Scholarly Literature Review: Management of Neurocognitive Late Effects with Stimulant Medication

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Objective To examine the extant literature on stimulant drug therapy for survivors of childhood cancer during the late-effects period. Methods A review of literature is provided on the mechanism of and cognitive toxicities for children and adolescents treated for acute lymphoblastic leukemia (ALL) and malignant brain tumors (BT) as well as the pharmacotherapy of stimulant medications, with a specific review of literature on the efficacy and safety of the stimulants for children with ALL and BT. Results Only four studies were found that have examined the effects of stimulant medication on the cognitive toxicities of childhood survivors of cancer during the late-effects period and only two of these investigations were controlled clinical trials. Findings suggest efficacy of the stimulants on parent and teacher ratings of attention and putative tasks of attention and executive functioning. Conclusions Although there is some preliminary support for the efficacy and safety of the stimulants for survivors of ALL and BT, more research is needed concerning the long-term effects of the stimulants among cancer survivors.

Key words neurocognitive late effects; childhood cancer; stimulants; acute lymphoblastic leukemia; malignant brain tumors.

Every year, approximately 12,500 children and adolescents are diagnosed with cancer in the United States (National Childhood Cancer Foundation, CureSearch). Although cancer is the leading cause of death by disease for children under 15 years (NCI, Cancer Facts), recently there have been significant advances in technology that have enhanced early detection and treatment, thereby markedly improving the survival rates for the most prevalent childhood cancers, including acute lymphoblastic leukemia (ALL) and malignant brain tumors. For example, recent data indicate a 5-year survival rate exceeding 80% for children diagnosed with ALL (Mulhern & Butler, 2004). With the increase in survival rate of these children and adolescents, many clinical researchers have begun to examine the sequelae of the disease as well as its associated treatment. Findings have revealed that childhood cancer and the associated multimodal therapies most commonly employed to treat this disease often result in adverse long-term central nervous system (CNS) related outcomes, commonly referred to as neurocognitive late effects. Multiple causes may account for these impairments or cancer late effects, including surgical intervention, cranial radiation therapy, and CNS chemotherapy. Many of these chemo- and radiation therapies are administered prophylactically into the spinal cord to prevent the cancer cells from entering the CNS (Morris, Krawiecki, Kullgren, Ingram, & Kurcynski, 2000; Waber & Mullenix, 2000). Although the treatments may prove life-saving for children with ALL, often they result in cognitive late effects that include neurotoxicities. Such toxicities produce declines in intellectual functioning, neurocognitive impairments, and delays in academic achievement (Moleski, 2000).

Problems with attention, learning, and memory are the primary characteristics of neurocognitive late effects (Mulhern & Palmer, 2003). Specifically, Mulhern and Butler (2004) defined the core neurocognitive deficits associated with cancer and specific chemotherapies and prophylactic cancer therapies as those involving (a) attentional, engagement, executive functions, processing, and fluid abilities, and (b) secondary deficits, which are knowledge-based and typically referred to as crystallized...
abilities. Neurocognitive late effects may manifest months or years after completion of cancer treatment, and are generally thought to be chronic, if not progressive in their course (Mulhern & Butler, 2004). There is frequently a delay in onset of effect due to the slow replication rate of most constituents of the CNS (Packer et al., 1987). It is believed that childhood survivors of leukemia, lymphoma, and pediatric brain tumors experience a greater risk of significant neurocognitive deficits because of the deleterious effects of radiation and chemotherapy on the young brain (Mulhern & Butler, 2004). Among children treated for both CNS tumors and ALL, being female and a younger age at time of treatment has been associated with an increased neurocognitive deficit (Brown et al., 1998; Cohen et al., 1993; Mulhern, Hancock, Fairclough, & Kun, 1992; Radcliffe, Bunin, Sutton, Goldwein, & Phillips 1994; Roman & Sperduto, 1995; Silber et al., 1992).

Some experts argue that stimulants, in addition to other forms of interventions, should play an important role in the rehabilitation process of children and adolescents who have completed treatment and experience resultant neurocognitive deficits (Butler & Mulhern, 2005; Moore, 2005; Mulhern & Butler, 2004). The rationale for this assertion is that children who survive ALL and malignant brain tumors exhibit neurocognitive sequelae and behavioral symptoms similar to those of children with attention deficit hyperactivity disorder (ADHD), particularly symptoms of the primarily inattentive type of ADHD that imitate impairments in attention, and stimulant drug treatment may prove effective in ameliorating the attentional and behavioral symptoms in these children, especially during the late-effects period (i.e., operationalized most frequently as 1–2 years following completion of treatment) (Butler & Mulhern, 2005). Unfortunately, there have been relatively few published clinical trials that have investigated the effects of stimulant medication on child and adolescent survivors of cancer. Nonetheless, results from the few published studies available indicate that stimulant medication may exert a similar positive effect on attentional and behavioral symptoms for childhood survivors of cancer as compared to those impairments found with otherwise healthy children diagnosed with ADHD (Mulhern et al., 2004; Thompson et al., 2001). Therefore, the stimulants may offer some hope in enhancing the quality of life among survivors of childhood cancer survivors.

First, we briefly review the medical background and treatment for the two most common forms of pediatric cancer: ALL and malignant brain tumors. Next, we describe the neurocognitive late effects that often result from the tumors and their treatment. Subsequently, we review evidence from the Attention Deficit/Hyperactivity literature to suggest that they share similar target symptoms to those of their peers who sustained late effects of neurocognitive toxicities that are likely to be responsive to the effects of stimulants. Finally, we discuss the use of stimulant medications in pediatric populations who have survived cancer.

