Predicting Methylphenidate Response in Long-Term Survivors of Childhood Cancer: A Randomized, Double-Blind, Placebo-Controlled, Crossover Trial

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Objective To investigate the methylphenidate (MPH) response rate among childhood survivors of acute lymphoblastic leukemia (ALL) and brain tumors (BTs) and to identify predictors of positive MPH response. **Methods** Cancer survivors ($N = 106$; BT = 51 and ALL = 55) identified as having attention deficits and learning problems participated in a 3-week, double-blind, crossover trial consisting of placebo, low-dose MPH (0.3 mg/kg), and moderate-dose MPH (0.6 mg/kg). Weekly teacher and parent reports on the Conners' Rating Scales were gathered. **Results** Following moderate MPH dose, 45.28% of the sample was classified as responders. Findings revealed that more problems endorsed prior to the medication trial on parent and teacher ratings were predictive of positive medication response ($p < .05$). **Conclusions** MPH significantly reduces attention problems in a subset of childhood cancer survivors. Parent and teacher ratings may assist in identifying children most likely to respond to MPH so prescribing may be optimally targeted.

Key words brain tumor; leukemia; stimulant medication; methylphenidate.

Survivors of childhood acute lymphoblastic leukemia (ALL) and malignant brain tumors (BTs) are at significant risk for cognitive impairments secondary to disease and treatment-related factors (e.g., Moleski, 2000; Mulhern & Bulter, 2004; Ris & Noll, 1994). Global cognitive declines, including declines on measures of intellectual functioning and academic achievement, are well established (e.g., Moore, 2005; Mulhern & Butler, 2004). Recent empirical findings suggest attention and/or working memory impairments are proximal contributors to these global declines (Reddick et al., 2003; Rogers, Horrocks, Gritton, & Kernahan, 1999; Schatz, Kramer, Ablin, & Matthay, 2000). Attention problems occur frequently among childhood cancer survivors, with estimates of approximately one-quarter of ALL survivors demonstrating significant dysfunction (Krull et al., 2008). Impairment in attentional processes has been shown to explain a significant proportion of the relationship between treatment-related neurological changes and subsequent declines in the intellectual and academic functioning of cancer survivors (Reddick et al., 2003). Cognitive impairments in childhood cancer survivors are of significant concern as they are associated with academic difficulties, high unemployment rates and a reduced quality of life (e.g., Haupt et al., 1994; Mostow, Byrne, Connelly, & Mulivhill, 1991). Despite these well-established findings, there have been few empirically validated interventions to remediate cognitive impairments emerging secondary to treatment for childhood cancer (for a review, see Butler & Mulhern, 2005).

Stimulant medications have been used for decades to successfully treat otherwise healthy children diagnosed with attention deficit hyperactivity disorder (ADHD;

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American Psychiatric Association, 1994; Brown & Daly, in press; Gadow, 1992). 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 (Guevara, Lozano, Wickizer, Mell, & Gephart, 2002; Robison, Sclar, Skaer, & Balin, 1999; Safer, Zito, & Fine, 1996). The most consistent benefits of MPH have been demonstrated on measures of attention and concentration, as well as observable classroom and social behavior (Brown et al., 2005). The majority of children treated with stimulant medications experience some adverse side effects; these are usually mild to moderate, and dose dependent (Brown & Daly, in press). Controlled clinical trials directly comparing MPH, amphetamines, and dextroamphetamine have not revealed group differences in efficacy or safety (Arnold, 2000; Brown et al., 2005; Grcevich, Rowane, & Marcellino, 2001; Wolraich, et al., 2001). Children who are neurologically compromised may evidence less response to MPH and a higher frequency of adverse effects in relation to healthy peers (Weber & Lutschg, 2002) such that the ADHD literature may not be generalizable to childhood cancer survivors.

The first randomized, double-blind, placebo-controlled between-groups trial of MPH in childhood cancer survivors was conducted by Thompson and colleagues (2001). Significant improvement was demonstrated on a continuous performance measure of sustained attention but not on measures of verbal memory or visual–auditory association. The same group of investigators later reported on 83 childhood cancer survivors who participated in a 3-week, placebo-controlled, double-blind, crossover study comparing low (0.3 mg/kg) and moderate (0.6 mg/kg) dose MPH to placebo (Mulhern et al., 2004). Significant improvement on MPH relative to placebo was noted on parent and teacher ratings of attention and teacher ratings of social skills. In this study, medication response was defined at the group rather than at the individual level, and factors predictive of a positive medication response were not evaluated. We are not aware of any studies that have investigated predictors of stimulant medication response in childhood cancer survivors.

