive problems/inattention scale, and hyperactivity scale are derived from responses. Participants were required to have a score ≥ 75 th percentile on one or more of these scales on the CPRS or CTRS. The CASS was only administered to participants within questionnaire age range (ie, ages 12 to 17 years). Parents completed the Social Skills Rating System (SSRS),²⁴ a measure of social behaviors that provides scores on two scales—Social Skills Scale and Problem Behaviors Scale. Parents also completed the Child Behavior Checklist (CBCL),²⁵ a measure of social competencies and behavior problems. For data reduction purposes, we chose to include the internalizing composite (ie, withdrawn, somatic and anxious/depressed scales), externalizing composite (ie, delinquent behavior and aggressive behavior scales), total behavior problems composite (ie, social problems, thought problems and attention problems scales), and competence scales (ie, school, social and activities).

Statistical Analyses

Qualitative analyses of demographic and clinical variables were performed to characterize the two cancer groups. The two groups were also statistically compared by using t tests for continuous variables and χ^2 or Fisher's exact test for categorical variables to establish group similarity. To identify changes in attention, social, or academic abilities associated with medication status, a repeated measures analysis of variance (ANOVA) that used the mixed model was conducted. By using this model, within-group (ie, MPH or control) changes between baseline and 12-month post assessments were evaluated. This model was also used to compare performance at the 12-month time point between MPH and control groups, accounting for baseline scores. Given the open-label study design, our primary outcome measure

was the CPT, as it is a performance measure of attention not subject to potential rater biases and a measure previously demonstrated to be sensitive to MPH-related change.¹⁵ For additional measures, the Bonferroni correction was used to control for type 1 error associated with multiple comparisons. The Bonferroni threshold was set at 0.05 divided by the number of indices on a given measure. With a sample size of 68 in the MPH group and 54 in the control group, a difference of effect size of 0.46 between groups can be detected by a one-sided test, with significance level of .05 and power of .80.

RESULTS

Patient Group Characteristics

There were no statistically significant differences between the MPH and control groups with respect to sex, ethnicity, maternal education, cancer diagnosis, age at diagnosis, intensity of cancer treatment, or age at study participation. Both the MPH and control groups were largely white, contained similar numbers of boys and girls, and generally contained equal numbers of BT and ALL survivors. Patients were on average 5 years of age at diagnosis and 4 years out from treatment at the time of study participation (Table 1). There were no statistically significant differences between the MPH and control groups at baseline assessment on any cognitive or behavioral measures. There also were no statistically significant differences between the 68 participants completing the MPH trial and the 23 that did not complete on the examined demographic and clinical variables. The 23 patients who did not complete the MPH trial differed statistically from the 68 that did complete on five of 27 of the baseline measures reported in Table 2; those who failed to complete had higher levels of informant-rated problems at baseline.

Cognitive and Behavioral Change

For the MPH group, repeated-measures ANOVA revealed significant improvement on all indices of the primary outcome measure (CPT, $P < .05$). Likewise, significant improvements on parent (ie, CPRS, $P < .001$), teacher (CTRS, $P < .05$) and self-report (CASS, $P < .005$) measures of attention across the ADHD, cognitive problems/inattention and hyperactivity scales were found with the exception of the CTRS cognitive problems/inattention scale. Parents also rated significant improvement in social skills (SSRS) as well as internalizing and externalizing psychopathology (CBCL) over the 12-month trial ($P < .05$). There was no change in intellectual functioning (IQ), and there was no improvement in academic skills (WIAT). Spelling showed a significant decline from pretesting to post-testing ($P < .01$; Table 2; Figs 1, 2, 3, and 4).