Medical Background

Acute Lymphoblastic Leukemia

ALL is the most common malignancy among children in the United States, representing nearly one-third of all pediatric cancers and three-fourths of all cases of childhood leukemia (Margolin & Poplack, 1997). ALL accounts for 80% of the acute leukemias of childhood, with most cases occurring between ages 3 and 7. Approximately 2500–3500 new cases of childhood ALL are diagnosed each year (Butler & Mulhern, 2005). ALL is a malignant disorder of lymphoid cells that is generally thought to arise in the bone marrow and eventually spread to nearly every organ system—including the thymus, liver, spleen, lymph nodes, testes, and the CNS—via the circulatory system (Mulhern & Butler, 2004). Although a small percentage of leukemia cases are associated with possible causes such as inherited genetic syndromes (e.g., Trisomy 21), environmental, viral, or immunodeficiency factors, the definitive causes of ALL remains largely unknown (Mulhern & Butler, 2004).

The most common treatment option for ALL is a combination of various chemotherapies, with duration of treatment likely to vary between 30 and 36 months (Butler & Mulhern, 2005). In the event of CNS infiltration into the CNS or relapse, cranial irradiation is employed (Mulhern & Butler, 2004), and frequently for mild to moderate ALL, prophylactic chemotherapy is often used to prevent leukemia cells from infiltrating the CNS. Fortunately, due to recent advances in the treatment of ALL, 75–80% of patients achieve long-term disease-free survival (Ravindranath, 2003). Nonetheless, following completion of treatment, Margolin, Steuber, & Poplack (2002) report that ~20% of those children who will relapse do so in the first year off therapy, with a 2–3% risk of subsequent relapse per year in the remaining patients for the next 3–4 years. Treatment of ALL includes four phases: remission induction, CNS preventative or prophylactic therapy, consolidation, and maintenance (Butler & Mulhern, 2005). The CNS
provides a sanctuary site for occult leukemia cells. Therefore, preventative CNS therapy is needed because the leukemia cells that reside in the CNS are protected from the action of systemic chemotherapy by the blood–brain barrier (Westlake & Bertolone, 2002). CNS treatment plays a primary role in significantly decreasing the rate of disease relapse. One of the primary chemotherapeutic agents employed for CNS treatment for children with ALL is methotrexate (MTX), which has been associated with white-matter changes, perfusion defects, and brain atrophy (Miketova et al., 2005).

Malignant Brain Tumors (BT)

Brain tumors are the second most common type of pediatric cancer, and are the most frequent solid malignancy. Pediatric brain tumors account for an annual incidence of 3.3 per 100,000 (Butler & Mulhern, 2005). The most common childhood brain tumors are gliomas, astrocytomas, medulloblastomas, ependymomas, and brain stem gliomas (Strother et al., 2002). Childhood nervous system tumors are oftentimes characterized as either located below (infratentorial), or above the tentorium cerebelli (supratentorial). The etiology of most pediatric brain tumors is largely unknown, although genetic syndromes have implicated in ~5% of all diagnosed cases. Moreover, brain tumors have appeared as a secondary malignancy following the treatment of ALL with cranial irradiation (Mulhern & Butler, 2004). Although the treatment and probable outcome vary according to the site and type of the tumor, ability of the tumor to be completely removed by surgery, the response to therapy, and the age and general health of the child, the most common treatment for childhood malignant brain tumors includes surgical resection of the tumor, if possible, and systemic chemotherapy with or without cranial or craniospinal radiation therapy (Mulhern & Butler, 2004). Dosing schedules and combinations of chemotherapeutic agents are employed differentially depending on diagnosis, disease stage, and other factors (Moore, 2005). Recent data indicate a prognosis of ~65% long-term survival for medulloblastomas, whereas children with intrinsic brain stem glioma have a prognosis of <10% (Mulhern & Butler, 2004), indicating the increased lethality of brain tumors when compared to ALL (Bleyer, 1999).

Neurocognitive Late Effects

As mentioned previously, neurocognitive late effects may result from the tumor itself or the associated treatment, such as CNS-directed therapies of cranial radiation therapy or intraventricular/intrathecal chemotherapy. Late effects directly due to disease are associated especially with brain tumors. These tumors may disrupt the child’s neurocognitive status by nature of their location within the brain and its associated difficulties. For example, brain tumors that infiltrate or have a mass effect (i.e., pushing) on vital brain structures may have a negative effect on neurocognitive functionality (Moore, 2005).

Beyond the disease itself, treatment of ALL and brain tumors with chemotherapy and/or radiation therapy may damage the healthy tissue in the CNS, resulting in cognitive impairments. For ALL survivors, the neuropathology of CNS injury takes multiple forms that may include breakdown of the blood–brain barrier, demyelination, diffuse and multifocal white-matter abnormalities, microvascular occlusion, and calcifications in cortical gray matter and basal ganglia (Corn et al., 1994; Mulhern & Butler, 2004; Tsuruda et al., 1987). However, there is some suggestion that white matter injury may be the principle factor in radiation therapy and chemotherapy-related CNS damage (Mulhern & Butler, 2004). There are numerous studies documenting neurocognitive deficits among children surviving ALL and brain tumors that include decreases in performance on tests of attention and concentration (Brouwers, Riccardi, Poplack, & Fedio, 1984; Moleski, 2000; Reeves et al., 2006), cognitive abilities (Giralt et al., 1992; Mulhern, Fairclough, & Oches, 1991; Raymond-Speden, Tripp, Lawrence, & Holdaway, 2000), working memory (Hill, Ciesielski, Sethre-Hofstad, Duncan, & Lorenzi, 1997; Lesnik, Ciesielski, Hart, Benzel, & Saders, 1998; Schatz, Kramer, Ablin, & Matthay, 2000), visual-spatial abilities (Espe et al., 2001; Giralt et al., 1992), academic abilities (Brown et al., 1996; Espy et al., 2001; Kaemingk, Carey, Moore, Herzer, & Hutter, 2004; Waber et al., 1995), and nonverbal abilities (Brown et al., 1998; Moleski, 2000).