A seminal paper by Barkley that includes a comprehensive review of medication response in children diagnosed with ADHD indicates that approximately 75% of ''hyperkinetic'' children receiving stimulant medications respond favorably while the remaining 25% are unchanged or made worse (Barkley, 1977). This rate is consistent with more recent controlled clinical trials in children with ADHD; for example, Efron, Jarman, and Barker (1998) found an MPH response rate of 72% and Greenhill et al. (2001) found an MPH response rate of 77%. However, studies indicate that response rate can vary from approximately 50–80% depending on how rigorously medication response is defined (e.g., clinical judgment, arbitrary percent change in symptoms, or statistically derived threshold; Buitelaar, Van der Gaag, Swaab-Barneveld & Kuiper, 1995; Chabot, Orgill, Crawford, Harris, & Serfontein, 1999; Zeiner, Bryhn, Bjercke, Truyen, & Strand, 1999) and whether children diagnosed with ADHD are demonstrating significant overactivity (Chabot et al., 1999). The ADHD literature has revealed that the most consistent predictors of a positive medication response include higher levels of attention impairment on performance measures or behavioral ratings (Buitelaar et al., 1995; Chabot et al., 1999; Hermens, Cooper, Kohn, Clarke, & Gordon, 2005; Thomson & Varley, 1998); higher levels of hyperactivity based on parent or teacher ratings, clinical interviews, or direct observation (Denney & Rapport, 1999; Hermens et al., 2005; Zeiner et al., 1999); younger age (Buitelaar et al., 1995; Thomson & Varley, 1998; Zeiner et al., 1999); and higher intellectual functioning (Aman, 1996; Aman, Buican & Arnold, 2003; Buitelaar et al., 1995; Thomson & Varley, 1998). The most consistent predictor of a negative stimulant medication response is comorbidity of internalizing psychopathology (Buitelaar et al., 1995; DuPaul, Barkley, & McMurray, 1994; Pliszka, 1998; Zeiner et al., 1999). The literature is inconsistent with respect to the predictive value of comorbid externalizing psychopathology (Hechtman, 1999; Pliszka, 1998; Thomson & Varley, 1998). Demographic factors including gender, years of education, and socioeconomic status have generally not been predictive of medication response (Hermens et al., 2005; Spencer et al., 2005).

In the current study, we expand upon the existing literature by reporting on the results of a randomized, double-blind, placebo-controlled, crossover study assessing the benefits of MPH for learning-impaired cancer survivors based on parent and teacher ratings of attention. Given not all cancer survivors are likely to respond to MPH, and the need to balance response with adverse side effects in a vulnerable population, it is of significant clinical advantage to identify prior to treatment those patients most likely to benefit from MPH. Accordingly, the primary goals of this investigation were to evaluate the rate of MPH response in cancer survivors and to identify specific factors predictive of a positive medication response. Based on a demonstrated lower MPH response rate in children with comorbid ADHD and learning

disabilities (Grizenko, Bhat, Schwartz, Ter-Stepanian, & Jooper, 2006), we hypothesized that the response rate in this study would be lower than the 75% reported in the ADHD literature. Using the ADHD literature as a guide, we also hypothesized that higher levels of inattention and hyperactivity, younger age, and higher intellectual functioning would be predictive of a positive medication response. We further predicted that those children most likely to have had significant neurological impairment secondary to disease and treatment (i.e., BT diagnosis, younger age at treatment, and increased intensity of CNS-directed therapy, i.e., radiation, chemotherapy, or their combination) would have a lower response rate. Finally, the investigation of demographic characteristics and externalizing psychopathology as potential predictors of MPH response was exploratory given inconsistent findings in the ADHD literature. We were unable to investigate the predictive value of internalizing pathology given patients were excluded from the MPH trial for these diagnoses.

Methods

Patients

The present study represents the home-crossover phase of a multiphase, multisite MPH trial in childhood cancer survivors for which eligibility criteria have been previously described (Conklin et al., 2007; Mulhern et al., 2004). Individuals eligible for participation were treated for a malignant BT or ALL with chemotherapy and/or CNS-directed radiation therapy and completed treatment at least 12 months prior to study enrollment without evidence of recurrent disease. Eligible participants were between 6 and 18 years of age and were primary English speakers. Exclusion criteria included an ADHD diagnosis prior to cancer diagnosis, uncontrolled seizures, uncorrected hypothyroidism, severe sensory loss precluding valid psychological assessment, patient or family history of Tourette Syndrome, glaucoma, history of substance abuse, or current use of psychotropic medications. The study was approved by the Institutional Review Boards of the participating sites (St. Jude Children's Research Hospital, Duke University Medical Center, and Medical University of South Carolina). Written informed consent was required from a legal guardian prior to participation. Data collection occurred between January 2000 and May 2005.