The cancer control group showed significant improvement on select indices of the parent-rated measures of attention regulation (ie, CPRS, $P < .05$), social skills (ie, SSRS, $P < .05$), and externalizing psychopathology (ie, CBCL, $P < .05$). However, there was no statistical difference between pretesting and post testing for any indices from the performance measure of attention (ie, CPT) or the teacher or self-report measures of attention (ie, CRS). Consistent with the MPH group, there was no statistical improvement in intellectual functioning (ie, IQ), or academic skills (ie, WIAT; Table 2; Figs 1 through 4).

The repeated-measures ANOVA was also used to compare post-testing performance between the MPH and cancer control groups, accounting for baseline scores. The MPH group performed significantly better across almost all indices of the primary outcome measure (ie, CPT), on multiple indices of the parent rated measure of attention

Table 1. MPH and Cancer Control Group Demographic and Clinical Characteristics

Characteristic	MPH Group		Cancer Control Group		P*
	No.	%	No.	%	
Diagnosis					
Brain tumor	35	52	31	57	.51
Acute lymphoblastic leukemia	33	48	23	43	
Sex					
Female	31	46	27	50	.63
Male	37	54	27	50	
Ethnicity					
White	57	84	43	80	.49
African American	10	15	11	20	
Other	1	1	0	0	
Maternal education†					
Less than high school	3	4	6	12	.26
High school graduate	21	31	20	40	
Some college/technical school	26	38	14	28	
Bachelor's degree	14	21	9	18	
Graduate degree	4	6	1	2	
Intensity CNS therapy‡					
Mild	25	37	20	37	.90
Moderate	8	12	5	9	
High	35	51	29	54	
Age at diagnosis, years					.70§
Mean	5.21		5.43		
SE	0.36		0.43		
Range	1-14		1-15		
Age at baseline assessment, years					.80§
Mean	11.11		11.26		
SE	0.37		0.43		
Range	7-18		6-18		
Time since treatment, years					.85§
Mean	4.26		4.35		
SE	0.32		0.36		
Range	1-12		2-13		

Abbreviations: MPH, methylphenidate; SE, standard error.

* χ^2 or Fisher's exact test.

†Maternal education information missing for four control group participants.

‡Mild CNS therapy was defined as systemic and/or intrathecal chemotherapy only; moderate, as 24 Gy cranial radiation therapy with or without chemotherapy; and high, as > 24 Gy with or without chemotherapy.

§Independent *t* tests.

(ie, CPRS), and on one index from the self-report measure of attention (CASS; Table 2).

DISCUSSION

This study revealed significant attention and behavioral improvements among childhood cancer survivors who participated in a year-long MPH trial. These findings indicate that benefits previously demonstrated during acute trials¹⁴⁻¹⁶ are sustained throughout a maintenance trial that more closely approximates real-world prescription practices. Often, these improvements in cancer survivors, who were identified as experiencing attention and learning problems, resulted in normalization of performance, in which post-test scores were in the average range relative to same-age peers. In addition, benefits