Neurocognitive Late Effects from Treatment for ALL

Studies have demonstrated that the treatment for ALL results in significant neurocognitive impairment (Meadows et al., 1981). In a review of the literature of children treated for ALL, Moleski (2000) reported that two-thirds of the studies indicated declines in intelligence, neurocognitive involvement, and delays in academic achievement. In addition, the most pronounced findings were for deficits in attention and nonverbal
memory. Bleyer et al. (1990) conducted a randomized clinical trial that evaluated the effect of cranial irradiation, with or without concurrent intrathecal MTX, for CNS prophylaxis of ALL on the intellectual functioning of children and adolescents. Findings revealed that children younger than 5 years at time of treatment and had received radiation therapy and intrathecal chemotherapy had lower intellectual quotients (IQ) scores than those who received craniospinal radiation therapy alone. Similar findings were reached in another study where children treated with 24 Gy (a relatively large dose) of cranial radiation combined with IT MTX demonstrated a significant decline in intellectual functioning, compared to childhood cancer survivors who received no CNS-directed therapy (Meadows et al., 1981). A longitudinal study that employed intrathecal MTX, intravenous MTX, and a reduction of the traditional CRT dose from 24 Gy to 18 Gy for CNS prophylactic treatment of children who had survived ALL also found significant neurocognitive deficits (Rubenstein, Varni, & Katz, 1990). For example, findings indicated significant declines in full-scale, verbal, and performance IQ scores at the 4-year follow-up testing, with a mean loss of 6–7 IQ points (i.e., one-half of a standard deviation). This finding is important because it suggests that reducing the CRT dose from 25 Gy to 18 Gy does not necessarily minimize neurocognitive toxicity, at least in the domain of intellectual functioning. Finally, Riva et al. (2002) conducted a recent controlled clinical trial that evaluated cognitive impairment following radiotherapy to the brain and systemic and intrathecal chemotherapy after malignant brain tumor treatment in children. The investigation compared children who underwent surgery for cerebellar medulloblastoma with cousins and siblings who were free of cancer. Dependent measures included intellectual functioning, executive function, attention, visual perception, and short-term memory. Based on their data, the investigators conclude that the administration of intrathecal MTX to children with medulloblastoma worsens the cognitive deficits induced by chemotherapy and radiotherapy.

Although radiation therapy and/or the combination of radiation therapy and chemotherapy have been found to exert neurocognitive toxicities, some research also has suggested that various chemotherapeutic agents may also adversely affect cognitive functioning. In one clinical trial, Brown et al. (1992) studied 48 children treated for leukemia without cranial radiation therapy. Impairments were found in tasks of higher-order cognitive functioning, such as attention, memory, and visual construction ability, as well as learning disabilities in mathematics. In another clinical trial, Hill et al. (1997) examined the effects of intrathecal chemotherapy on memory in children with ALL relative to case controls without cancer. Findings revealed deficits in both visual-spatial and verbal single-trial memory tasks. IQ scores were 10–20 points lower in the ALL group relative to the comparison control group. Consistent with the aforementioned studies, Waber et al. (1995a,b) also provided important data to demonstrate mild visual and verbal short-term memory deficits in leukemia survivors who were treated with intrathecal chemotherapy but without radiation therapy. It should be noted other studies that have examined the effect of chemotherapy on neurocognitive status have found minimal or no adverse effect on neurocognitive functioning following treatment with chemotherapy alone (Copeland, Moore, Francis, Jaffe, & Culbert, 1996; Von der Weid et al., 2003).

**Neurocognitive Late Effects from Treatment for Malignant Brain Tumors (BT)**

Studies have provided evidence to demonstrate neurocognitive late effects resulting from the three main treatments for brain tumors, including surgery, chemotherapy, and radiation therapy, administered either alone or in combination. Glauser & Packer (1991) reported that 40–100% of long-term brain tumor survivors have been found to have some form of cognitive dysfunction as assessed with various psychometric instruments. For example, Steinlin et al. (2003) reported that children who were treated for benign cerebellar lesions with surgery alone demonstrated significant postoperative deficits in attention, memory, processing speed, and visual-constructive copying. Packer et al. (1987) indicate that cranial or craniospinal radiation therapy results in significant detrimental effects on the CNS, including impairments revealed in neuropsychological tests. Mulhern et al. (1992) conducted a review of the literature on the neuropsychological status of children treated for brain tumors. They found a 14-point difference in intellectual functioning between younger children treated with cranial whole-brain irradiation as compared with their older counterparts. No differences were revealed as a function of tumor location. Children under 4 years were found to be at greatest risk for intellectual decline due to radiation therapy.