Procedures

Screening Phase

Those patients identified as potentially eligible for the study, based on medical record review, were contacted via mail or approached during routine clinic visits. If interested in participation, the patient was screened using a battery of psychological tests and parent/teacher rating forms. This battery was used to identify participants with a cognitive phenotype hypothesized to be responsive to MPH (Thompson et al., 2001); specifically, participants were screened for adequate global cognitive functioning, attention problems, and academic difficulties. By including participants with both attention and academic problems, we were able to target those individuals in greatest need of intervention and also increase the likelihood of participation in a stimulant medication trial.

The screening phase has been described previously (Conklin et al., 2007) and is only summarized here. To establish adequate global cognitive functioning, participants were required to have an estimated IQ $\geq$ 50 based on the Information, Similarities, and Block Design subtests from the age-appropriate Wechsler scale [Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991) and Wechsler Adult Intelligence Scale, Third Edition (WAIS-III; Wechsler, 1997)], using a formula provided by Sattler (1992) [IQ = (Information + Similarities + Block Design) $\times$ 2 + 40)]. Attention problems were defined as omission errors $\geq$75th percentile on the Conners' Continuous Performance Test (Conners, 1995), a computerized measure of sustained attention, as well as a score $\geq$75th percentile on the Conners' Rating Scales—Revised (Conners, 2000) ADHD, Hyperactivity, or Cognitive Problems/Inattention scales based on parent or teacher report. To establish academic difficulties, participants were required to perform $\leq$25th percentile on one of five subtests (Basic Reading, Reading Comprehension, Spelling, Numerical Operations, and Mathematics Reasoning) from the Wechsler Individual Achievement Test (Wechsler, 1992). The Child Behavior Checklist (Achenbach & Edelbrock, 1991) was used to screen for emotional problems that may impact MPH responsiveness (e.g., DuPaul et al., 1994). A standard score $\geq$70 on the anxious/depressed scale prompted a diagnostic interview to rule out a mood or anxiety disorder. The Social Skills Rating System (Gresham & Elliott, 1990) was completed by a parent during screening as an additional measure of attention abilities and problem behaviors to independently corroborate the Conners' Parent Rating Scales and more fully assess social competence. Of 469 participants screened, 210 met screening criteria and of those meeting screening criteria, 135 agreed to participate in an MPH trial.

In-Clinic Trial Phase

Participants meeting the inclusion criteria outlined above took part in a consecutive 2-day, in-clinic, crossover

MPH trial. Participants were stratified on the basis of age at CNS treatment (<4 years and ≥4 years) and intensity of CNS therapies [mild-systemic and/or intrathecal chemotherapy only; moderate ≤24 Gy cranial radiation therapy (CRT) with or without systemic and/or intrathecal chemotherapy; high >24 Gy CRT with or without systemic and/or intrathecal chemotherapy] due to differential cognitive risk associated with these factors. Following stratification, participants were assigned randomly to either receive a single dose of MPH (0.60 mg/kg; maximum dose 20 mg) on day 1 and placebo on day 2, or the reverse, in a double-blind crossover design. Randomization was conducted by the pharmacist at St. Jude. Other personnel were blind to the order of MPH and placebo administration.

Approximately 90 min following MPH/placebo ingestion, testing was completed to investigate acute neurocognitive response. This battery has been previously described (Conklin et al., 2007) and included: a brief continuous performance test developed in-house using SuperLab Pro v2.0 (Cedrus Corp., Phoenix, AZ); the Stroop Word–Color Association Test as a measure of selective attention, impulsivity, and cognitive flexibility (Golden, 1978); the California Verbal Learning Test—Children's Version as a measure of verbal list learning (Delis, Kramer, Kaplan & Ober, 1994); the Visual–Auditory Learning subtest from the Woodcock Johnson Cognitive Battery (Woodcock & Johnson, 1989) as a measure of visual–auditory associative learning; and the math subtest from the Wide Range Achievement Test (Wilkinson, 1993) as a measure of academic productivity. Barkley's Side Effects Rating Scale (SERS), which assesses 17 common adverse side effects of stimulant medication rated on a severity scale from 0 (absent) to 9 (severe), was administered to evaluate medication side effects (Barkley, 1981). A SERS score ≥7 precluded participation ($n = 2$) in the subsequent home-crossover trial. An additional 14 patients declined participation in the home-crossover trial, leaving a total of 119 participants.

Home-Crossover Trial Phase

For the 3-week home-crossover phase, each patient was randomly assigned to three dose conditions consisting of placebo, low-dose MPH [LD; 0.30 mg/kg (10 mg maximum) bid] and moderate dose MPH [MD; 0.60 mg/kg (20 mg maximum) bid], each administered for 1 week. MPH or placebo was administered 5 days per week, with a weekend washout period. Randomization was conducted by the pharmacist at St. Jude using a computerized database developed in-house by biostatisticians, which assigned one of six medication orders to each participant. Parents and teachers completed report forms with the study nurse via telephone calls at the end of each of the 3 weeks. Rating scales included the SERS described above, as well as the Conners' Rating Scales—Revised, and the Social Skills Rating System, described below.