Table 2. Change in Performance From Pretesting to Post-Testing

Variable	MPH Group (n = 68)					Cancer Control Group (n = 54)					MPH – Control ^a		
	Baseline	SE ^b	Post-Test	SE ^b	P ^c	Baseline	SE ^b	Post-Test	SE ^b	P ^c	P ^d	Difference	SE
CPT													
Omissions, percentile	92.95	0.89	79.48	3.31	< .001 ^e	94.27	0.78	89.65	1.94	.1127	.0016 ^e	–8.78	2.75
Commissions, T-score ^f	50.52	1.36	46.79	1.32	.0063 ^e	49.84	1.32	51.13	1.49	.3913	< .001 ^e	–4.84	1.34
Hit reaction time, T-score	40.11	1.73	46.23	1.36	< .001 ^e	41.91	1.82	44.75	1.79	.0855	.0478 ^e	2.83	1.42
Reaction time variability, T-score	61.31	1.33	54.26	1.58	< .001 ^e	61.21	1.73	62.58	1.69	.4616	< .001 ^e	–8.49	1.65
d', T-score	61.65	1.11	54.85	1.38	< .001 ^e	61.52	1.07	60.36	1.49	.3642	< .001 ^e	–5.66	1.20
β, T-score	78.81	2.06	72.18	2.54	.0155 ^e	81.99	2.29	79.23	2.57	.3626	.0669	–4.96	2.69
CPT index ^g	9.69	0.81	6.85	0.82	.0031 ^e	9.74	0.79	10.66	0.95	.4942	< .001 ^e	–3.71	0.94
CPRS													
ADHD, T-score	60.84	1.34	52.07	1.13	< .001 ^e	57.56	1.58	53.66	1.50	.0013 ^e	< .001 ^e	–4.07	1.08
Cog prob/inattention, T-score	62.72	1.39	53.16	1.19	< .001 ^e	58.07	1.61	55.42	1.64	.0289	< .001 ^e	–5.69	1.19
Hyperactivity, T-score	56.62	1.60	50.96	0.98	< .001 ^e	57.61	1.69	53.30	1.63	.0029 ^e	.2434	–1.46	1.25
CTRS													
ADHD, T-score	59.64	1.56	53.47	1.35	< .001 ^e	58.00	1.68	55.08	1.77	.1274	.1275	–2.83	1.85
Cog prob/inattention, T-score	62.85	1.44	59.81	1.50	.0420	62.91	1.74	62.92	1.74	.8078	.0690	–3.00	1.64
Hyperactivity, T-score	56.22	1.63	52.29	1.53	.0126 ^e	54.58	1.73	52.08	1.67	.2415	.4597	–1.47	1.98
CASS^h													
ADHD, T-score	52.36	1.74	47.62	1.51	< .001 ^e	47.47	1.85	46.00	2.00	.2283	.0862	–3.39	1.95
Cog prob/inattention, T-score	57.45	1.52	51.15	1.54	< .001 ^e	49.37	1.98	50.83	2.46	.7037	.0135 ^e	–5.61	2.22
Hyperactivity, T-score	46.50	1.28	43.56	1.24	.0033 ^e	42.74	1.52	43.25	1.69	.3332	.1175	–2.21	1.39
SSRS													
Problem behavior, SS	98.59	1.64	94.28	1.27	.0035 ^e	101.20	1.73	97.75	1.75	.0414	.1991	–1.83	1.42
Social skills, SS ⁱ	96.84	1.97	104.8	2.01	< .001 ^e	95.50	2.32	101.10	2.50	.0073 ^e	.0604	3.35	1.77
CBCL													
Internalizing, T-score	51.47	1.32	46.07	1.21	.0033 ^e	54.49	1.97	50.66	1.81	.0119	.3261	–1.42	1.44
Externalizing, T-score	48.08	1.43	43.80	1.43	.0022 ^e	52.41	1.54	48.00	1.57	< .001 ^e	.7794	0.33	1.17
Total Problems, T-score	51.61	1.54	46.05	1.44	.0010 ^e	55.41	1.85	50.50	1.76	< .001 ^e	.7659	–0.39	1.30
Activities, T-score ^j	43.68	1.17	43.80	1.13	.6907	43.08	1.23	42.74	1.25	.9657	.6124	0.61	1.21
Social, T-score ^j	43.49	1.34	44.00	1.22	.4515	40.87	1.37	42.79	1.07	.1270	.8418	–0.22	1.12
School, T-score ^j	34.42	1.26	37.30	1.41	.0154	36.03	1.52	36.75	1.26	.6254	.0748	2.13	1.19
WISC III estimated IQ, SS ^k	89.39	1.89	90.37	1.82	.2850	86.28	2.16	87.70	2.26	.1954	.8439	–0.20	1.03
WIAT													
Reading composite, SS ^l	85.41	1.72	85.21	1.93	.8278	83.43	1.86	84.63	2.13	.1801	.1083	–1.64	1.02
Spelling, SS ^l	86.54	1.59	84.13	1.61	.0032 ^e	85.91	1.60	86.17	1.88	.7734	.0020 ^e	–2.65	0.85
Math composite, SS ^l	84.57	1.70	84.79	1.86	.8328	81.87	1.25	82.92	2.13	.4122	.5713	–0.63	1.12