Treatment approaches that employ combination therapies also have been demonstrated to result in toxic effects to the CNS. Reddick et al. (2003) examined
whether the association between reduced volumes of normal-appearing white matter and intellectual/academic achievement deficits could be explained by impairments in memory and attention among survivors of pediatric brain tumors. Children included in this study were 40 long-term survivors of pediatric brain tumors who were treated with radiation therapy with or without chemotherapy 2–15 years earlier (median, 5.7 years). The children ranged in age from 1.7 to 14.8 years (median, 6.5 years). Dependent measures for this investigation included quantitative tissue volumes from magnetic resonance imaging scans as well as neurocognitive assessments (including standardized tests of intelligence, measures of attention, memory, and academic achievement). Findings provided evidence of significant impairment in attention and decrement in intellectual functioning. Moreover, measures related to attention and concentration, but not memory, explained a significant amount of the variance in normal-appearing white matter and intellectual functioning. Improvements in attention and concentration also were associated with academic skills deficits, including reading, spelling, and mathematics. Reddick et al. (2003) interpret their findings to suggest that the primary consequence of reduced normal-appearing white matter among pediatric patients treated for brain tumors is diminished attentional capacities, thereby leading to a decline in intellectual functioning and academic achievement. In a follow-up study, Reddick et al. (2005) again found that children and young adults treated for medulloblastoma exhibited observably less normal-appearing white matter volume development when compared to healthy peers. Further support for these results was demonstrated in a recent study by Reddick et al. (2006) that investigated whether survivors of childhood ALL experienced deficits in neurocognitive performance, and if there was any association between the deficits and smaller white-matter volumes. Neurocognitive assessments included standardized tests of intelligence, measures of attention, and academic achievement. Participants included in this study were 112 long-term survivors of ALL and 33 healthy siblings that served as the control group. Findings revealed that the survivors of childhood ALL demonstrated deficits in attention and smaller white-matter volumes that were associated with impaired neurocognitive performance. In addition, deficits were demonstrated on measures of intelligence and academic achievement, although they did not reach the level of significance. Finally, cranial irradiation was found to exacerbate these deficits.

Recent research affirms the presence of attentional impairments in childhood survivors of medulloblastoma treated with surgical resection, risk-adapted craniospinal irradiation, and primary site conformal irradiation and chemotherapy. Reeves et al. (2006) conducted a retrospective chart review of long-term childhood survivors of medulloblastoma who were administered standardized tests of intelligence, attention, memory, and academic achievement identical to those assessment instruments employed by Reddick et al. (2003). Findings indicate that specific aspects of attentional functioning were impaired (specifically, sustained attention, selective attention, impulsivity, risk taking), with no evidence for impairments in verbal-memory abilities. Findings were interpreted to suggest that participants exhibited problems with attention and concentration comparable for children who also meet diagnostic criteria for ADHD.

Stimulant Medication for Attention Deficit Hyperactivity Disorder

Stimulants are the pharmacological agents that produce excitation of the CNS. Stimulant medications, including methylphenidate (MPH), dextroamphetamine, and d- and l-amphetamine racemic mixture, represent the class of psychotrophic agents most commonly prescribed for school-aged children and adolescents indicated for the management of ADHD (Jensen et al., 1999; Teitelbaum et al., 2001; Zito et al., 2003). The stimulants may be grouped according to their approximate duration of action: short-acting (effects lasting 3–4 h); intermediate-acting (effects lasting 6–8 h); and long-acting (effects lasting 8–12 h) (Wolraich, 2003). Controlled clinical trials comparing the efficacy of the various stimulants (e.g., MPH, amphetamines, dextroamphetamine) for children with ADHD have generally failed to demonstrate group differences in efficacy and safety (Arnold, 2000; Brown et al., 2005). Although the mechanisms of action for stimulants is not fully understood, many stimulants (e.g., MPH) are posited to increase extracellular dopamine levels by selective binding of the presynaptic dopamine transporter in the CNS (prefrontal and striatal areas) in addition to norepinephrine transporter blockage (Solanto, Arnsten, & Castellanos, 2001). The most important affected area of the human brain is the striatum (Volkow et al., 1995). MPH is a mixture comprised of the d- and l-isomers, with the d-isomer being the predominant pharmacologically active compound (Patrick, Caldwell, Ferris, & Breese, 1987; Srinivas, Hubbard, Quinn, & Midha, 1992). MPH is eliminated from the plasma with
a mean half-life of 2.4 h in children (Brown & Daly, in press) and the drug is entirely metabolized within 12–24 h (Barkley, DuPaul, & Costello, 1993). Following oral administration of methylphenidate, 78–97% of the dose is excreted in the urine and 1–3% in the feces in the form of metabolites within 48–96 h (Brown & Daly, in press). The time to peak serum concentration in children has been reported to be $\sim 2$ h (range: 0.3–4.4 h) (Brown & Daly, in press). The most common adverse side effects described by patients receiving stimulants include appetite suppression, sleep disturbances, irritability, anxiety, and behavioral rebound.

