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Psychotropic Medication Use in the Pediatric Cancer Population

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UNIVERSITY OF MIAMI

PSYCHOTROPIC MEDICATION USE IN THE PEDIATRIC CANCER
POPULATION

By

Mary Whitney Ward

A DISSERTATION

Submitted to the Faculty
of the University of Miami
in partial fulfillment of the requirements for
the degree of Doctor of Philosophy

Coral Gables, Florida

December 2010

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Psychotropic medications commonly used with children have been associated with side effects significant enough to warrant warnings from the Food and Drug Administration. The risks of these side effects are potentially increased in children who are long-term survivors of childhood cancer because of damage to the heart and central nervous system (CNS) due to chemotherapy and radiation therapy. There are few empirical studies addressing whether children treated for cancer have greater exposure to psychotropic medications than the general population, the reasons for use of psychotropic medications in cancer survivors, or whether risks associated with cancer treatment are considered when psychotropic medications are used. The specific aims of this study were: (1) to examine the prevalence of psychotropic medication use among children treated for cancer, (2) to obtain descriptive data regarding variables associated with medication usage, and (3) to develop a model to predict which children are likely to be prescribed psychotropic medication. A cross-sectional sample of 69 children, ages two to 17 years, who were undergoing treatment or had successfully completed treatment for leukemia/lymphoma, central nervous system (CNS) tumors, or other non-CNS related cancers were recruited. Caregivers completed measures of psychosocial functioning, medication use, and developmental history. Medical history was also obtained. Results indicated that 15% of subjects were taking psychotropic medication, specifically

stimulants and antidepressants. The Classification and Regression Trees (CART) algorithm was used to develop a predictive model. Results indicated gender, age, and presence of school difficulty explained a total of 46% of the variance in psychotropic medication use in the pediatric cancer population; children treated for cancer who were male, age 10 or older and had reported school difficulty were more likely to be prescribed psychotropic medication. No cancer variables were found to influence psychotropic medication use. Several limitations likely influenced results including limited sample size, inclusion of multiple diseases in the non-CNS involved solid tumor diagnosis group, and recruitment limited to three sites. Results indicate a need for continuous examination of psychotropic medication use and possible side effects in the childhood cancer population.

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Chapter 1: Introduction

More than 70% of the nearly 12,500 children diagnosed with cancer annually in the United States will successfully complete treatment and be considered long-term survivors with no disease recurrence (SEER cancer incidence rates, 2007) (see Appendix A). For many, once treatment is completed late effects of the cancer and its treatment begin to emerge. The emergence of some late effects, such as neurocognitive deficits, has been well identified (Armstrong et al, 2010). Deficits in processing speed, attention and concentration have been consistently observed in the pediatric cancer population (Reddick et al., 2006; Butler & Mulhern, 2005; Moore, 2005; Moore, Copeland, Ried and Kopecky, 1992). A variety of factors, specifically type of treatment and age at time of treatment, contribute to the neurocognitive consequences. Neurocognitive deficits are similar for children who have been treated for acute lymphoblastic leukemia (ALL), non-Hodgkins lymphomas, and malignant brain tumors. This is especially true for those children treated with cranial radiation therapy (CRT) and/or intrathecal chemotherapy (Butler & Mulhern, 2005). In children with brain tumors, high risk ALL with the potential of metastasis to the brain, or lymphomas with potential for metastasis, the brain is a primary target for therapy.

Cranial radiation therapy (CRT) is commonly used when treating central nervous system (CNS) tumors and CNS-involved ALL. The majority of children with brain tumors (i.e., medulloblastoma, ependymoma, high grade astrocytoma and high grade gliomas) often receive CRT following surgical resection, with dose exposure reaching 5000-6000 cGy. Children with high-risk ALL involving CNS disease also often receive CRT, but at lower doses (usually <2400 cGy) (Armstrong et al, 2010). Higher doses of

CRT have been associated with more severe neurocognitive dysfunction (Mulhern et al, 1998); however doses as low as 1800 cGy have also been associated with neurocognitive deficits (Armstrong, 2010). Recent neuroimaging studies have shown that white matter in the frontal cortex slows in development following CRT (Reddick et al., 2005; Reddick et al., 2006).

Chemotherapy is also associated with changes in brain development and neurocognitive impairment (Armstrong et al, 2010). Methotrexate is a commonly used chemotherapy agent and it is highly effective in the treatment of ALL. It is administered intrathecally (injected directly into the spinal fluid), intravenously, or taken orally. Intrathecal methotrexate has been associated with structural and functional CNS changes, as well as neurocognitive declines (Butler and Mulhern, 2005). The dosing of systemic methotrexate used in treatment has gradually increased over the past 20 years (i.e., from 1 gm/m² to 5gm/m² depending on the treatment protocol). Dosing increases have led to a greater incidence of neurocognitive late effects and changes seen on neuroimaging and biochemistry (Armstrong et al, 2010; Cole et al., 2009).

Although significant concerns about psychological adjustment have been suggested, the bulk of research, both acute and long term, suggests that children treated for cancer do not differ, as a group, from the general population with regard to psychological functioning. This has been consistently supported for most cancer diagnoses with the exception of children with central nervous system disease and complications (i.e., brain tumors) (Patenaude & Kupst, 2005; Zebrack & Zeltzer, 2003; Lavigne & Faier-Routman, 1992; Gray et al., 1992; Cella & Tross, 1986) (Appendix C).

Despite the fact that few studies have reported significant psychological and behavioral disturbances in childhood cancer survivors, an ongoing, prospective intervention trial for cognitive late effects being conducted at the University of Miami has found an unusually high frequency of characteristics of autism spectrum disorder (ASD) among children who have been treated for leukemia (ALL). Specifically, results have demonstrated seven of 44 (16%) children treated for ALL displayed characteristics of ASD, while this was observed in only one of the children treated for brain tumors (Goldman et al., 2008). This finding and anecdotal reports across the country of sudden onset pervasive developmental disorders (PDD) may be the result of newer treatments (see Appendix E).

Over the last decade, efforts have intensified to identify effective methods of treating the late effects associated with childhood cancer treatment. One method of treatment for these late effects currently being pursued is the use of psychotropic medications, specifically antidepressants, stimulants, and antipsychotics (Daly & Brown, 2007; Pao et al., 2006).

The use of these medications with childhood cancer survivors raises concerns, particularly since childhood cancer survivors may be at an elevated risk for adverse side effects that have been identified for children in the general, non-cancer, population. Recently, the Food and Drug Administration (FDA) has released several “black box warnings” regarding use of stimulants, anti-depressants, and anti-seizure medications in the general child population. Antidepressants have been linked to increased suicidal ideation for children and adolescents, and there is evidence linking stimulant medication with sudden cardiac death (FDA, Public Health Advisory) (see Appendix D).

These risk factors in the general population may be exacerbated in childhood cancer survivors due to known risks of heart and CNS damage following successful cancer treatment (Armstrong et al., 2010). Because of these risks, use of psychotropic medications in children with late effects of cancer treatment may introduce a variety of pharmacologic challenges. Cancer and its treatment sometimes result in permanent alterations in CNS structure, vasculature, metabolism, and neurochemical functioning (see Appendix D). These CNS changes may lead to increased sensitivity to the effects of psychotropic medications, as well as increased risk for the serious side effects identified for children without cancer in the general population. Toxic agents may also increase sensitivity to a variety of other prescribed and over-the-counter medications or cause damage to the heart, placing the cancer population at greater risk for FDA-identified concerns regarding psychotropic medication use (Kalash, 1998).

Despite concerns about serious side effects of psychotropic medications, there are indications that they may be frequently prescribed and used in children treated for cancer for the treatment of late effects and acute adjustment during treatment. Portteus et al. (2006) examined the use of antidepressants in children diagnosed with cancer and found ten percent of children treated for cancer were prescribed antidepressant medication within one year of being diagnosed with cancer. The prevalence of antidepressant use in adolescents being treated for cancer was 23%, and 7% in younger children. Both rates are significantly higher than existing data for same-aged non-cancer controls (Portteus et al., 2006).

Pao et al. (2006) examined medical records of pediatric patients who had been enrolled in clinical research trials conducted by the Pediatric Oncology Branch of the

National Cancer Institute between 2000 and 2003 in an effort to determine rates of psychotropic medication use among children diagnosed with cancer. The overall rate of psychotropic use was determined to be 14% among these children, with anticonvulsants (37%) and antidepressants (35%) being the most common psychotropic medications prescribed (Pao et al., 2006).

Preliminary findings of a prospective intervention trial at the University of Miami identified that 14 of 65 (21.5%) children two to five years post-diagnosis, treated for ALL or a brain tumor had been prescribed a psychotropic medication. The majority of these children were taking stimulant medication; however, other psychotropic medications included antidepressants and antipsychotics (i.e., paroxetine, risperidone, and olanzapine) (Ward et al., 2008) (see Appendix D).

Statement of the problem and study hypothesis

Children who are receiving active treatment for cancer may experience a variety of psychosocial challenges during treatment, and childhood cancer survivors whose treatment involved the CNS are more likely to experience difficulty with psychosocial adjustment (Kazak, 2005; Madan-Swain et al., 1994). In addition, it is well documented that children who have been treated for cancers involving the CNS often experience neurocognitive deficits that emerge over time. Taken together, these children may have a greater need for psychotropic medication, particularly in light of the structural, neurodevelopmental, neurochemical, neuroendocrine, and metabolic alterations that may occur as a result of the cancer and its treatment. These alterations, called late neurocognitive effects of treatment, may also affect how the developing brain responds to psychotropic medications in ways that are not yet known (see Appendix D). To date,

only two existing reports have described psychotropic medication use in the pediatric cancer population; however, there are several limitations to these studies (Pao et al., 2006; Portteus et al., 2006). Both studies analyzed medication use during cancer treatment or within one year of diagnosis only. In addition, one of these studies analyzed antidepressant use only (Pao et al., 2006; Portteus et al., 2006). Evaluating psychotropic medication use in this population in greater depth is a clinically relevant direction for cancer research. Additionally, with the FDA's warning about newly-observed increased suicide ideation in children using some antidepressants, this topic is even more relevant and suggests a greater need for early intervention. The use of psychotropic medication in the pediatric cancer population warrants specific attention as these children may have additional chronic medical complications (i.e., CNS damage and cardiomyopathy) that may place them at greater risk of side effects of psychotropic medication use.