The Conners' Parent Rating Scale (CPRS), Conners' Teacher Rating Scale (CTRS), and Conners' Adolescent Self-Report Scale (CASS) are designed to assess symptoms and behaviors associated with ADHD (Conners, 2000). The short form used in the current study comprises 27 (parent and adolescent) or 28 (teacher) items rated on a scale from 0 (not true at all) to 3 (very much true). From these items, an ADHD Index and scales for Hyperactivity and Cognitive Problems/Inattention are derived. Internal consistency reliabilities for this measure range from .86 to .94 for the parent form, .88 to .95 for the teacher form, and .75 to .85 for the adolescent form. Evidence for criterion-oriented validity includes significant correlations with the Conners' CPT (Conners, 1995). The adolescent form is designed for youth between 12 and 17 years of age.

The Social Skills Rating System (SSRS) assesses social skills for children at three developmental levels: preschool, elementary, and secondary. The SSRS comprises 51–57 items, depending on age, that load onto Social Competence and Problem Behavior scales for the parent version and Social Competence, Problem Behaviors, and Academic Competence scales for the teacher version. The test–retest reliability of the parent form is .87 and ranges from .75 to .93 for the teacher version. This scale has been used previously to evaluate treatment effects in children diagnosed with ADHD (Pfiffner & McBurnett, 1997).

Definition of Clinical Response

All participants in the home-crossover phase were categorized as an MPH responder or nonresponder based on improvements noted on the ADHD Index of the CTRS following MD MPH relative to placebo. Teacher report was chosen over parent report given teachers observed participants during the active medication time frame; participants received MPH after breakfast and at lunch at school. Given the duration of action of standard MPH is 1–4 h (Kimko, Cross, & Abernethy, 1999), parents were not typically observing participants during optimal medication dosing. The ADHD Index was chosen because the Cognitive Problems/Inattention scale contains items that are unlikely to be sensitive to change during a 1-week MPH trial (e.g., ''poor in spelling'' or ''not reading up to par'') and the Hyperactivity scale (e.g., ''is always on the go'' or ''has difficulty waiting his/her turn'') contains items that are less characteristic of cognitive

impairment in cancer survivors (see Butler & Mulhern, 2005, for a review). Finally, the moderate dose was chosen over the low dose to optimize sensitivity to response in participants. The Reliability Change Index (RCI; Jacobson & Truax, 1991) was chosen as a measure of magnitude of change between the MD and placebo weeks as it takes into account reliability of the response measures and can also be used by the practicing clinician to measure response in an individual patient, enhancing the generalizability of findings.

Statistical Considerations

Demographic, clinical, and psychometric data from the screening phase were subjected to qualitative analyses to establish indices of central tendency and distribution (see Tables I and II). The response variable is the RCI, which was calculated for each patient using the formula $X_2 - X_1/S_{diff}$, where X_2 is the score on the CTRS ADHD scale at the end of the MD MPH week, X_1 is the score on the CTRS ADHD scale at the end of the placebo week, and S_{diff} is the standard error of the difference between the two test scores. In statistical terms, S_{diff} is the standard deviation of the difference of two scores under the assumption that the mean of the difference is 0. The standard error of difference is calculated from the test–retest reliability of the test and the standard deviation of the group. An RCI score greater than 1.96, indicating a less than 5% probability of finding a change in score of that magnitude just by chance, was used to define a positive medication response.

Following classification of the entire sample into responder/nonresponder categories, logistic regression analyses were conducted to identify factors predictive of a positive medication response. All factors in Tables I and II, as well as individual clinical scales from the CBCL, were entered into the univariate logistic regression as predictor variables. Only factors that were statistically significant in univariate models were subsequently combined in multivariate analyses. This stepwise method of

Table I. Demographic and Clinical Characteristics of the Childhood Cancer Survivor Sample ($N = 106$)

	n	%
Gender		
Male	63	59.43
Female	43	40.57
Ethnicity		
Caucasian	88	83.02
African American	15	14.15
Other/Unknown	3	2.83
Diagnosis		
Brain Tumor	51	48.11
ALL	55	51.89
CNS treatment intensity		
Chemotherapy only	42	39.62
≤24 Gy CRT[b] ± chemotherapy	15	14.15
>24 Gy CRT ± chemotherapy	49	46.23
	Mean ± SD	Range
Age at cancer treatment (years)	5.41 ± 2.87	0.58–13.97
Age at study participation (years)	11.92 ± 3.00	7.03–18.55
Years after cancer treatment	4.70 ± 2.92	1.13–14.51

Notes. ALL, acute lymphoblastic leukemia; CRT, cranial radiation therapy.