**Cognitive Effects of Stimulants for ADHD**

Mulhern and Butler (2004) postulate that the common neurocognitive toxicities among children treated for ALL and malignant brain tumors may be grouped into two categories: core symptoms and secondary symptoms. The core symptoms include problems with attention, working memory, and processing speed; the secondary symptoms include difficulties with loss of intellectual functioning, academic failure, problems with peer relationships, and difficulties in employment settings. Recent research has indicated that children who survive ALL and brain tumors may demonstrate impairments including attentional problems, impaired memory functions, and reduced arousal (Riva & Giorgi, 2000). Research also has demonstrated that children surviving ALL differ from their typically developing peers without CNS pathology on measures of cognitive functioning, including attention, intellectual functioning, and social and learning problems (Armstrong, Blumberg, & Toledano, 1999; Moleski, 2000; Ris & Noll, 1994). Given that children and adolescents with ADHD share neurocognitive impairments similar to the core and secondary symptoms experienced by their peers treated for ALL and malignant brain tumors, we turn to a brief review of the literature on the use of stimulant medications for treating children and adolescents diagnosed with ADHD.

**Core Symptoms**

Research has demonstrated that stimulants are effective in the management of cognitive and behavioral symptoms associated with ADHD (e.g., inattention, impulsivity, and overactivity) that occur in multiple settings such as the classroom, home, and in social settings involving peers (Brown & Daly, in press). For example, studies of the cognitive effects of MPH for children diagnosed with ADHD have shown significant improvements in performance on measures of attention (e.g., Test of Everyday Attention for Children) compared to placebos (Hood, Rankin, & Isaacs, 2005). Moreover, research also suggests that stimulants exert a positive effect on laboratory measures of specific cognitive tasks such as indices of executive function, including vigilance, reaction time, short-term memory, and learning of verbal and nonverbal material (Brown & Daly, in press; Brown & Sammons, 2002; Brown & Sawyer, 1998; Rapport & Kelly, 1991). Barnett et al. (2001) reported deficits in executive functions related to spatial working memory for unmedicated children with ADHD, but did not provide evidence for similar deficits in children who were receiving stimulants. These data are particularly important as executive functioning of children surviving cancer is one of the primary areas affected due to neurotoxicity associated with cancer treatment (Mulhern & Butler, 2004). Stimulants also have been demonstrated to improve specific laboratory measures of attention and distractibility, inhibitory control, and perceptual-motor function (Brown & Daly, in press). Further evidence of improved working memory and attentional-set shifting was found in a study of 14 boys who met criteria for ADHD and received a relatively low dose of MPH (0.5 mg/kg) (Mehta, Goodyer, & Sahakian, 2004).

Amphetamines, another type of stimulant medication for children with ADHD, have been demonstrated to be effective on tasks of memory consolidation and long-term retention when administered after a learning session (Soetens, Casaer, D’Hooge, & Hueting, 1995). Additional studies have reported increases in overall speed and accuracy on choice reaction time and target-detection tasks as a function of amphetamines (Denney & Rapport, 2001; Douglas, 1999; Klorman, Brumaghim, Fitzpatrick, & Borgstedt, 1991). Moreover, children who have received amphetamines have been found to demonstrate enhanced performance on measures of sustained attention, attentional allocation, as well as the speed and organization of the motor response processes and motor inhibitory control (Konrad, Gunther, Hanisch, & Herpertz-Dahlmann, 2004).

**Secondary Symptoms**

There is a preponderance of research data to demonstrate that children with ADHD suffer from significant functional impairments, the most pervasive of which are academic impairments (Brown & Daly, in press). Researchers have long been perplexed by the fact that although the stimulants improve short-term gains in
academic efficiency and productivity (Carlson, Pelham, Milich, & Dixon, 1992; DuPaul & Rapport, 1993), the long-term efficacy of the stimulants on academic achievement has yet to be demonstrated (Bennett, Brown, Craver, & Anderson, 1999; Jadad et al., 1999; McCormick, 2003). Other studies have provided data to suggest that the stimulants increase compliance with academic demands in the classroom setting (Benedetto-Nasho & Tannock, 1999; Jacobvitz, Sroufe, Stewart, & Leffert, 1990), and improve reading and arithmetical problem-solving (Pelham & Hoza, 1987).

Few researchers have studied the effects of stimulants on children with specific learning disabilities. However, results from studies in this area indicate that there is no compelling evidence to suggest that stimulants improve basic learning disabilities (Alto & Frankenberger, 1994; Barkley & Cunningham, 1978; Weber, Frankenberger, & Heilman, 1992). Moreover, the literature suggests that there is little or no improvement for children with reading disorders who are treated with stimulant medication (Aman & Werry, 1982; Ballinger, Varley, & Nolen, 1984; Cooter, 1988; Gittleman, Klein, & Feingold, 1983).

Social skills deficits are common among both childhood survivors of leukemia and brain tumors as well as children and adolescents with ADHD (Mulhern et al., 2004; Nangle & Erdley, 2001). Studies that have investigated the use of stimulants in ameliorating social problems for children and adolescents with ADHD have generally indicated that stimulants improve social interactions (Wilens & Spencer, 2000), communication and responsiveness (Hinshaw, Heller, & McHale, 1992), and peer relationships (Brown & Sawyer, 1998). Stimulant treatment also has been shown to reduce negative social behaviors (Gadow, Nolan, Sprafkin, & Sverd, 1995; Gillberg et al., 1997; Hinshaw, Henker, Whalen, Erhardt, & Dunnington, 1989; Klein & Abikoff, 1997; Whalen et al., 1987) and enhance peer appraisal of children with ADHD (Whalen, Henker, Hinshaw, & Granger, 1989). Overall, the evidence indicates that although stimulants often are associated with improved social functioning, they rarely normalize the behavior of ADHD children to that of their typically developing peers (Hoza et al., 2005; Pfiffner, Calzada, & McBurnett, 2000).