Since treatment for CNS tumors usually involves CRT in doses above 2400 cGy, and since CRT has been most consistently linked to deficits in attention, concentration, and processing speed, as well as difficulties with psychosocial adjustment, this group is most likely to experience problems that may require treatment with stimulants or antidepressants. Children treated for ALL are also at risk for neurocognitive difficulties, but not as predictably as children who receive CRT. These children may also experience difficulties that may require psychotropic medication but to a lesser extent than children treated for CNS tumors. Children treated for cancers not involving the CNS have not been found to be at risk for either neurocognitive or psychological difficulties, so their likelihood of treatment using psychotropic medications is considered less than children with either CNS tumors or ALL.

This study was designed to investigate whether (a) children treated for cancer were likely to be treated with psychotropic medications, (b) there were differences in psychotropic medication use between children treated for CNS tumors, ALL, or non-CNS cancers, (c) psychotropic medications were prescribed for children who have elevated FDA-identified risks because of their treatment, and (d) whether other factors, such as school problems, age, or gender contributed to psychotropic medication prescription and/or use. The answers to these questions will provide a more comprehensive understanding about the prevalence of psychotropic medication use in this population and the possible relationship between cancer treatment protocols and medication use. Most importantly, it will offer guidance about use of these medications in a higher-risk population and inform clinicians and investigators in their continued pursuit to find ways to intervene or prevent neurocognitive late effects.

The three specific study aims were as follows:

Study Aim 1: To analyze subgroup differences in the prevalence of psychotropic medication use among children treated for leukemia/lymphoma, CNS tumors, and non-CNS related cancers in a sample of children treated in pediatric oncology centers in Florida.

Hypothesis 1: It was hypothesized that the use of psychotropic medication would be significantly higher in subgroups of patients treated for CNS tumors and leukemias versus patients treated for solid, non-CNS related tumors. Treatment for CNS tumors and leukemia is known to adversely affect the CNS, often resulting in neurocognitive deficits and psychological maladjustment in a selected subgroup (i.e., patients with CNS tumors).

Use of psychotropic medication both within and across diagnoses was expected to vary by class of drug and treatment protocol. Specific hypotheses follow.

Stimulant Hypothesis: Treatment of CNS tumors involving cranial radiation therapy may place children at an increased risk for developing problems with attention and concentration (Butler & Mulhern, 2005; Moore, 2005). Therefore, it was hypothesized that children treated for brain tumors with cranial radiation will be more frequently prescribed stimulant medication for late effects than those children with ALL/lymphomas and non-CNS related solid tumors.

Intrathecal methotrexate, alone or in combination with hydrocortisone and cytarabine, and systemic high dose methotrexate are also associated with deficits in attention and concentration. These deficits are observed less frequently in children treated for ALL than in children treated for CNS tumors with cranial radiation, but are identified in a substantial subset of children with ALL (Armstrong et al., 2010; Butler & Mulhern, 2005). Children diagnosed with ALL should therefore have a lower frequency of stimulant medication usage compared to those children diagnosed with brain tumors; however a higher frequency of stimulant medication use should be observed in this group (i.e., the ALL group) than in the group of children diagnosed with non-CNS tumors,

Neither cranial radiation nor intrathecal methotrexate is used in the treatment of most non-CNS related solid tumors; therefore, children with solid tumors should have the lowest rate of stimulant medication use of the cancer groups.

Antidepressant Hypothesis: Depression in childhood cancer survivors could be related to the biological mechanisms associated with varying types of cancer and treatment. Change in neurochemistry, specifically dopamine and serotonin disruption,

have been indicated following treatment with chemotherapy and/or cranial radiation therapy. Stress associated with more intense CNS treatment (e.g., that involving cranial radiation therapy) may place certain children at increased risk for depression during treatment (Portteus et al., 2006). It was, therefore, hypothesized that antidepressant use would be highest in children diagnosed with CNS tumors. It was also hypothesized that the ALL disease group would have a lower frequency of antidepressant use than the CNS tumor group; however it would be higher than the frequency of use in the non-CNS, solid tumor group.

Antipsychotic Hypothesis: As discussed in Appendix E, a subgroup of children treated for ALL seem to exhibit symptoms consistent with Pervasive Developmental Disorder (PDD). As a result of this finding and the behaviors sometimes associated with PDD (e.g., aggression), survivors of ALL were hypothesized to be more likely to be treated with antipsychotics than other cancer groups.

Study Aim 2: To obtain descriptive data regarding critical variables related to how psychotropic medication decisions are made (e.g., who is the prescribing physician), to determine what level of risk is assigned to cancer treatment exposure, and to identify gender and/or ethnicity differences. To date no studies have examined these variables. The goal of this study aim was simply exploratory; therefore, no hypotheses were developed.

Study Aim 3: To develop a model which may help predict which children are likely to be prescribed psychotropic medication, in order to eventually assist in prevention and/or early intervention.

Hypothesis 2: Findings of the previous study aim guided the development of this model. Based on late effects research, the neurodevelopmental model, and clinical observation, it was hypothesized that treatment method, diagnosis, and age at time of diagnosis would all be critical variables associated with psychotropic medication use.

Chapter 2: Method

Participants

Participants enrolled were 69 children treated for one of three categories of childhood cancer: (1) leukemia/lymphoma whose treatment included triple intrathecal chemotherapy for CNS prophylaxis (methotrexate, hydrocortisone, and cytarabine), corticosteroids (prednisone or dexamethasone), and/or high dose systemic methotrexate (2) a solid tumor of the CNS with treatment involving cranial radiation and/or chemotherapy (cyclophosphamide, vincristine, cisplatin/carboplatin), and (3) other cancers (in which the CNS was unaffected) who received radiation and/or chemotherapy that did not target the CNS. All participants were undergoing treatment or had previously been treated for their cancer at one of the member institutions of the Florida Association of Pediatric Tumor Programs, Inc. (FAPTP).

Measures

Behavior Assessment System for Children, Second Edition (BASC-2).

The BASC-2 is a multidimensional approach to evaluating the behavior and perceptions of children ages 2 to 21 years. The BASC-2 Parent Rating Scale (PRS) measures both a child's adaptive and problem behaviors in the community and home setting. Parents can complete forms at three age levels, specifically preschool (ages 2 to 5), child (ages 6 to 11), and adolescent (ages 12 to 21). A Spanish form is also available. The BASC-2 PRS was standardized on 4,800 persons representative of the general population across the United States, as well as on a clinical sample. Both the PRS composite scores and individual scales all show high internal reliability (median coefficient alpha reliabilities range from .80 to .86). The BASC-PRS has been correlated

with the Achenbach System of Empirically based Assessment (ASEBA) Child Behavior Checklist, the Conners' Parent Rating Scale-Revised (CPRS-R), the Behavior Rating Inventory of Executive Functioning (BRIEF), and the original BASC Parent Rating Scale. High correlations were obtained between the BASC and the Child Behavior Checklist. Correlations between the BASC and specific scales of the CPRS-R are moderately to highly correlated, except for the correlation between anxiety scales which is .41 in the child sample and .35 in the adolescent sample. Overall, moderate to high correlations were found to exist between the BASC-PRS and the BRIEF. Lastly, correlations between the corresponding BASC and BASC-2 scales were extremely high. Reliability coefficients of the BASC-2 Spanish forms varied from those obtained with the English forms. The median internal reliabilities for the PRS scales are adequate, however lower than those obtained in the English-form samples (Median reliability coefficients are .71(preschool), .74(child), and .73 (adolescent)). Composite scale reliabilities are moderate to high (Reynolds & Kamphaus, 2004).

Medication Use and Neuropsychological Assessment Questionnaire.

This form was developed specifically for use in this study. It consists of 31 items addressing issues related to medication use, psychological diagnoses, medication prescribing, side effects, and family history (see Appendix F). Items included in this form were determined based on clinical experience and a review of the childhood cancer literature. Parents can complete this form for a child of any age included in the study.

Medical Treatment Summary.

The medical staff at each pediatric center also completed a brief form that included information about the child's specific diagnosis and treatment protocol (See

appendix G). Specifically, it included checklists of possible chemotherapy agents used in treatment, dosing of CRT, and whether treatment required a bone marrow transplant (BMT) and possible related complications. It also included a list of psychotropic medications; the medical staff was asked to indicate which, if any, of these medications had been prescribed for the child. Forms completed by the medical staff also provided information regarding any medical condition (e.g., cardiomyopathy) that might place these children at an increased risk for negative side effects/outcomes as identified by the Food and Drug Administration. This form was developed specifically for use in this study.

Design and Procedures

Participants recruited were a cross-sectional sample of children, ages two to 17 years, who were undergoing treatment or who had successfully completed treatment for (1) leukemia/lymphoma (blood cancers), (2) a CNS tumor, or (3) other non-CNS related cancers. Eligibility required that all children received radiation therapy, chemotherapy, or both.