Table II. Psychological Test Findings from Baseline Screening

Measure	*n*[a]	Mean ± *SD*	Range
Estimated IQ (SS)	106	87.58 ± 15.58	50–118
WIAT Reading Composite (SS)[b]	106	83.33 ± 14.12	42–119
WIAT Mathematics Composite (SS)	106	82.48 ± 13.78	53–112
CPRS—Cognitive Problems/ Inattention (T)[c]	106	64.22 ± 12.41	41–90
CPRS—Hyperactivity (T)	106	58.16 ± 13.07	44–90
CPRS—ADHD Index (T)	106	62.28 ± 11.15	41–90
CTRS—Cognitive Problems/ Inattention (T)	87	64.29 ± 10.56	44–90
CTRS—Hyperactivity (T)	87	56.36 ± 12.88	43–90
CTRS—ADHD Index (T)	87	59.52 ± 11.50	42–90
CASS—Cognitive Problems/ Inattention (T)	38	55.97 ± 9.55	38–79
CASS—Hyperactivity (T)	38	46.66 ± 6.67	35–57
CASS—ADHD Index (T)	38	52.26 ± 9.44	37–74
SSRS—Social Competence (SS)	106	93.85 ± 17.79	52–130
SSRS—Problem Behavior (SS)	106	102.10 ± 13.22	84–138
CPT—Omission (%ile)	106	93.33 ± 6.91	74.51–98.90
CPT—Commission (T)	106	51.00 ± 9.93	23.36–78.30
CPT—Hit Reaction Time (T)	106	40.54 ± 13.12	1.43–70.99
CPT—Overall Index[d]	106	9.86 ± 6.62	0.00–20.74
CBCL—Total Problems (T)	49	54.57 ± 9.94	37–79
CBCL—Internalizing Problems (T)	49	54.69 ± 10.30	32–84
CBCL—Externalizing Problems (T)	49	49.92 ± 10.81	32–79
CBCL—Activities (T)	49	43.98 ± 7.53	28–55
CBCL—Social Skills (T)	49	40.96 ± 8.41	23–55
CBCL—School Problems (T)	49	34.23 ± 7.92	23–55

Notes. WIAT, Wechsler Individual Achievement Test; CPRS, Conners' Parent Rating Scale; CTRS, Conners' Teacher Rating Scale; CASS, Conners' Adolescent Self-Report Scale; SSRS, Social Skills Rating System; CPT, Conners' Continuous Performance Test; CBCL, Child Behavior Checklist.

[a]CTRS ($n = 87$) due to failure of teachers to return forms, especially over summer break; CASS ($n = 38$) given only 38 participants ≥ 12; CBCL ($n = 49$) as was implemented half-way through study.

[b]SS = standard score; mean = 100, $SD = 15$.

[c]T Score; mean = 50, $SD = 10$. Higher scores indicate better performance for estimated IQ, WIAT, SSRS—Social Competence, and CBCL (Activities, Social Skills, and School Problems). Higher scores indicate more problems for CPRS, CTRS, CASS, SSRS—Problem Behaviors, CPT, and CBCL (Total Problems, Internalizing Problems, and Externalizing Problems).

[d]Weighted average of CPT Scores: <8 normal; 8–11 borderline; >11 impaired.

analysis is more conservative than conducting multivariate analyses without first conducting univariate analyses, resulting in a lower chance of false positive results. Factors were carefully considered with respect to intercorrelation to reduce multicollinearity in the multivariate analyses; only two or three predictors were included in the same model. There were missing data for the following screening variables gathered at premedication baseline: CASS ($n = 38$) that was only completed by participants of at least 12 years of age, CTRS ($n = 87$) that was not always mailed back by teachers in the community, or loss due to summer break, and the CBCL ($n = 49$) that was added to the screening phase half-way through the study to more objectively assess internalizing psychopathology as an exclusion criterion.

Results

Participant Characteristics

Of the 469 screened participants, 249 were ineligible based on neurocognitive performance: 4 for IQ < 50, 82 failed to demonstrate attention difficulties on the CPT and/or CRS, 61 failed to demonstrate achievement difficulties on the WIAT, and 102 failed to demonstrate achievement difficulties on the WIAT and attention difficulties on the CPT and/or CRS. Ten patients did not qualify based on other medical (e.g., progressive disease or contraindicated medications) or psychological (e.g., depression) reasons. For those children that qualified but whose parents refused study participation ($n = 75$), the most common reason cited was concern about placing their child on a stimulant medication. Other less frequently cited reasons for not participating included disinterest in having their child take any more medication, with no specific objection to stimulant medication, and disinterest in dedicating time for study participation. There were no statistical differences between those children refusing participation ($n = 75$) and those participating in the 3-week home-crossover ($n = 106$) with respect to diagnosis, intensity of CNS-directed therapy, gender, race, or age at screening. The group refusing participation was younger at the time of cancer treatment; however, as described above, the treatment group was stratified based on age at treatment prior to being randomized to MPH and placebo weeks.