Abbreviations: MPH, methylphenidate; SE, standard error; CPT, Conners' Continuous Performance Test; CPRS, Conners' Parent Rating Scale; ADHD, attention deficit hyperactivity disorder; Cog prob, cognitive problems; CTRS, Conners' Teacher Rating Scale; CASS, Conners' Adolescent Self-Report Scale; SSRS, Social Skills Rating System; SS, standard score; CBCL, Child Behavior Checklist; WISC III, Wechsler Intelligence Scale for Children, third edition; IQ, intelligence quotient; WIAT, Wechsler Individual Achievement Test.

^aThe difference is estimated from the statistical model and represents group differences (ie, MPH minus control group) at post-test assessment.

^bMean and SE are calculated from observed values.

^cP value from the repeated measure analysis of variance that used the mixed model for within-group comparison between baseline and post-test assessments.

^dP value from the repeated measure analysis of variance that used the mixed model for comparison between the MPH and control groups at post-test assessment, accounting for baseline scores.

^eP < .05 for the CPT; for all other measures, the P value is less than the threshold for the Bonferroni-corrected P value (ie, P < .025 for SSRS; P < .017 for CPRS, CTRS, CASS, and WIAT; P < .008 for CBCL).

^fT-score has a mean of 50 ± 10; SS has a mean of 100 ± 15.

^gCPT index score < 8 is normal, 8–11 is borderline, and > 11 is impaired.

^hThe CASS was only administered to participants between the ages of 12 and 17 years. This included 20 and 18 individuals with baseline and post-test scores for the MPH and control groups, respectively.

ⁱReversed coded, such that a higher score indicates better performance in contrast to other scores in the table for which a higher score indicates worse performance.

were observed across home and school settings and across performance-based and observational measures.

Among childhood cancer survivors prescribed MPH, significant improvements were identified on the primary outcome measure, a performance measure of sustained attention, as well as on parent, teacher and self-report measures of attention and on parent report of behavior problems and social competencies. On the performance measure of attention, there was also evidence for improved processing

speed. In contrast, the cancer survivors not participating in the MPH trial showed improvements on parent report measures of attention, behavior problems, and social competencies but were unable to demonstrate improvement on any indices of the performance measure of sustained attention, the teacher or self-report measures of attention regulation. Notably, neither group demonstrated significant change on either the measure of intellectual functioning (ie, IQ) or academic skills. As mentioned in the Methods, the sample size for this study was

Fig 1. Conners' Parent Rating Scale (CPRS) pretesting to post-testing change by group. MPH, methylphenidate; ADHD, attention deficit hyperactivity disorder; CogProb/Inatt, cognitive problems or inattentiveness.

designed to detect a difference of effective size of 0.46 with 80% power, such that there may be insufficient power to detect differences smaller than 0.46.

Lack of convergent evidence from teacher, self-report, or performance measures for the parent-rated finding in the cancer control group calls into question the reliability of that finding. It may be that parents tend to accommodate to deficits exhibited by their children, such that there is less reporting of problems over time. Teachers, who have other students to serve as a benchmark for typical behavior, may not be subject to this drift. Alternatively, there may have been contextual factors that created a response bias at the time of baseline assess-

ment. Pretesting for both groups took place during overt screening to participate in a stimulant medication trial. It may be that this context created greater motivation to report problems at pretesting than post-testing, resulting in some decline in parent-reported problems for both groups. Regardless of the source of potential parent-reporting error, these findings highlight the importance of using multiple methods of measurement, preferably ratings from multiple types of informants and performance-based measures. Had this study relied on parental report, we may have erroneously concluded that childhood cancer survivors show attention and behavioral improvement irrespective of stimulant medication use.