Participants were recruited at member institutions of the Florida Association of Pediatric Tumor Programs, Inc. (FAPTP) who agreed to be part of the study. Using support from the Sylvester Comprehensive Cancer Center and the Micah Batchelor Award for Excellence in Child Health Research, the University of Miami has worked with the Florida childhood cancer programs to establish a statewide research network for childhood cancer survivorship collaborative research. The protocol for this study was implemented in collaboration with several FAPTP member institutions, specifically All Children's Hospital in St. Petersburg and Nemours Children's Clinic in Jacksonville.

Each of the participating FAPTP institutions was assisted in identifying a staff member who was trained to determine eligibility and responsible for recruitment at their cancer center. Several avenues for recruitment were pursued. The goal of recruiting was to obtain a sample that was as heterogeneous as possible; therefore, the populations targeted for data collection varied. Recruitment took place at each pediatric oncology center according to the guidelines and recommendations set forth by the institution's IRB. Parents were recruited while at their children's routine appointments at the pediatric oncology clinic and asked to complete questionnaires/forms at this appointment. For those children who had completed treatment and therefore attended clinic less frequently, recruitment involved contacting parents via the internet or postal system. Approximately 850 letters were sent to all children who had been treated for cancer at the Holtz Children's Hospital at the UM/Jackson Memorial Medical Center. Parents were sent a study flyer and a letter from the director of hematology/oncology at the hospital explaining his support of the study. Contact information was provided if parents were interested in participating. All clinical patients (N=62) of Dr. Daniel Armstrong at the Mailman Center for Child Development, who were appropriate for the study, were also sent e-mails or letters by postal mail, of which 17 were returned undelivered. Parents were notified about the study and asked to participate. Of those patients contacted, approximately half participated in the study. Greater than 50% of the long-term follow-up patients who would have been appropriate for the study were over the age of 18 and were no longer eligible for participation. At the University of Miami participants were also recruited based on their participation in one other existing study evaluating cognitive functioning in children with cancer, and from children who were referred for clinical

neuropsychological evaluations. When children were brought to the Holtz Children's Hospital at the UM/Jackson Memorial Medical Center to be evaluated, parents and children were approached about also participating in this study. No compensation was given to families for participation.

The trained staff member at each FAPTP center obtained informed parental consent and child assent when applicable (children above a specific age, as designated by the IRB). The caregiver was then asked to complete the BASC-2 (specific to the child's age) and a medication use form (developed for the study). These forms took approximately 30 minutes for the parent to complete.

The staff member at each FAPTP center was also responsible for completing the medical form regarding the child's treatment protocol and medical history. Medical forms were completed based on information obtained from the child's medical records. Data was sent via mail to the research site, where the measures were scored and entered into the database.

IRB Study Review and Approval.

Regulatory documents required by the Institutional Review Board (IRB) at the University of Miami Miller School of Medicine were developed, submitted, and approved. Approval was also obtained at each FAPTP center's research review board.

Training.

A Manual of Operations (MOO) was developed for standardization of project procedures. The identification and recruitment of a cooperating staff member at each FAPTP center in the state was completed. Training of the staff members was done at each cancer center by an investigator at the University of Miami Miller School of Medicine.

As part of the training, the MOO was provided outlining explicit instruction and information regarding the project procedures and staff member responsibilities (i.e., obtain informed consent/child assent, provide the BASC-2, developmental history forms, and medical forms).

Training of the research team on all measures of the study (i.e., BASC-2) was also completed as needed. All forms and questionnaires were designed to be completed independently; therefore training of the staff on the measures required minimal time. In the event that a parent was unable to read the forms, the identified medical staff member was instructed to read each item to the parent and allow the parent to determine the answer independently.

Standardized Suicidality Procedure.

As part of the training mentioned above, specific emphasis was placed on suicidal concerns. Each identified staff member was trained to review completed BASC-2 forms prior to the family's departure from the clinic and to identify if the specific items targeting suicidal thoughts and behaviors were positively endorsed on the BASC-2. If a parent endorsed that his/her child reported wanting to hurt himself/herself and/or if the specific items on the BASC-2 indicating suicidal ideation were positively endorsed, the staff member contacted an on-site social worker/psychologist prior to the departure of the family from the clinic. This contact person was pre-identified at each site and assessed any risk and follow-up with the family and child in a manner consistent with the individual center's standard procedures. Five subjects across sites endorsed suicidal ideation on the BASC-2, requiring a risk assessment. All risk assessments led to referrals for clinical intervention.

Data Analysis Plan

To test the study hypotheses, several statistical analyses were performed.

Study Aim 1: *To analyze subgroup differences in the prevalence of psychotropic medication use among children treated for leukemia/lymphoma, CNS tumors, and non-CNS related cancers in a large sample of children treated in Florida.*

Hypothesis1: *It was hypothesized that the use of psychotropic medication would be significantly higher in subgroups of patients treated for CNS tumors and leukemias versus solid, non-CNS related tumors. When comparing the prevalence of psychotropic medication use across subgroups, binary logistic regression was used. The model yielded an overall test of prevalence and estimated overall odd ratios of disease groups.*

Stimulant Hypothesis: *Treatment of CNS tumors involving cranial radiation therapy will place these children at an increased risk for developing problems with attention and concentration (Butler & Mulhern, 2005; Moore, 2005). Therefore, children treated for brain tumors with cranial radiation will be more frequently prescribed stimulant medication for late effects than those children with ALL/lymphomas and non-CNS related solid tumors. Intrathecal methotrexate is also associated with deficits in attention and concentration. However these deficits are observed less frequently in ALL than in children treated for CNS tumors with cranial radiation, and are only identified in a subset of children with ALL. Higher doses of systemic methotrexate during consolidation are also associated with more attention and concentration problems (Butler & Mulhern, 2005). Children diagnosed with ALL should therefore have a lower frequency of use of stimulant medications compared to those children diagnosed with brain tumors; however a higher frequency of stimulant medication use should be*

observed in this group than in the group of children diagnosed with non-CNS tumors. Neither cranial radiation nor intrathecal methotrexate is used in the treatment of non-CNS related solid tumors; therefore, children with solid tumors should have the lowest rate of stimulant medication use of the cancer groups. These hypotheses were to be tested using an appropriate variant of binary logistic regression to estimate crude odd ratios.

Antidepressant Hypothesis: Increased depression in the pediatric oncology population may relate to the biological mechanisms associated with varying types of cancer and treatment involved. Change in neurochemistry, specifically dopamine and serotonin disruption, have been indicated. Stress associated with more complex treatment may place certain children at increased risk for depression during treatment (Portteus et al, 2006). It is, therefore, hypothesized that antidepressant use in children diagnosed with CNS tumors would be highest. It was also hypothesized that the ALL disease group would have a lower frequency of antidepressant use than the CNS tumor group; however it would be higher than the frequency of use in the non-CNS, solid tumor group. This hypothesis was to be tested using an appropriate variant of binary logistic regression to estimate crude odd ratios.

Antipsychotic Hypothesis: As previously discussed, a subgroup of children treated for ALL seem to exhibit symptoms consistent with PDD. As a result of this finding and the behaviors sometimes associated with PDD (e.g., aggression), survivors of ALL were hypothesized to be more likely to be treated with antipsychotics than other cancer groups. In order to test this hypothesis, an appropriate variant of binary logistic regression was again to be used to estimate crude odd ratios.

Study Aim 2: To obtain descriptive data regarding critical variables related to how

psychotropic medication decisions are made (i.e., who is the prescribing physician) and to identify gender and/or race/ethnicity differences. To date no research has studied these critical variables. The goal of this study aim was simply exploratory; therefore no hypotheses were developed. Statistical analyses for this study aim involved the examination of descriptive statistics.

Study Aim 3: *To develop a model, which may help predict which children are likely to be prescribed psychotropic medication.*

Hypothesis 2: *Findings of the previous study aim guided the development of this model. Based on late effects research, the neurodevelopmental model, and clinical observation, it was hypothesized that treatment method, diagnosis, and age at time of diagnosis would be critical variables to consider in model development. A predictive model was developed to determine which combinations of factors lead to psychotropic medication use. Because there are few a priori indicators and many potentially relevant predictors, a model-building technique was selected that allowed for the incorporation of variable selection and interaction detection. The technique used in this study analysis was a top-down induction of decision trees, specifically the Classification and Regression Trees (CART) algorithm (Breiman et al., 1984). CART is a statistical technique that is used to find subgroups within a sample that are differentially influenced by each independent variable. It uses a binary searching routine to divide a sample into those influenced in one manner by an independent variable and those influenced in a substantially different manner by the same variable (Lemmon et al., 2007). This statistical technique tests one variable at a time. Following each split of the sample by an independent variable the amount of variance explained by that variable is calculated*

and is presented as an R^2 statistic. CART has been used across disciplines, including genetics and oncology. This methodology has several advantages over other forms of statistical analysis (e.g., ease of interpretation, no parametric assumptions, increased sensitivity and specificity in identifying at-risk groups in comparison to regression). It is especially advantageous when results are determining an at-risk population (Lemmon et al., 2007).