Demographic and clinical characteristics of the sample participating in both placebo and MD MPH weeks of the home-crossover trial are presented in Table I. Thirteen children participating in the home-crossover trial had incomplete data (eight had the MD week omitted due to adverse side effects during the 2-day in-clinic phase, four discontinued the MD week early, and one teacher did not complete the CTRS after the MD week). Accordingly, the final sample consisted of 106 participants (63 males, 43 females) between the ages of 7 and 18 years (mean = 11.92; $SD = 3.00$) who were 1–14 years (mean = 4.70; $SD = 2.92$) posttreatment initiation at the time of study participation. The sample was primarily Caucasian (83%) and balanced by diagnosis (48% BT; 52% ALL). Of the sample, 40% were treated with chemotherapy only (mild intensity), 14% with ≤24 Gy CRT with or without chemotherapy (moderate intensity), and 46% with > 24 Gy CRT with or without chemotherapy (high intensity). The BT sample received more intense treatment with 5.88%, 0.00%, and 94.12% receiving mild, moderate, and high intensity treatment, respectively, versus 70.91%, 27.27%, and 1.82% of the ALL sample receiving mild, moderate, and high intensity treatment, respectively.

Table II summarizes results from the screening battery of psychological tests and parent/teacher rating forms. Average estimated IQ at the time of screening was in the low-average range (mean = 87.58; $SD = 15.58$). Participants diagnosed with BT did not differ significantly from those diagnosed with ALL on estimated IQ (BT mean = 85.80; $SD = 16.31$ vs. ALL mean = 89.24; $SD = 14.84$; $p = .26$). Consistent with study selection, average group performance was below age expectations on measures of reading and math (mean = 83.33; $SD = 15.58$ and mean = 82.48; $SD = 13.78$, respectively), performance-based attention measures (e.g., CPT Overall Index—mean = 9.86; $SD = 6.62$ where scores < 8 are considered normal), and parent and teacher report of attention problems [e.g., Cognitive Problems/Inattention—CPRS (T-score) mean = 64.22; $SD = 12.41$; CTRS mean = 64.29; $SD = 10.56$]. In contrast, adolescents did not indicate attention problems on the self-report attention measure, CASS. Parent ratings on the CBCL were not suggestive of clinical elevations with respect to symptoms of internalizing or externalizing psychopathology for the entire sample. Borderline significant school problems were endorsed by parents on the CBCL [School Problems (T-score) mean = 34.23; $SD = 7.92$, lower scores indicate greater problems].

MPH Response Rate

Based on the RCI for CTRS–ADHD Index following MD MPH, 45.28% of the childhood survivor sample demonstrated a positive medication response. Therefore, nearly half the sample showed a decrease in teacher ratings of attention problems, larger than expected by chance ($p < .05$), following the MD MPH week relative to the placebo week. Consistent with our first hypothesis, this

rate of response is significantly lower than that typically reported in the ADHD literature. If we assume 75% is the MPH response rate in the ADHD population (Barkley, 1977; Efron et al., 1998; Greenhill et al., 2001), then the proportion of cancer survivors with a positive MPH response is significantly less based on the binomial test (95% CI = 35.81–54.76, $p < .0001$). Of note, there was no statistical difference in the response rate for children with an IQ < 70 ($n = 16$; response = 43.75%) relative to participants with an IQ ≥ 70 ($n = 90$; response = 45.56%; $p = .89$).

Predictors of Positive Response

Logistic regression was used to estimate the effects of demographic, clinical, and psychometric variables on positive medication response. Table III contains β weights, odds ratios, and 95% confidence intervals for predictors found to be statistically significant ($p < .05$) in univariate logistic regressions. No demographic factors (e.g., age, gender, or ethnicity), clinical factors (e.g., diagnosis, CNS treatment intensity, or time since treatment), or global cognitive measures (i.e., IQ and academic skills) were predictive of MPH response. Parent (SSRS—Problems Behaviors, CBCL—Thought Problems and Attention Problems) and teacher (CTRS—Hyperactivity and ADHD Index) report of attention and behavior problems at screening were predictive of a positive medication response. Prior to conducting multivariate logistic regression analyses, the multicollinearity of these positive predictors was investigated using Pearson correlations. Table IV indicates there were a number of significant correlation coefficients among these variables. Only variables that were not significantly correlated were entered into the same model and a backward selection process ($p > .05$) was used to fit the model. Table V displays these multivariate models. The sample size for these