Although it is not yet known regarding the specific mechanisms of action of the stimulants for survivors of childhood cancer, for healthy children, the stimulants exert their beneficial effects on the core symptoms exhibited by these children including impairments in attention, impulsivity and for some children overactivity (for review see, Brown & Daly, in press). In general, the stimulants have a poorer track record with the functional behaviors of these children that include academic achievement and peer relationships (Brown & Daly, in press).

Research on Stimulants and Childhood Cancer

Early studies that evaluated the efficacy of stimulants on neurocognitive late effects associated with childhood cancer are of the case study variety (DeLong, Friedman, Friedman, Gustafson, & Oakes, 1992; Torres et al., 1996). More recent studies of stimulant medication for survivors of malignant brain tumors or acute lymphoblastic leukemia are randomized controlled clinical trials (Mulhern et al., 2004; Thompson et al., 2001). The main findings from the case studies are equivocal, with one study reporting no benefit of stimulant medication for learning (Torres et al., 1996), while the other study indicated that the majority of enrolled children demonstrated a favorable response to treatment with stimulant medication (DeLong et al., 1992). Evidence from the randomized controlled trials is more consistent, with both trials reporting improvements in attention skills (Mulhern et al., 2004; Thompson et al., 2001). A detailed discussion of these studies and their findings are examined in the next section and also are displayed in Table I.

Case Studies

Two preliminary investigations were among the first to examine the effect of stimulant drug treatment for youth with cancer treatment-related learning problems. Torres et al. (1996) investigated six subjects, aged 6–20 years, who had received radiation therapy 3–12 years earlier for malignant brain tumors. Initial testing indicated that all subjects had mild attentional problems with four subjects also demonstrating mild impairments in immediate and delayed memory. The subjects received a maintenance dose of 0.3 mg/kg of MPH. Outcome measures included the Rey Auditory Verbal Learning (RAVL; an instrument that evaluates the ability to learn word lists; Rey, 1964), Symbol digit modalities (SDMT, an attentional measure that also taps executive functions; Smith, 1973), Trail-making parts A–B (a measure of mental processing speed; Reitan & Wolfson, 1993), and the Conner’s Continuous Performance Test (CPT, a measure of sustained attention; Conners, 1995). Although findings revealed no significant immediate or delayed benefits associated with MPH treatment for attention or memory measures, the data
must be interpreted judiciously given the small sample size. The second preliminary study included 12 children who survived malignant brain tumors or ALL and were treated with an unspecified dose of MPH for 6 months to 6 years (median period of treatment = 23 months) (DeLong et al., 1992). Results revealed that, as rated by parents and teachers, eight children had a “good” response, two had a “fair” response, and two had a “poor” response. Children who received the most intensive radiation therapy (24 Gy) and the most intensive chemotherapy (e.g., MTX) demonstrated a poorer response to MPH compared to children who received less intensive radiation therapy and chemotherapy. In addition, children with supratentorial neoplasms did not respond as well to treatment with MPH. These findings are important as they indicate that for children who suffer from severe neural tissue damage caused by either the illness or its associated treatment, the stimulants (e.g., MPH) may be less efficacious.

Controlled Trials

Thompson et al. (2001) conducted the first randomized, double-blind, controlled clinical trial of children receiving MPH compared to those receiving placebo. All of the study participants were childhood survivors of ALL compared to those receiving placebo. All of the study participants were childhood survivors of ALL and malignancy brain tumors. Participants qualified for the study on the basis of significant delays in academic achievement and problems with sustained attention. Of the children who were screened, 22 met eligibility criteria and were randomized to receive placebo or MPH (0.3 mg/kg to maximum of 20 mg). Outcome measures included the Wechsler Intelligence Scale for Children-III (WISC-III, an abbreviated measure of intelligence; Psychological Corporation, 1992), the California Verbal Learning Test–Children’s (CVLT-C, an instrument assessing short-term and long-term memory via recall and recognition tasks; Delis, Kramer, Kaplan, & Ober, 1994), and the Woodcock–Johnson Cognitive Battery (Woodcock & Johnson, 1989). Findings revealed that the group receiving MPH demonstrated significantly greater improvement in the composite index of the CPT (0.77) compared to placebo (0.27). MPH was more effective than placebo on measures of sustained attention and the composite index on the Connor’s Continuous Performance Test, but not for errors of commission or reaction times. MPH more effective than placebo for parental and teacher report of attention skills. MPH more effective than placebo for teacher, but not parent, report of social skills. No consistent dose-effects were found for reaction time or errors of commission on the CPT, the overall score on the Woodcock-Johnson Cognitive Battery, or the Visual-Auditory Learning Test on the Woodcock-Johnson Cerebral Functioning Battery. These results indicate that for children who suffer from severe neural tissue damage caused by either the illness or its associated treatment, the stimulants (e.g., MPH) may be less efficacious.