Chapter 3: Results

Demographic Variables

Table 1 presents frequencies for the following categorical demographic variables: gender, ethnicity (African American, Haitian American, Black, Hispanic-not of Black origin, Hispanic-of black origin, White- not of Hispanic origin or Other), cancer diagnoses, and prescription of psychotropic medication. With regards to treatment, approximately 40% of the sample was treated using methotrexate (systemic and/or intrathecal) and approximately ten percent required whole brain radiation as part of their treatment. Table 2 presents psychotropic medication use by cancer diagnosis. In the current study sample diagnoses of leukemia and CNS tumors were slightly overrepresented compared to statistics reported in the general childhood cancer population, whereas non-CNS involved solid tumors were somewhat underrepresented (SEER cancer incidence rates, 2007). Over-representation of leukemia and CNS tumors in this sample is expected given their more frequent long-term follow-up visits and study recruitment from clinical referral programs. Table 3 presents descriptive statistics (i.e., mean, standard deviation) for the following continuous demographic variables: age at time of study, age at diagnosis, and time since diagnosis. Skewness and kurtosis were also examined for continuous variables. Based on the guidelines indicated by Curran, West, and Finch (1996) no concerns with non-normality were identified. The majority of the sample was recruited from the University of Miami/Holtz Children's Hospital (74%). All Children's Hospital collected 14% of the data and Nemours Children's Clinic recruited 12% of the sample.

Study Aim 1: *It was hypothesized that the use of psychotropic medication would be significantly higher in subgroups of patients treated for CNS tumors and leukemias versus solid, non-CNS related tumors.* A binary logistic regression analysis was performed with psychotropic medication use as the outcome and cancer diagnosis as the predictor. Dummy coding was conducted to code for the dependent variable (i.e., use of psychotropic medication). Contrary to expectations, results indicated that type of cancer diagnosis did not predict psychotropic medication use, $\chi^2(1, N=66) = .20$ $p = .64$. Using Cohen's criteria, the effect size was large, $Exp(B) = 1.50$. Table 4 shows the regression coefficient, Wald statistic and odd ratio ($Exp(B)$). Due to insignificant findings, this same analysis was conducted again excluding the non-CNS involved cancer diagnoses in an effort to determine if the difference between the CNS tumor diagnoses group and the ALL/lymphoma group reached significance. Results were again non-significant, confirming the original analysis including all diagnoses groups.

Because psychotropic medication use did not significantly differ by cancer diagnosis, proportions of medication use and cancer diagnoses were reviewed. Frequencies of medication use per cancer diagnoses and proportions are presented in Table 5.

Medication use was not further broken down by type of medication (i.e., stimulant, antidepressant and antipsychotic) and analyzed using binary logistic regression due to a lack of significance with overall medication use. This information, however, will be explored further in the following study aim.

Study Aim 2: *To obtain descriptive data regarding critical variables related to how psychotropic medication decisions are made (i.e., who is the prescribing physician) and to identify gender and/or race/ethnicity differences. To date no research has studied these critical variables. The goal of this study aim is simply exploratory; therefore no hypotheses were developed.* Statistical analyses for this study aim involved the examination of descriptive statistics. Table 6 presents frequencies and descriptive statistics for a variety of relevant variables of the subjects who had been prescribed some form of psychotropic medication. Variables included in the table are as follows: prior neuropsychological/psychoeducational evaluation, formal diagnosis, type of physician prescribing, side effects, family psychological history, academic functioning, and treatment variables.

In order to identify differences in psychotropic medication use based on gender, ethnicity, age, and treatment, univariate analyses were performed. A binary logistic regression was conducted in order to determine if gender predicted psychotropic medication use. Results indicated that gender did significantly predict psychotropic medication use $\chi^2(1, N=66) = 9.10, p < .05$, with males more likely to be taking psychotropic medication. Separate binary logistic regressions were also conducted in order to determine if age or ethnicity predicted psychotropic medication use. Results failed to demonstrate a significant relationship between age and medication use $\chi^2(1, N=66) = 3.60, p = .06$. Results also failed to demonstrate a significant relationship between ethnicity and psychotropic medication use $\chi^2(1, N=66) = .04, p = .85$. In order to determine the relationship between treatment and psychotropic medication use several analyses were performed. A binary logistic regression was conducted to determine if

receiving methotrexate as part of a child's cancer treatment predicted psychotropic medication use. Contrary to expectations, exposure to methotrexate did not lead to significantly greater use of psychotropic medication $\chi^2(1, N=66) = .08, p = .79$. A second binary logistic regression was performed to determine if whole brain radiation predicted psychotropic medication use. Again results failed to demonstrate a significant relationship between whole brain radiation and psychotropic medication use $\chi^2(1, N=65) = 2.76, p = .09$, although results were approaching significance. Table 7 shows regression coefficients, Wald statistics and odd ratios (Exp(B)) for the above analyses.

Study Aim 3: *To develop a model that may help predict which children are likely to be prescribed psychotropic medication.*

Hypothesis 2: *Findings of the previous study aim guided the development of this model. Based on late effects research, the neurodevelopmental model, and clinical observation, it was hypothesized that treatment method, diagnosis, and age at time of diagnosis would be associated with psychotropic medication use.* A predictive model was developed to determine which combinations of factors led to psychotropic medication use. Because there are few a priori indicators and many potentially relevant predictors, a model-building technique was selected that allows for the incorporation of variable selection and interaction detection (CART). The number of potentially relevant predictors entered into the model was limited to nine based on the sample size. These variables included: child's age, gender, cancer diagnosis, age at diagnosis, time since diagnosis, exposure to methotrexate, whole brain radiation, use of anthracycline in cancer treatment, and presence of school problems as reported by subject's parent. These variables were

included in the model analysis for a number of specific reasons (See Table 8). For the majority of variables included in the analysis, selection was based on empirical knowledge of factors associated with the development of late effects. This was the rationale for including the following variables: gender, cancer diagnosis, age at diagnosis, time since diagnosis, exposure to methotrexate, and whole brain radiation. Use of anthracycline, child's age and presence of academic difficulties were included due to their clinical associations. The results of the CART analyses are presented in Figure 1. The first split explained 16% of the variance ($R^2 = .16$) in psychotropic medication use; males were more likely to be on psychotropic medication than females. Following the first split females could not be split any farther leaving only males ($N=32$) in the analysis. The second split (additional $R^2 = .12$) demonstrated that children whose parents reported the presence of school difficulty were more often on medication than those without reported school difficulty. Following this split, only those children whose parents reported school difficulty remained in the analysis ($N= 14$). The last split (additional $R^2 = .18$) showed that subjects who were 10 years of age or older were on psychotropic medication more often than those subjects who were younger than ten. In summary, gender, presence of school difficulty, and age explained a total of 46% of the variance in psychotropic medication use in the pediatric cancer population; children treated for cancer who were male, age 10 or older and had reported school difficulty were more likely to be using psychotropic medication.

Chapter 4: Discussion

There is a substantial literature in psycho-oncology that supports a link between psychosocial functioning and cancer. In addition, it is well documented that children who have been treated for cancers involving the CNS often experience neurocognitive deficits. Taken together, these children may be more likely to be prescribed psychotropic medication. Psychotropic medications commonly used with children have been associated with side effects significant enough to warrant warnings from the FDA (FDA, Public Health Advisory). Of particular concern for survivors of childhood cancer is the effect that late neurocognitive effects may have on the developing brain's response to psychotropic medications. To date, there are few empirical data regarding whether children treated for cancer have greater exposure to psychotropic medications than the general child population. The overarching objective of the current study, therefore, was to examine factors associated with overall psychotropic medication use in the pediatric cancer population. Specific aims of this study were to: (1) examine the prevalence of psychotropic medication use in children treated for cancer, (2) obtain descriptive data regarding variables associated with medication usage, and (3) develop a model to predict which children are likely to be prescribed psychotropic medication. Findings from this study will be discussed and their implications will be examined below. Study limitations will be detailed and future research will be suggested.

Consistent with findings previously obtained by Portteus et al. (2006) and Pao et al. (2006), the current study found that a much higher proportion of children diagnosed with cancer had been prescribed psychotropic medication than percentages reported in the general pediatric population. Specifically, current findings indicated that 15% of

children included in this study had been treated with some type of psychotropic medication compared with an overall rate in the pediatric non-cancer, general population of approximately six percent (Pao et al., 2006; Thomas et al., 2006). The vast majority of these children were being treated with stimulants in an effort to minimize attentional difficulties. Contrary to findings of increased antidepressant use in the pediatric cancer population reported in previous studies (Portteus et al. (2006) and Pao et al. (2006)), only two of the children in this sample were taking antidepressants. It is important to note, however, that the sample was a combination of children both on and off cancer treatment while prior studies primarily examined antidepressant use in children actively undergoing cancer treatment. It is likely children actively undergoing treatment are more likely to require treatment with antidepressants to assist with coping and adjustment; individuals who are several years post-treatment are more likely to need stimulant medication to treat neurocognitive late effects (e.g., deficits in attention and concentration).

It was hypothesized that the prevalence of psychotropic medication use would vary across cancer diagnoses, with children treated for leukemia/lymphoma and brain tumors being more likely to be taking psychotropic medication than those children treated for non-CNS involved solid tumors. Surprisingly, study results failed to indicate a significant relationship between cancer diagnosis and psychotropic medication use. Several study limitations may have contributed to insignificance and will be discussed later. While results of statistical significance were inconsistent with hypotheses, review of proportions of psychotropic medication use within each cancer diagnosis demonstrate findings more in line with hypotheses. Specifically, findings indicated that 19% of children diagnosed with brain tumors were being treated with psychotropic medication,

but only 11% of children diagnosed with leukemia/lymphoma were. Higher medication use in children treated for brain tumors than children treated for ALL is consistent with hypotheses and knowledge of neurocognitive late effects found in the literature. Twenty percent of children diagnosed with non-CNS involved solid tumors that had been prescribed a psychotropic medication; however, this diagnosis group was significantly smaller than the other two and consisted of only 10 children. Only two children in this group were prescribed a psychotropic medication. Additionally, both of these children had been treated for a Wilm's tumor (cancer of the kidneys), which often results in the removal of all or part of a child's kidneys. Research has consistently reported neurocognitive and psychosocial difficulties in children with chronic kidney disease (Gerson et al., 2006). Therefore, it is possible that children in this subset of non-CNS involved solid tumors will be more likely to experience difficulties leading to a need for psychotropic medication; however the mechanism leading to this need may be different than those with CNS-involved cancers and related treatments.