Fig 2. Conners' Teacher Rating Scale (CTRS) pretesting to post-testing change by group. MPH, methylphenidate; ADHD, attention deficit hyperactivity disorder; CogProb/Inatt, cognitive problems or inattentiveness.

Fig 3. Conners' Continuous Performance Test (CPT) pretesting to post-testing change by group. MPH, methylphenidate; RT, radiation therapy.

The findings in this study are consistent with the ADHD literature that support the long-term efficacy of MPH.²⁶⁻²⁸ MPH benefits in children diagnosed with ADHD are most frequently found on measures of attention and concentration as well as on observable classroom and social behaviors.¹⁰ Improved processing speed in the MPH group is also consistent with findings in the ADHD literature.¹⁰ Increased processing speed may be a separate MPH benefit and/or may serve to mediate improvement in attention. Similar to the findings of this study in cancer survivors, there is less evidence to support academic benefits associated with MPH use in the ADHD literature.²⁹⁻³⁰

Although disappointing, this finding may relate to the way in which academic outcomes are measured.

In this study, the academic measure assessed basic skill acquisition (eg, single-word reading and mathematical computation). Despite an inability to detect improvements on this measure, many parents reported that children participating in the MPH trial experienced an improvement in school grades related to behaviors, such as planning ahead for projects, studying in advance for tests, and remembering to complete and turn in assignments. These behaviors, which may be considered executive aspects of school performance, were not

Fig 4. Wechsler Individual Achievement Test (WIAT) pretesting to post-testing change by group. MPH, methylphenidate.

assessed in this study. Future studies may be able to detect improvements in academic skills if they include measures that assess executive components of academic performance.

The findings of this study should be considered in the context of potential study limitations. Although earlier phases of the overarching study included randomized, placebo-controlled trials, the study phase discussed here was a prospective, longitudinal, open-label trial. Because participants were not randomly assigned to the MPH or control group, there is the possibility for introduction of assignment bias. That said, the groups were found to be balanced on those factors most consistently associated with cognitive late effects (eg, age at treatment, treatment intensity, time since treatment)² and did not demonstrate any differences on psychometric measures at baseline. Given that these children were already identified as MPH responders in a short trial, ethical standards precluded random assignment to a 12-month placebo condition. With an open-label study design, there is also potential for biases in rater reporting, such as placebo effects in parents and teachers aware of medication status. The strong and consistent finding of group differences on the primary outcome measure (ie, CPT), not subject to rater biases, adds convergent support for the rater-based findings. There was a 25% attrition rate, and those who did not complete the MPH trial had higher informant-rated attention problems at baseline, which has been shown to predict better MPH response.³¹ Therefore, it is possible that the response rate in the MPH group is an underestimate. As discussed earlier in the Discussion section, this study also lacked measures of executive function, which may have added value in detecting MPH benefits on the basis of the ADHD literature.³²⁻³³

Overall, the findings of this study are encouraging, as they put forward an empirically supported intervention for childhood cancer survivors who experience attention and learning problems. Cognitive deficits are well established in this population,¹⁻³ yet there are few empirically supported options for intervention. Initial findings from MPH trials indicated acute benefits for cancer survivors¹⁴⁻¹⁶; this is the first time that long-term effectiveness has been demonstrated in a prospective, longitudinal trial. In this study, benefits were found not only for attention regulation but also for social skills and for internalizing and externalizing behavior problems. Coupled with other recently published findings that indicate the relative safety of MPH for cancer survivors with respect to adverse effects³⁴ and

growth,¹⁷ these results indicate that MPH may be recommended as a treatment option to families searching for a means to mitigate the impact of cognitive late effects experienced by their children. For survivors who demonstrate attention problems, MPH may be an integral component of the treatment plan that would also likely include academic accommodations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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