Table III. Prediction of MPH Response on the CTRS–ADHD Index for MD Week versus Placebo-Univariate Logistic Regression

Predictor	n[a]	β	SE	OR	95% CI	p[b]
CTRS—Hyperactivity (T)[c]	87	.044	.019	1.045	1.007–1.085	.019*
CTRS—ADHD Index (T)	87	.042	.020	1.043	1.003–1.085	.036*
SSRS—Problem Behavior (SS)[d]	106	.031	.016	1.032	1.001–1.064	.045*
CBCL—Thought Problems (SS)	49	.108	.051	1.114	1.009–1.230	.033*
CBCL—Attention Problems (SS)	49	.075	.036	1.078	1.004–1.157	.038*

Notes. CTRS, Conners' Teacher Rating Scale; SSRS, Social Skills Rating System; CBCL, Child Behavior Checklist.
[a]CTRS ($n = 87$) due to failure of teachers to return forms; CBCL ($n = 49$) as was implemented half-way through study.
[b]Only significant predictors ($p < .05$) are presented here. All variables from Tables I and II, in addition to individual scales from the CBCL were evaluated.
[c]T Score; mean = 50, $SD = 10$.
[d]SS, Standard Score; mean = 100, $SD = 15$.
*$p < .05$.

Table IV. Pearson Correlations among Predictor Variables

R *p*-value *n*	CTRS—ADHD Index	CTRS—Hyperactivity	SSRS—Problem Behavior	CBCL—Thought Problems	CBCL—Attention Problems
CTRS—ADHD Index	*********				
CTRS—Hyperactivity	.661	*********			
	<.0001**				
	87				
SSRS— Problem Behavior	.183	.056	*********		
	.092	.609			
	86	86			
CBCL— Thought Problems	.368	.271	.177	*********	
	.011*	.066	.230		
	47	47	48		
CBCL— Attention Problems	.343	.268	.597	.635	*********
	.018*	.068	<.0001**	<.0001**	
	47	47	48	48	

Notes. CTRS, Conners' Teacher Rating Scale; SSRS, Social Skills Rating System; CBCL, Child Behavior Checklist.
*$p < .05$; **$p < .01$.

Table V. Prediction of MPH Response on the CTRS—ADHD Index for MD Week Versus Placebo-Multivariate Logistic Regression

Model	Predictor	*n*	β	SE	OR	CI	*p*
1[a]	SSRS—Problem Behavior	86	.041	.018	1.042	1.005–1.079	.024
2[b]	CBCL—Thought Problems	47	.105	.050	1.110	1.006–1.225	.037
3[c]	CTRS—Hyperactivity	86	.046	.020	1.047	1.008–1.088	.019
	SSRS—Problem Behavior		.040	.018	1.041	1.004–1.080	.283

Note. SSRS, Social Skills Rating System; CBCL, Child Behavior Checklist; CTRS, Conners' Teacher Rating Scale.

[a]Model included the CTRS–ADHD Index and SSRS–Problem Behavior.

[b]Model included CTRS–Hyperactivity, SSRS–Problem Behavior, and CBCL–Thought Problems.

[c]Model included CTRS–Hyperactivity and SSRS–Problem Behavior.

models was restricted by the measure with the smallest sample size, as indicated in Table V, and no more than three predictors were included in the same model.

Discussion

Findings from this prospective, placebo-controlled, crossover trial indicate that MPH provides improvement for cognitive and behavioral symptoms of inattention in childhood cancer survivors. Approximately one-half the sample demonstrated a positive medication response based on a conservative, statistically defined response criterion. As predicted, this rate is lower than the 75% response rate that has been reported in the ADHD literature (Barkley, 1977; Efron et al., 1998; Greenhill et al., 2001). This discrepancy may be attributed to a difference in etiology of attention problems in cancer survivors as well a difference in clinical presentation including a higher rate of comorbid learning problems, less frequent overactivity, and more frequent neurological impairment, all factors that have been associated with a lower MPH response rate among healthy children with ADHD (Grizenko et al., 2006; Chabot et al., 1999; Weber & Lutschg, 2002, respectively). With respect to different underlying etiology, it has been proposed that attention difficulties in ALL survivors may relate to polymorphisms of the folate pathway rather than dopamine transport or reuptake, as suspected in developmental ADHD, such that the site of action of stimulants might be inconsistent with observed cognitive difficulties (Krull et al., 2008). The lower response rate to MPH also may be secondary to how response was defined. For example, a study of MPH response in children diagnosed with ADHD that also used the RCI for an abbreviated Conners' Scale yielded a lower response rate, two-thirds of the sample, than typically reported in the ADHD literature (Buitelaar et al., 1995).