Study finding of increased psychotropic medication use in childhood cancer survivors supports the need for further exploration of medication use and associated variables within the cancer population. Exploratory descriptive analyses revealed many interesting findings. Of those children who were treated with psychotropic medication, few reported serious side effects. Some of the side effects that were reported included: insomnia, diminished appetite, nervousness, headache and nausea (see Table 6). None reported suicidal thoughts, which is especially important given more recent research suggesting increased suicidal ideation associated with use of antidepressants (Hammad, Laughren, & Racoosin, 2006). However, only two of the subjects were prescribed

antidepressants, as the majority of subjects were taking a stimulant medication.

The use of stimulants is of particular concern considering possible medication side effects and FDA warnings surrounding stimulant medication and sudden cardiac death. The use of anthracycline, a type of chemotherapy included in a number of childhood cancer treatment protocols, has been found to lead to cardiomyopathy. This may place some long-term childhood cancer survivors at a greater risk for cardiac-related side effects (Kalash, 1998). In the current sample, only one child taking psychotropic medication had received anthracycline as part of his cancer treatment. Additionally, none of these children had been diagnosed with cardiomyopathy. Findings may suggest that prescribing physicians may be aware of the increased cardiac risks for children with cardiomyopathy and may be cautious in prescribing these medications.

Interesting findings were also identified regarding the specialty or practice of physicians responsible for prescribing psychotropic medication. Prescribing physicians included pediatricians and child psychiatrists. Pediatric oncologists and neurologists were not reported to have prescribed these medications in this sample. Unfortunately, whether prescribing physicians were in contact with the pediatric oncologists or whether they were aware of possible increased side effects or drug interaction risks associated with cancer and its treatment was not assessed.

The majority of children treated with psychotropic medication had received neuropsychological evaluations previously and more than half of these children had received a formal diagnosis as a result. Diagnoses included anxiety, aphasia, attention deficit hyperactivity disorder (ADHD), and post-traumatic stress disorder (PTSD). None of the children identified with autism spectrum disorder (ASD) symptoms from the

University of Miami program were included in this study, so PDD and ASD diagnoses were not indicated. The high number of reported neuropsychological evaluations confirms the presence of school difficulties in children treated for cancer. Additionally, the majority of parents reported difficulties in a variety of school domains. Specific school difficulties are reported in Table 6. School difficulties may be associated with neurocognitive late effects and may lead to treatment with psychotropic medication (e.g., stimulant medication prescribed to treat deficits in attention).

While descriptive statistics were examined for many variables (See Table 6), only some of these variables were thought to predict psychotropic medication use. Univariate analyses and CART demonstrated generally consistent findings with regards to predictive variables. Specifically, gender, age and presence of school difficulty influenced psychotropic medication use among childhood cancer survivors. Using a binary logistic regression, age did not independently significantly predict medication use; however results were approaching significance. When a group of variables were entered into the CART analysis, age was found to explain a substantial portion of the variance in psychotropic medication use. Overall, findings indicated that children treated for cancer who were male, age 10 or older and had reported school difficulty were more likely to be prescribed psychotropic medication. These results are consistent with prescribing trends identified in the general child population. Findings suggest that factors influencing prescribing may be similar regardless of the presence of cancer in a child's medical history.

It was surprising, however, that no treatment variables significantly predicted psychotropic medication use, especially given countless findings linking treatment

method with the emergence late effects. When conducting binary logistic regressions with treatment variables, exposure to whole brain radiation was approaching significance. When entered into the CART analysis, however, it did not explain much of the variance. This may be due to the strong correlation between exposure to radiation and the presence of school problems identified in the current study data. This correlation is not unexpected given that research has found that exposure to whole brain radiation is a contributing factor to the development of late effects and neuropsychological deficits (Noll et al, 1997). While no cancer treatment variables were found to predict psychotropic medication use as hypothesized, given that exposure to radiation was approaching significance, it is possible that with a larger sample size findings would be more in line with hypotheses.

Consistent with previous findings, results clearly indicated a higher percentage of children with cancer were prescribed psychotropic medication than the percentage reported in the general child population. Despite this finding, results did not significantly identify any cancer specific variables that predicted psychotropic medication use within the sample. This finding, as well as the lack of differences in prevalence across cancer diagnoses, was likely impacted by several limitations of this study.

The first limitation was the small sample size. With only 15% of the sample taking psychotropic medication, the subsample was likely not large enough to fully capture an accurate description of this subgroup. The sample size also limited evaluation of study hypotheses. Small sample size especially hindered analyses of subsamples divided by type of psychotropic medication prescribed. A power analysis revealed that a sample size of 300 should provide adequate power to detect moderate differences in the

prevalence of psychotropic medication across subgroups. While this sample size was not feasible for the current study, continued data collection (with adequate funding) may result in findings more consistent with hypotheses.

There were also several limitations regarding how cancer variables were measured and defined. In the current study, treatment involving cancer variables were defined and measured. Methotrexate (MTX) was a variable of interest when considering factors contributing to psychotropic medication use. In this sample, patients were coded either as having received methotrexate or not. Future studies may want to consider the dose of systemic methotrexate ($\leq 1 \text{ gm/m}^2$, $\geq 1 \text{ gm/m}^2$ to $\leq 2 \text{ gm/m}^2$, and $> 2 \text{ gm/m}^2$) and intrathecal combination (MTX vs. combination MTX, hydrocortisone, and cytarabine) rather than just the general inclusion of this chemotherapy agent. Additionally, the current study included Wilm's tumors in the category coded as non-CNS involved tumors. As previously discussed, Wilm's tumors often are treated with total or partial resection of a kidney. A non-functioning or partially functioning kidney has been found to be associated with cognitive deficits, independent of cancer (Gerson et al., 2006). In future studies, subjects treated for Wilm's tumors should perhaps be coded as an independent subset of non-CNS involved tumors. This coding variation may lead to a more accurate understanding of cancer diagnoses and their link to the need for psychotropic medication.

Lastly, all subjects were recruited from three hospitals within Florida, with the vast majority of subjects recruited from within Miami. Therefore, findings from this study may not generalize well to a broader sample for a variety of reasons. Specifically, Miami's diverse population may have differing cultural perspectives regarding

psychotropic medication use than the general population. Additionally, physicians' willingness to prescribe these medications and practice philosophies may vary both within and outside of Florida. Future studies should examine children across a variety of hospitals and states. This would help in obtaining a larger sample, leading to greater generalizability.

Conclusions

The current study supports previous findings of a higher prevalence of psychotropic medication use in the pediatric cancer population. Model analysis indicated children treated for cancer who were male, age 10 or older and had reported school difficulty were more likely to be taking psychotropic medication. This suggests that psychotropic medications are being prescribed for children who might potentially benefit from the treatment. Fortunately, children whose treatment placed them at higher risk for FDA-identified side effects were generally not prescribed psychotropic medications, particularly those with CNS treatment or treatment that affects the heart. Nevertheless, these findings remain concerning given the relatively small sample size for this study and 1) the current FDA warnings regarding psychotropic medication use and children, and 2) the possible increased risk of side effects associated with cancer and its treatment. This study provides insight into the need for continued examination of psychotropic medication use in the pediatric cancer population, specifically differences in prevalence across diagnoses and the possible impact of cancer treatment on medication need. This study reports preliminary findings; however data collection will continue in an effort to better understand psychotropic medication use in the pediatric cancer population.

Since preliminary findings of the model analysis found similar results to prescribing trends observed in the general child population, future studies may benefit from the inclusion of a control group. Specifically, recruitment from another chronic illness population that has not been linked to neurocognitive deficits may be most useful as a control group. Additionally, since stimulant medication was the most frequently prescribed based on preliminary results, the inclusion of a measure of attention (e.g., a continuous performance test) in addition to parent report may be useful in future studies. This will allow for a more accurate measure of a participant's attention and provide additional insight into the need and benefits of stimulant medication. While preliminary results of the current study revealed interesting findings, continued data collection and future studies will be important in order to gain a better understanding of psychotropic medication use in children with cancer.