### Table I. Studies of Stimulant Medication for Survivors of Pediatric Cancer (Acute Lymphoblastic Leukemia (ALL) and Malignant Brain Tumors)

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<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>N</th>
<th>Study design</th>
<th>Treatment</th>
<th>Treatment phase</th>
<th>Drug (mg/kg)</th>
<th>Dose</th>
<th>Results</th>
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<tr>
<td>Torres et al.</td>
<td>Malignant BT</td>
<td>6</td>
<td>Case study</td>
<td>Radiation therapy</td>
<td>3–12 years</td>
<td>MPH</td>
<td>0.3</td>
<td>No significant immediate or delayed benefit on learning</td>
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<td>posttreatment</td>
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<tr>
<td>DeLong et al.</td>
<td>Malignant BT or ALL</td>
<td>12</td>
<td>Case study</td>
<td>Radiation therapy &amp; chemotherapy</td>
<td>6 months to 6 years posttreatment</td>
<td>MPH</td>
<td>UNK</td>
<td>Eight children had a “good” response; Two had a “fair” response; Two had a “poor” response. MPH more effective than placebo on measures of sustained attention and the composite index on the Connor’s Continuous Performance Test, but not for errors of commission or reaction times. MPH more effective than placebo for parental and teacher report of attention skills. MPH more effective than placebo for teacher, but not parent, report of social skills. No consistent dose-effects were found for reaction time or errors of commission on the CPT, the overall score on the Woodcock-Johnson Cognitive Battery, or the Visual-Auditory Learning Test on the Woodcock-Johnson Cerebral Functioning Battery. These results indicate that for children who suffer from severe neural tissue damage caused by either the illness or its associated treatment, the stimulants (e.g., MPH) may be less efficacious.</td>
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<tr>
<td>Thompson et al.</td>
<td>Malignant BT or ALL</td>
<td>32</td>
<td>Randomized, double-blind placebo-controlled</td>
<td>Radiation therapy &amp; chemotherapy</td>
<td>&gt;24 months posttreatment</td>
<td>MPH</td>
<td>0.3–0.6 (max)</td>
<td></td>
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<td>(2001)</td>
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<tr>
<td>Mulhern et al.</td>
<td>Malignant BT or ALL</td>
<td>83</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Radiation therapy &amp; chemotherapy</td>
<td>1.1–14.2 years posttreatment</td>
<td>MPH</td>
<td>0.3–0.6 (max)</td>
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<td>(2004)</td>
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BT, brain tumor; ALL, acute lymphoblastic leukemia; MPH, methylphenidate; UNK, unknown.
findings, the investigators conclude that MPH exerts its primary therapeutic effect on capacities associated with attention and concentration in these children rather than on more complex tasks assessing higher order cognitive processes such as working memory, problem-solving, or language processing.

Mulhern and colleagues (2004) extended the investigation of Thompson et al. (2001) by examining the short-term effectiveness of MPH for improving cognitive and social functioning among children surviving ALL and malignant brain tumors. In this investigation, the participants were children (n = 83) identified as having attentional deficits and problems with academic achievement. The primary outcome measures included behavioral ratings completed by parents and teachers on the Conners’ Rating Scales (Conners, 1996) and the Social Skills Rating System (Gresham & Elliot, 1990). The investigators also evaluated how two different doses (i.e., low, 0.3 mg/kg of body weight; and high, 0.6 mg/kg of body weight) of MPH would affect attention and social skills. Findings revealed significant improvement in attention with MPH as reported by parents and teachers on the Conners’ Rating Scales and significant improvement in social competence and academic competence as reported by teachers, but not by parents, on the Social Skills Rating System. Effect sizes based on comparisons that reached statistical significance ranged from small to medium (e.g., .37–.73), with the effect sizes derived from teacher reports being generally higher than those derived from parent report. No differences were found as a function of dose. These findings were interpreted not to support a consistent advantage of moderate-dose MPH over low-dose MPH for the primary endpoints. The investigators conclude that MPH therapy may reduce some attentional and social deficits in the short-term among survivors of childhood ALL and malignant brain tumors.

Conclusions and Future Directions

This article summarizes the extant late-effects literature related to the management of cognitive toxicities with the use of stimulant medication. Findings from this review reveal that there is a dearth of studies available to guide the clinical safety and efficacy of the management of cognitive toxicities with the use of stimulant medication.

The field of psychopharmacology of late-effect cognitive toxicities associated with childhood cancer is in its infancy. The stimulants show promise in managing the target symptoms associated with attention and concentration that are frequently encountered among cancer survivors during the late-effects period. Specifically, data from clinical studies, as well as controlled clinical trials, suggest that the stimulants enhance attention at home and at school. Further, there are some preliminary data to suggest that the stimulants enhance attention and concentration for cancer survivors (e.g., children and adolescents with ALL and brain tumors) in the laboratory setting. As a group, the adverse effects associated with these agents are not dissimilar from those of their healthy peers with ADHD (e.g., irritability, anxiety, sleep and appetite disturbances, and behavioral rebound). However, Conklin et al. (unpublished manuscript) have cautioned that the adverse effects associated with the stimulants may be more severe for survivors who have sustained more neurological impairments either from the cancer (e.g., brain tumors) or from the treatment for cancer (e.g., chemotheraphy, radiation therapy, or the combination of both) that are generally manifested in survivors by lower intelligence test scores. Finally, Conklin et al. suggest that the effects of the stimulants on a putative task of attention and concentration may not be as robust as has been noted in those studies reviewed for this article.

Although the preliminary data pertaining to the use of stimulants and cancer survivors suggests some promise, important empirical questions remain. First, although more studies on the acute efficacy of the stimulants are warranted, there are no data with regard to the long-term efficacy and, more importantly, safety with the use of stimulant medications. More knowledge is needed with regard to the use of the stimulants over a period of months or even years and how these agents affect important variables (e.g., growth and cardiac outcome). To address these important research questions, we will need to compare efficacy and safety of various doses of the stimulants as well as examine delivery systems of the different types of available stimulants (e.g., long-acting versus short-acting) across several domains, including variables related to both safety and efficacy. Finally, the comparison of the stimulants (including MPH and dextroamphetamine) across dependent measures is an important area of research for the next decade.