Based on study findings, there was mixed support for our hypotheses regarding positive MPH predictors. Consistent with the ADHD literature, premedication baseline ratings of attention problems were most predictive of a positive medication response. The data are consistent across raters (i.e., teachers and parents) and clinical measures. This finding is not just a tautology as four out of five of the identified predictive measures were different from the response measure and response was based on the difference in ratings between placebo and MPH, not premedication baseline and MPH. In contrast to our predictions, younger age, higher intellectual functioning, and greater neurological impairment (as measured by diagnosis and treatment intensity) were not predictive of the MPH response. While these findings are in contrast to our hypotheses, a similar lack of predictive relationship in the ADHD literature has been found for IQ (Chabot et al., 1999) and younger age (Chabot et al., 1999, Hermens et al., 2005). Further, one study has found that neurological impairment is actually a positive rather than negative indicator of medication response for children diagnosed with ADHD (Thomson & Varley, 1998). No other demographic factors (e.g., gender or ethnicity) or clinical factors (e.g., diagnosis or CNS treatment intensity) were predictive of MPH response.

Unfortunately, cognitive late effects are frequent and impairing sequelae of childhood cancer and related therapies. As survival rates continue to improve, healthcare providers are increasingly called upon to assist patients and families in managing these deficits to optimize the overall quality of life. There is empirical, group based, evidence to support the efficacy of MPH for improving attention and social problems experienced by some cancer survivors (Conklin et al., 2007; Mulhern et al., 2004; Thompson et al., 2001). While these findings are encouraging, clinicians are responsible for treating *individual* patients thereby mandating that we increase our understanding of individual response to MPH. Determining who is likely to respond prior to commencing a medication trial is especially relevant in this vulnerable population for whom parents routinely express concerns regarding trying a stimulant medication (Conklin et al., 2007). This study indicates that parent and teacher reports are useful not

only in identifying children with the most significant attention and learning problems but also children most likely to benefit from a stimulant drug trial. Accordingly, prescribing practices may be optimally targeted by gathering information from multiple informants prior to prescribing a stimulant medication. Further, efficacy always needs to be balanced with safety. We recently demonstrated that MPH is well tolerated by childhood cancer survivors, with similar frequency and severity of adverse side effects as those seen in the ADHD literature (Conklin et al., in press). However, a subgroup at increased risk for side effects was identified and included participants of female gender, lower IQ, and a BT diagnosis. Therefore, while patients who are more neurologically impaired may demonstrate similar treatment efficacy, they may show lower medication tolerance making MPH a less viable treatment option for children who evidence neurological impairment.

Our findings need to be considered in the context of study limitations. As part of study screening, children with significant internalizing psychopathology were excluded from participation such that the predictive value of these symptoms could not be evaluated. Outcome measures included only behavioral ratings. It has yet to be demonstrated that the same factors identified in this study would be predictive of performance-based measures of attention. The addition of the CBCL midway through the study, as well as some missing CTRS, limited power in our multivariate models. By selecting those patients in greatest need of intervention, children with both attention and learning difficulties, we may have limited the generalizability of our findings to those patients with only attention problems. Finally, while inclusion of children with an IQ less than 70 did not appear to affect the MPH response rate, the addition of an adaptive functioning measure would have allowed us to determine if any of these children met criteria for mental retardation. It is likely that low IQ was acquired subsequent to treatment and none of these children were believed to have qualified for a mental retardation diagnosis prior to cancer treatment.

Future studies need to identify alternative treatments for those cancer survivors who either do not respond positively to MPH or cannot tolerate the medication due to adverse side effects. Atomoxetine is a nonstimulant medication with some demonstrated efficacy in the ADHD population that may be a viable alternative to stimulants among cancer survivors with attention and learning problems (Gibson, Bettinger, Patel, & Crismon, 2006; Mohammadi & Akhondzade, 2007; Wolraich, McGuin, & Doffing, 2007). There is also emerging support in the child oncology literature for cognitive remediation programs that do not include pharmacotherapy (Butler et al., 2008). These programs offer initial encouragement; however, the personnel time and financial requirements are great, the benefits modest, and they are offered at limited locations. There is an obvious need for identification of less expensive, less time-intensive, and portable interventions with demonstrated efficacy. With respect to identifying predictors of response, direct measures of neuropathology including neuroimaging findings warrant further investigation. Studies examining the benefits of stimulant medication should include not only attention response measures but also measures of executive function, given these identified deficits in cancer survivors (Schatz et al., 2000; Spiegler, Bouffet, Greenberg, Rutka & Mabbott, 2004) as well as the finding of enhanced executive functioning for stimulant medications (e.g., Pietrzak, Mollica, Maruff, & Snyder, 2006). Finally, findings from this 3-week home-crossover study are encouraging regarding short-term efficacy but long-term studies should be conducted to evaluate whether benefits are sustained.

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