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Figure 1

Results of CART analysis

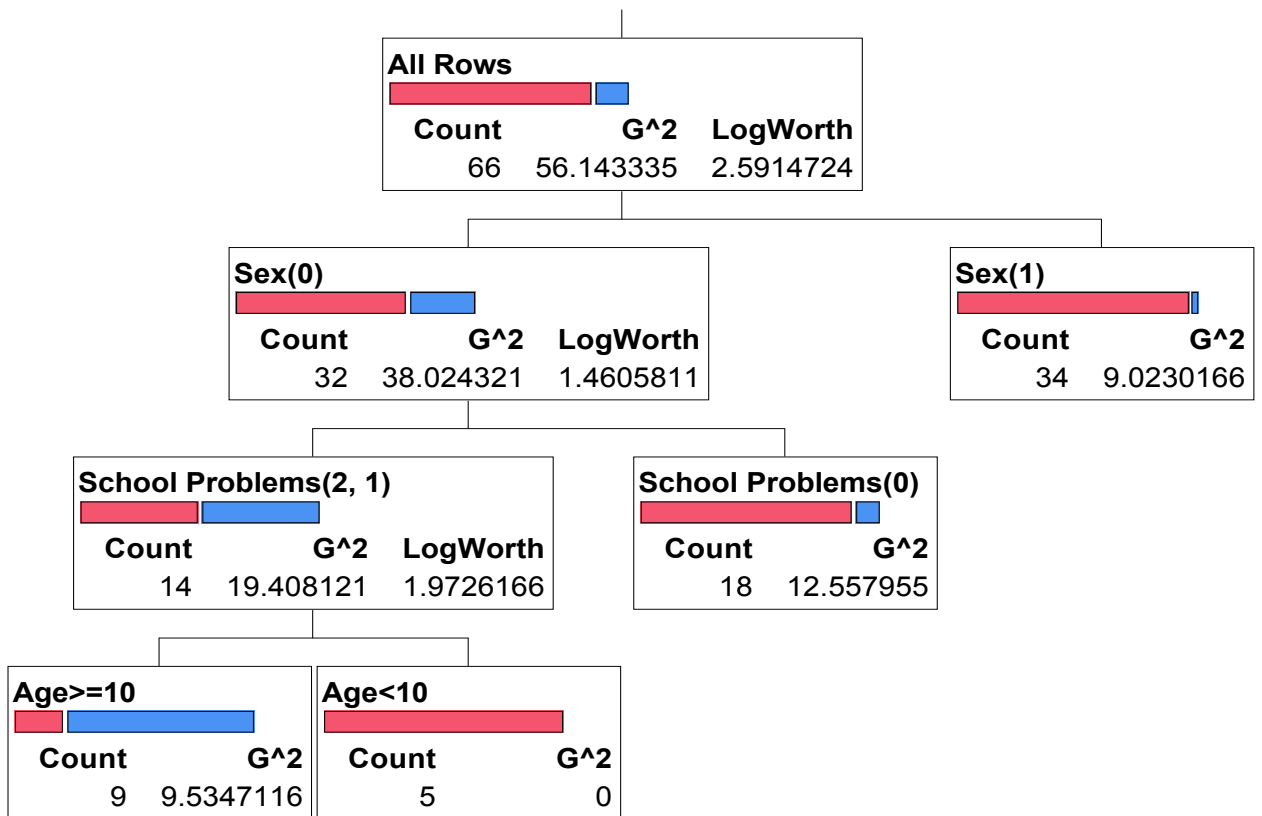


Table 1

Frequencies for categorical data (N=66)

<i>Variable</i>	<i>Frequency/Percentage</i>			
	<i>CNS Tumor</i>	<i>Leukemia</i>	<i>Non-CNS Tumor</i>	<i>Total</i>
Gender				
Male	8	19	5	32/48.5
Female	13	16	5	34/51.5
Ethnicity				
African American	1	2	0	3/4.5
Haitian American	0	0	1	1/1.5
Black	0	1	0	1/1.5
Hispanic- not of Black origin	6	7	2	15/22.7
Hispanic- of Black origin	1	0	0	1/1.5
White- not of Hispanic origin	12	22	5	39/59.1
Other	1	3	2	6/9.1
Prescription of Psychotropic Medication				
None	17	30	9	56/84.8
Stimulant	4	2	2	8/12.1
Antidepressant	0	2	0	2/3.0
Antipsychotic	0	0	0	0/0
Cancer Diagnosis				
Leukemia/Lymphoma				35/53.0
Brain Tumor				21/31.8
Non-CNS Related Solid Tumor				10/15.2

Table 2

Frequency of psychotropic medication used by cancer diagnoses

<i>Type of Medication</i>	<i>Brain Tumor</i>	<i>ALL/Lymphoma</i>	<i>Other Tumor</i>
Stimulant	4	2	2
Antidepressant	0	2	0
Antipsychotic	0	0	0

Table 3

Descriptive statistics for continuous variables (N=66)

<i>Variable</i>	<i>Mean</i>	<i>Standard Deviation</i>
Age at Time of Study	10.25	3.62
Age at Diagnosis	4.87	4.16
Time Since Diagnosis	4.58	3.22

Table 4

Logistic regression statistics for cancer diagnoses and psychotropic medication use

<i>Regression Coefficient</i>	<i>Wald Statistic</i>	<i>Exp(B)</i>
.41	.21	1.5

Table 5

Frequency and proportions of medication use per cancer diagnoses (N=10)

Diagnosis	Frequency	Proportion
Leukemia/Lymphoma	4	11
Brain Tumor	4	19
Non-CNS involved solid tumors	2	20

Table 6

Frequencies for categorical data for subjects taking psychotropic medication (N=10)

<i>Variable</i>	<i>Frequency</i>
Prior Neuropsychological Evaluation	
Yes	9
No	1
Formal Diagnosis	
Yes	5
No	4
Not Reported	1
Prescribing Physician	
Pediatrician	3
Pediatric Oncologist	1
Child Psychiatrist	0
Child Neurologist	0
Nurse Practitioner/Physician's Assistant	0
Not Reported	6
Side Effects Endorsed	
Insomnia	2
Depression	2
Diminished Appetite	1
Nervousness	1
Fever	1
Muscle Stiffness or Spasm	1
Anxiety	0
Confusion	0
Psychotic Behavior	0
Suicidal Thoughts	0
Hallucinations	0
Agitation/Restlessness	0
Dizziness	0
Numbing or Tingling	0
Nausea or Vomiting	0
Severe Headache	0
Fainting Spells	0

Chest Pain	0
Irregular or Fast Heartbeat	0
Chest Pain	0
Skin Rash	0
Joint Pain	0
Dry Skin	0
Blurred Vision or Eye Pain	0
Seizures	0
Difficulty Urinating/Loss of Bladder Control	0
Tremor	0
Yellowing of Eyes or Skin	0
Difficulty Breathing	0
Continuous Painful Erection	0
Other	0
Family History of Psychological Difficulties	
Yes	5
No	4
Not reported	1
Child Receives Special Education Services	
Yes	8
No	1
Not Reported	1
School Difficulties	
Handwriting	6
Organization	6
Completing Work on Time	5
Maintaining Attention	4
Slow Response or Reaction Time	4
Reading Recognition	4
Written Expression	4
Planning	4
Reading Comprehension	3
Memory of Oral Information	3
Remembering Sequences of Commands	3
Taking Tests	2
Memorizing Multiplication Tables	2
Sustaining Energy	2
Comprehension of Oral Information	1
Verbal Expression	1
Learning Novel Information	1

Use of Methotrexate	
No	6
Yes	4
Use of Anthracycline	
No	8
Yes	1
Not Reported	1
Presence of Cardiomyopathy	
No	10
Yes	0
Whole Brain Radiation	
No	8
Yes	2
Localized Radiation	
No	6
Yes	4

Table 7

Logistic regression statistics for gender, ethnicity, age, and treatment variables

<i>Variable</i>	<i>Regression Coefficient</i>	<i>Wald Statistic</i>	<i>Exp(B)</i>	<i>Significance</i>
Gender	-2.6	5.5	.08	<.05
Ethnicity	-.04	.04	.96	.85
Age	.19	3.2	1.2	.06
Methotrexate use	-.19	.07	.83	.79
Whole Brain Rad	1.5	3.0	4.3	.09

Table 8

Variables included in CART analysis and reason for inclusion

<i>Variable</i>	<i>Reason for Inclusion</i>
Child's Age	Research has demonstrated higher rates of psychotropic medication use in adolescents compared to young children
Gender	Cancer literature has found gender to be associated with the development and severity of neurocognitive late effects
Cancer Diagnosis	Development of late effects has been found to vary based on cancer diagnosis, with greater deficits associated with CNS disease
Age at Diagnosis	Research has demonstrated greater neurocognitive late effects in children diagnosed at younger ages
Time Since Diagnosis	Late effects emerge in years following treatment; therefore need for psychotropic medication may increase with time
Exposure to Methotrexate	Cancer literature has established an association between use of methotrexate and the development of late neurocognitive effects
Whole Brain Radiation	An association between brain radiation and late neurocognitive effects has also been identified
Use of Anthracycline	Anthracycline may place children at greater risk of side effects associated with psychotropic medication
School Difficulties	Cancer treatment has been linked to changes in brain structures leading to cognitive deficits, which often impact academic functioning

Appendix A

Cancer

While childhood cancer is rare, it is nevertheless affecting thousands of children annually, and is therefore a research area of significant focus. Approximately 8,600 children were diagnosed with a form of cancer in the year 2001, and of these 8,600, approximately 7,100 survived longer than 3 years from time of diagnosis (Moore, 2005). Estimates of cancer rates in children appear to be increasing. In the year 2007, it is believed approximately 10,400 children under the age of 15 years in the United States will have be diagnosed with some form of cancer, with nearly 80% surviving longer than 5 years after time of diagnosis (NCI, Cancer Facts). Although childhood cancer is diagnosed in only 1 or 2 children per 10,000, it is the leading cause of death by disease in children younger than 15 years of age (Moore, 2005). In the past, childhood cancer was usually considered fatal; however, advances in technology have led to earlier diagnoses and more effective means of treatment, leading to increased rates of survival. Today, an estimated 85% of children and adolescents with cancer in the United States will survive longer than 5 years from the time of diagnosis (Moore, 2005). While survival rates are increasing, the methods of insuring survival are not without costs. A recent focus of research in the area of pediatric cancer has been on methods of decreasing the neurocognitive consequences resulting from treatments. Psychological functioning is another focus of research, with the area of psycho-oncology developing and evolving.

Among the twelve major types of childhood cancer, leukemias and tumors of the central nervous system account for over half of newly diagnosed cases (NCI, Cancer Facts). Leukemia is a form of cancer that originates in the blood-forming cells found in

bone marrow. Stem cells produced in bone marrow are responsible for producing platelets, red blood cells, and white blood cells. Leukemia creates an uncontrollable proliferation of lymphocytes, a subtype of the white blood cells. Approximately 5% of healthy bone marrow consists of this type of cell. When an uncontrollable growth of these cells occurs, the bone marrow is prevented from producing other healthy blood cells (i.e., platelets, red blood cells, and other subtype white blood cells).