Another important area of inquiry is the integration of therapeutic techniques (e.g., cognitive rehabilitation and stimulant medication) and whether lower doses of stimulants may be employed when combining stimulant medication with empirically supported interventions (e.g., cognitive remediation, rehabilitation, behavior therapy). It is also important to examine the comparative
efficacy of the use of stimulants to nonsomatic interventions as well as the combination of the stimulants and these intervention approaches (e.g., cognitive remediation) to either approach employed alone in managing cognitive toxicities associated with the late-effects period. Another critical issue that needs to be systematically examined is the notion of treatment sequencing (i.e., whether stimulant medication should precede the use of various cognitive and/or behavioral intervention approaches, or whether such approaches should follow the use of stimulant medication). These questions have emerged as areas of primary importance in the literature of children with ADHD (Brown et al., in press) and remain areas ripe for investigation among survivors of children with cancer.

The stimulants have been meticulously investigated among healthy children with psychopathology and perhaps provide a model in which to empirically validate any type of treatment be it medical or psychological. The research exemplifies the highest standard of evidence-based medicine in the reduction of symptoms associated among children with attentional problems. Clearly additional research is needed prior to making definitive conclusions about the safety and efficacy for children having survived cancer. One cannot be certain that the stimulants will demonstrate a similar safety profile for children with cancer as they do for children who are healthy and much more research is needed. Nonetheless, if the practitioner elects to enroll childhood survivors of cancer in a controlled clinical trial of stimulants, caution should be the standard, together with ongoing meticulous monitoring regarding adverse effects.

Finally, meticulous study of the stimulants among childhood cancer survivors during the late-effects period will, we hope, provide a model for the study of other pharmacologic and psychotropic agents for childhood cancer survivors. One possibility is that these agents may be used to target specific cognitive toxicities, including impairments in memory and academic achievement, both of which are pervasive among survivors during the late-effects period. Over the past decade there have been compelling achievements in the neural sciences and a concomitant proliferation of psychotropic agents now being employed among healthy children and adolescents. These agents are frequently used “off label” where they are not yet approved for use in children and adolescents by the Food and Drug Administration. Thus, careful research must parallel the exciting developments in the neural sciences, especially among children and adolescents. It is hoped that this article will inspire such research efforts in the future.

The review presented here raises several issues that are of interest to practicing pediatric psychologists as well as those who are involved in research endeavors in this important programmatic area of research. First, given that survival rates of pediatric cancer are increasing over time and that the presence of late effects are not apt to dissipate with the sustained use of chemotherapy and radiation therapy, many pediatric psychologists will be faced with issues pertaining to the management of these late effects at increasing rates. Late effects clinics are now an important part of pediatric cancer clinics and the care for these youth and young adults is an ever increasing responsibility of pediatric psychologists. Thus, treatment development and the evidence-base of these treatments will also assume an increasing responsibility of pediatric psychologists, particularly those who are employed in tertiary care facilities and major cancer centers that are charged with important research activities related to treatment. Given the preponderance of attentional problems among children with chronic diseases including those with cancer during the late effects period as well as those with sickle cell disease (for review see, Brown, Mulhern & Simonian, 2002), it will be important to develop approaches to ameliorate the attentional problems characteristic of these youth. Thus, it is likely that pediatric psychologists will be charged with the responsibility of conducting controlled clinical trials to evaluate both the efficacy as well as the safety of various treatments including cognitive remediation approaches and psychopharmacology. Given the expertise of psychologists in assessment and research design, there is a natural affinity between the research training of practicing psychologists and the evaluation of psychopharmacological approaches for survivors of childhood cancer during the late effects period. Clearly, there promises to be major challenges in the conduct of this research including the ascertainment of an appropriate sample size of cancer survivors for the purpose of assessing the efficacy and safety of these various intervention approaches. The use of multi-site clinical trials will be of increasing importance in conducting this type of research. Pediatric psychologists’ participation in consortium groups including the Children’s Oncology Group (COG) will likely assume even greater importance over the next several years in an effort to conduct controlled clinical trials with samples that will provide adequate power to address the myriad of questions that we will have with regard to the safety and efficacy of these various pharmacotherapies and psychotherapies (Armstrong, Reaman; & Children’s Oncology Group, 2005).
While the stimulants do show some particular promise in the management of attentional problems among survivors of childhood cancer at present, other important issues also remain. These include the willingness of caregivers to allow their children and adolescents to participate in this type of research given the fact that these survivors have been involved in numerous studies previously and the potential risk of the stimulants in the long-term. While acute trials may address some of these issues, clearly longitudinal research is needed and some caregivers may be reluctant to participate in clinical trials given the potential trauma associated with the cancer clinic (Stuber, 2006) and the commitment that longitudinal research would require of participants and their families. Still, others in the face of learning problems at school and difficulties in a world requiring increasing capacity for sustained attention and concentration may be quite eager for these new and innovative treatments only to potentially find problems with these agents and possible safety concerns. Clearly, while any novel therapies offer the hope for enhanced quality of life during the late effects period, they also pose potential risks that will need to be carefully assessed. Given these issues, pediatric psychologists will be key providers on the late effects service both in the assessment of individual response to treatment as well as in the design of clinical trials and the selection of measurement approaches to evaluate both safety and efficacy of these treatments.

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References


intradural chemotherapy for leukemia: Enhanced data analysis using an effect size model. *Archives of Neurology, 55*, 1561–1568.