The most common type of childhood cancer is acute lymphoblastic leukemia (ALL). It is a disorder of lymphoid cells located in bone marrow. If left untreated, it can spread to all organ systems, including the central nervous system (Butler & Mulhern, 2005). An estimated 16 to 22 per 1 million children are diagnosed with ALL (Mulhern, Ochs & Fairclough, 1992). A child diagnosed with ALL 40 years ago would have typically survived only a few weeks following diagnosis (Mulhern, et al, 1992). Presently, a child diagnosed with ALL has approximately a 90% chance of long-term survival (i.e., >5 years) (Moore, 2005). Survival for children diagnosed with ALL is influenced by many variables, but the most common risk factors are white blood cell count at time of diagnosis (high is greater risk), age at diagnosis (older is greater risk), involvement outside the bone marrow and blood (e.g., solid mass or central nervous system), some cytogenetic factors, and the cell line involved (early Pre-B, pre-B, mature B, or T-cell). Diagnosis at a young age is associated with higher survival rates, but also poses greater risk for neurological deficits in a subset of children with other risk factors (Moore, 2005). A less common type of cancer, accounting for approximately 15% of childhood malignancies, is lymphoma. Lymphoma is a type of cancer that originates in the lymphoid tissue, a major part of the immune system. Lymphoma, like leukemia, is

characterized as an abnormal proliferation of lymphocytes, causing abnormal enlargements of the lymph nodes, as well as other body organs containing lymphocytes. Treatment methods for lymphomas are also similar to those used for leukemia. 5-year survival rates vary from 72-91% depending on type of lymphoma (Percy et al., n.d.).

Pediatric brain tumors are considerably more varied than ALL/lymphoma. Brain tumors are solid tumors that arise in the central nervous system, most commonly in the brain but sometimes in the spinal cord. There are many types of childhood brain tumors, and these are characterized by their location and their histology. Brain tumors are often described as supratentorial or infratentorial. The tentorium is a membrane separating the brain stem and cerebellum from the remainder of the brain (Butler & Mulhern, 2005). They are also characterized as low grade (slow-growing) or high grade (fast-growing). Common types of tumors include: supratentorium low grade tumors, medullblastomas, brain stem gliomas, cerebellar astrocytomas, supratentorial high-grade tumors, and craniopharyngiomas (Stoother et al., 2002; Butler and Mulhern, 2005). Of the variety of common tumors that exist, medullblastomas are the most common malignant brain tumors in childhood (Butler & Mulhern, 2005). They account for approximately 10-20% of all central nervous system tumors diagnosed in children (Palmer et al., 2003).

Brain tumors are the second most frequently diagnosed type of childhood cancer. Approximately 3 per 100,000 children are diagnosed with a brain tumor per year (Butler & Mulhern, 2005). The causes of most brain tumors remain unknown; however, they have been noted to sometimes appear following ALL treated with cranial radiation therapy. Common symptoms of brain tumors include nausea and headaches, although

symptoms vary based on type of tumor present. For example, balance and coordination may be affected by the presence of a medullablastoma. Survival rates of children diagnosed with brain tumors vary based on type of tumor. Although intrinsic brain stem glioma has a survival rate of less than 10%, long-term survival of children diagnosed with medullablastoma is greater than 65% (Butler & Moore, 2005). Similar to ALL, many factors contribute to prognosis. Although many gains have been made in terms of diagnosis and treatment of brain tumors, much research is still needed in order to better identify means of preventing, or at least minimizing, late effects of their treatments.

A number of other solid tumors occur outside the central nervous system as well. While these tumors have significant effects on children, their treatment does not generally result in the same level of neurocognitive impairment seen in survivors of childhood brain tumors, leukemias, or lymphomas.

Treatment

Treatment plans vary significantly between individuals. Although at one time considered fatal, currently many cancer forms are successfully treated with chemotherapy, radiation therapy, and/or surgery. Other methods of treatment exist; however, they are less commonly used (e.g., bone marrow transplantation). Treatment plans usually involve at least one of these primary forms of treatment, either alone or in some combination of them. Treatment varies based on diagnosis, stage of the cancer, and the size and weight of the child.

Treatment for ALL usually consists of some combination of chemotherapy, and the duration of treatment is usually between 30 to 36 months. Other methods of treatment are also used; however, they are typically used only when exposure of the CNS to

cancerous cells has occurred. Since the early 1990s, treatment has been limited primarily to chemotherapy (intrathecal and systemic) due to CNS toxicity resulting from other radiation therapy to the brain. Systemic chemotherapy is administered orally, intravenously, or intramuscularly. This type of treatment is theorized to have less damaging effects on cognitive functioning because it does not cross the blood-brain barrier, prohibiting the CNS from exposure to chemotherapeutic agents. Intrathecal chemotherapy (IT chemotherapy), however, is injected directly into the spinal cord and, as a result, is allowed access to the CNS by crossing the blood-brain barrier. The results of exposure of the CNS to intrathecal chemotherapy agents will be discussed later. IT chemotherapy is typically used as a preventive or prophylactic treatment; when cancer cells are detected in the CNS, the standard treatment includes cranial radiation to the brain and possibly spinal cord, typically in a dose between 1800 and 2400 cGy (cited in Mulhern, Ochs, & Fairclough, 1992). Intrathecal CNS prophylaxis most commonly includes methotrexate, and may also be given in combination with other drugs, most commonly hydrocortisone and cytosine arabinoside (ARA-C) (Armstrong & Briery, 2004). Cranial irradiation is typically used only for those children who have CNS disease at diagnosis or experience a CNS relapse (Butler & Mulhern, 2005). The CNS has been found to be a primary area affected by advancing leukemia and therefore treatment in the past has often targeted the CNS as a preventative measure. Treatment of the CNS, however, has become less common as a result of the neurocognitive effects found to result from this type of treatment. Following initial treatment and entrance into remission, the risk of fatality remains due to the presence of undetectable levels of leukemia

possibly still present. Maintenance therapy becomes an important aspect of treatment and is required for an extended period of time following initial treatment and remission (Butler & Mulhern, 2005).

Surgical resection is the most frequently used means of treatment for CNS tumors. Chemotherapy is often used in addition to surgical resection, and may also be used in conjunction with cranial radiation therapy (CRT). CRT is a form of treatment that uses gamma rays, and is typically delivered in measured doses daily for a period of 6 weeks. The irradiation may be delivered to either the whole brain field or partial brain fields in the case of brain tumors. Recent research has begun to explore better methods of delivering CRT to treat tumors without damaging surrounding healthy tissue (Butler & Mulhern, 2005).

A necessity in developing treatment plans is a balance between effective therapy and safe levels of toxicity. Research shows aggressive surgery and high levels of radiation and chemotherapy are the most effective at insuring survival. However, these methods of treatments are also the most impairing in terms of neurocognitive deficits (Moore, 2005). Although treatment efficacy is the primary focus when treating children with cancer, the costs of such treatment in terms of long-term impairment also must be considered.

Appendix B

Cognitive Effects

Recent research has progressed from focusing merely on treatment survival rates, to also focusing on the costs of such treatments. Although presently survival rates are more encouraging than they once were, the costs of insuring survival are still great. Research has shown that a variety of factors, specifically type of treatment and age at time of treatment, contribute to the neurocognitive consequences that result from pediatric cancer treatments. The neurocognitive deficits seen in pediatric cancer survivors are similar for children who have been treated for ALL, non-Hodgkins lymphomas, and brain tumors. This is especially true for those children treated with brain irradiation and/or intrathecal chemotherapy (Butler & Mulhern, 2005). In children with brain tumors, high risk ALL with the potential of metastasis to the brain, or lymphomas with potential for metastasis, the brain is a primary target for therapy.

Neurocognitive effects that result from cancer and its treatment may contribute to psychosocial functioning in the pediatric cancer population and therefore are important to review. Neurocognitive deficits may place these children at a greater risk for needing psychotropic medication, particularly in light of the structural, neurodevelopmental, neurochemical, neuroendocrine, and metabolic alterations that may occur as a result of the cancer and/or its treatment. These alterations, or late neurocognitive effects of treatment, may also affect the developing brain's response to psychotropic medications in ways that are not yet known.

Typically, the late effects of CRT begin to emerge within the first 1 to 2 years following treatment. However, recent research suggests that the emergence of

neurocognitive deficits may sometimes be delayed as much as 7 years following treatment (Butler & Mulhern, 2005). It is currently believed that CRT causes more damaging effects than does intrathecal chemotherapy; however, intrathecal therapy is not without costs as well. As many as 30% of children treated with intrathecal chemotherapy experience some deficits following treatment (Butler & Mulhern, 2005).

While much research suggests chemotherapy has a significant impact on cognitive functioning, the findings are equivocal. Contrary to the findings previously reported, Von der Weid et al. (2003) found children treated with chemotherapy alone displayed intellectual abilities within the normal range, suggesting chemotherapy alone did not have additional negative consequences (Moore, 2005).

CRT is a primary method of treatment that is often used, and it has been found to have severe consequences on neurocognitive functioning, as well as suspected influences on psychological functioning. It is believed that CRT is largely responsible for the majority of late effects seen in childhood cancer survivors. The late effects of CRT begin to emerge within the first 1 to 2 years following treatment and can be seen as much as 10 years later. This may be a result of uneven development of white and gray matter, leading to an imbalance in their relative mass (Moore, 2005). Deficits in attention, working memory and processing have all been linked to cranial radiation therapy, and research has also demonstrated impaired attention/executive functioning resulting from CRT. Pediatric cancer survivors who have received CRT have been found to have difficulty with automatic shifting, attentional focusing, and are more susceptible to distraction (Butler & Mulhern, 2005). Additionally, processing speed is another area that appears to be affected by CRT. A study by Moore, Copeland, Ried and Kopecky (1992)

showed that children treated with CRT not only performed significantly lower on neuropsychological testing, but also had significantly slower reaction times than did those pediatric cancer children not treated with CRT. Observations of slowed processing speed in survivors of childhood brain tumors, ALL, or lymphomas, may be attributable to changes in white matter resulting from treatment of these childhood cancers. Since white matter assists with conduction velocity, it is possible that the CRT causes a decline in neuronal transmittal speed by interrupting the development of white matter (Moore, 2005; Reddick et al, 2006). This deficit in processing speed may contribute, in part, to the deficits also found with regards to working memory in pediatric cancer survivors. Alterations in white matter resulting in deficits in attention and processing speed, may contribute to psychological difficulties in a subgroup of the pediatric cancer population. Specifically, these identified deficits may contribute to both attentional disorders and social skills deficits identified in some children with cancer (Patenuade & Kupst, 2005).

Surgery alone can also have significant consequences on a variety of intellectual domains. Steinlin et al. (2003) showed the effects of treatment using only surgery for benign cerebellar lesions in children. The study demonstrated that although the global intellectual abilities of these children were intact, they experienced significant deficits in the following areas: attention, memory, processing speed, and visual-constructive copying (Beebe et al, 2005). Similar links to those described above may be made between deficits resulting from surgery and psychosocial functioning in the pediatric cancer population.

Deficits resulting from cancer, and from its treatment, may lead to a decline in academic performance, as well as impaired functioning in other areas of life. When

compared with their siblings, long-term brain tumor survivors experience greater incidence of unemployment and greater limitations in their daily activity (Palmer et al., 2003). Pediatric brain tumor survivors may also be at risk for social difficulties following treatment (Butler & Mulhern, 2005). These deficits may be secondary results of neurocognitive deficits found in this population and will be discussed in greater detail.

Several factors contribute to the extent and severity of neurocognitive deficits found in pediatric cancer survivors, which subsequently affects psychological functioning and psychotropic medication use in this population. On average, children diagnosed under 4 years of age demonstrate significantly lower IQ scores ($M = 71.9$) than those diagnosed above the age of 4 years ($M = 92.6$) (Moore, 2005). Young age at the time of cranial radiation therapy causes the largest detrimental effects on neurocognitive outcome. Children treated for medulloblastoma with CRT at a young age may experience declines in IQ up to 10 or more years following treatment (Mulhern et al., 1999). Mulhern et al. (2001) also evaluated the relationship between neurocognitive functioning and volume of white matter present. Results indicated that age at treatment time was significantly associated with volume of white matter. The study demonstrated a significant relationship between volume of white matter and IQ, basic fund of factual information, and abstract thinking abilities. The study concluded that deficits resulting from CRT may be attributable to sub-cortical and cortical white matter damage. Research concludes that neurocognitive deficits seen in pediatric cancer survivors may result from their inability to learn new information as opposed to the loss of previously acquired information (Moore, 2005).

Other factors that may impact the extent and severity of neurocognitive deficits found in pediatric cancer survivors following treatment include gender, tumor location, and amount of time since treatment. Some studies have demonstrated that females may show greater cognitive deficits following treatment. Von der Weid et al. (2003) found three times more females than males had IQ scores that fell at least one standard deviation below the mean (Waber, Tarbell, & Kahn, 1992). Studies have examined similar effects in regard to greater impairment in females in psychosocial functioning as well (Vanatta et al, 1998). Research assessing the association between tumor location and late effects is varied. Mulhern, Hancock, Fairclough, and Kun (1992) performed a meta-analysis of 22 studies, and found no significant association between brain tumor location and cognitive functioning. In contrast, Ater et al. (1996) found an association between tumors located in the cerebral hemispheres and difficulty with attention, motor abilities, performance IQ and academic functioning. Children diagnosed with posterior fossa tumors had difficulty with motor abilities and memory only, and finally children diagnosed with tumors of the brainstem were found to have no areas of difficulty. Brain tumor location has also been considered in the psychological literature, being that brain tumor patients have been identified as an at-risk population for maladjustment (Patenuade & Kupst, 2005)

Appendix C

Psychological Adjustment

Until the 1980's little was known about the psychological adjustment of children with cancer. While neurocognitive effects interfering with social and academic functioning have been documented in a number of studies, psychological maladjustment in this population is less understood. The extent to which these neurocognitive effects impact psychological functioning is also unclear. When the area of psycho-oncology first emerged much of the emphasis was placed on parents' coping with the death of their child. Research predominantly focused on the parents of children with cancer, particularly because at the time children were being less informed of their illness than is observed today. It was through observation and study of children in cancer centers that psycho-oncologists became aware that children often understood their illness much more than was believed and that children also often knew the seriousness of their diagnoses. It was then identified that by avoiding discussing the seriousness of their illness and the child's potential death, children were left to cope with these issues independently. It was these studies and findings that created a new outlook to psycho-oncology and established open communication between children, their parents and healthcare professionals. It is now common practice for psychologists and psychiatrists to be present in pediatric cancer care centers. Their presence has fostered an awareness of the psychological challenges and struggles faced by these children and their families (Patenaude & Kupst, 2005).

In the 1980's the National Cancer Institute increased the amount of funding to address questions regarding the impact of diagnosis, treatment, and late effects in cancer populations. Studies focused on areas of treatment-related stressors (e.g., procedural

distress), as well as examined intrapersonal effects of cancer on the patient's psychological and general functioning (Patenaude & Kupst, 2005).

Koocher and O'Malley (1981) were the first to examine a large number of survivors. This study used clinical interviews, self-report measures of depression, anxiety, self-esteem, and socialization, as well as projective personality assessment cards to assess the psychological functioning of 117 childhood cancer survivors. On the basis of a global adjustment rating, 59% of the participants were identified as having adjustment difficulties, and 23% of participants were found to be impaired on the basis of their symptoms. Socioeconomic status was found to be positively associated with adjustment. Certainty of treatment outcome was also linked to levels of distress (Koocher & O'Malley, 1981). This study is one notable exception to the numerous studies that have followed indicating that despite the stressors and fears associated with a cancer diagnosis, significant psychopathology in the pediatric cancer population was not the normative outcome, but rather was relatively rare (Patenaude & Kupst, 2005). Koocher and O'Malley's conclusions have been challenged on the basis of their categorization of adjustment difficulty as being too liberal, methodological issues, and a lack of comparison with a healthy norm (Gray et al., 1992).

Koocher and O'Malley (1981) termed a tenuous sense of longevity which cancer survivors may experience as the Damocles Syndrome. This syndrome was hypothesized to produce anxiety, depressive mood, fear of relapse, and damaged body image. This syndrome, along with other effects of cancer on psychosocial functioning, has been reviewed in studies since Koocher and O'Malley. Cella and Tross (1986) found that male survivors of Hodgkin disease did not differ from non-patients on most measures of

psychological dysfunction, emphasizing the finding that psychopathology is rare in pediatric cancer survivors. This study identified possible existential gains in life appreciation resulting from the cancer experience; however, possible residual effects were also demonstrated. Subtle findings indicated increased avoidant thinking, lower intimacy motivation, and diminished work capacity in cancer survivors. When participants were categorized as low- and high-risk groups, determined by disease severity and time since treatment, high-risk participants showed increased distress. Increased avoidant thinking has been consistently observed in the literature and denial is believed to be a major coping mechanism for pediatric cancer patients. The use of psychotropic medication was also analyzed in this study comparing use of participants in treatment versus out of treatment. Percent of psychotropic use was found to be 22% in patients in treatment and 13% for those off treatment; however, this finding was not significant (Cella & Tross, 1986).

Consistent with earlier studies in the 1980's, most psycho-oncology studies have not found evidence of serious maladjustment or psychopathology in the pediatric cancer population (Patenaude & Kupst, 2005). Zebrack & Zeltzer (2003) sent a questionnaire to over 5,000 pediatric cancer survivors. Results demonstrated depression rates in long-term pediatric cancer survivors to be comparable to rates identified in the general population. A review of various studies examining the psychological functioning of children with an array of chronic illnesses demonstrated children with cancer were at a lower risk for maladjustment than were those children with other types of chronic illnesses (Lavigne & Faier-Routman, 1992).

Gray et al. (1992) examined adjustment and psychological functioning in adult survivors of childhood cancer in comparison to healthy age-matched peers. Participants were administered standard self-report inventories, a projective picture task, and an experience-sampling technique. The experience sampling-technique involved frequent cueing of participants by electronic pagers to answer questions regarding their current thoughts, behaviors, and feelings. This study found support for the consistent belief that survivors of childhood cancer are generally well adjusted. In fact, results derived from the sampling-technique suggested better mental health than their healthy peers. Specifically survivors expressed more positive affect, less negative affect, more perceived control, and high motivation for interpersonal motivation. Findings of high interpersonal motivation were contradictory to findings by Cella and Tross; however, differences in population and measurement were suggested reasons for such differences (Gray et al., 1992).

Elkin, Phipps, Mulhern and Fairclough (1997) studied psychological functioning in 161 cancer survivors using the Symptom Checklist-90-Revised (SCL-90-R), a self-report designed to assess the psychological symptom patterns of both medical and psychiatric patients. Consistent with previous findings, the sample of adolescent and young adult survivors of pediatric cancer were characterized by low levels of general psychological distress and an absence of psychopathology. Survivors were actually found to be significantly healthier than expected based on normative data. This study, however, also cited evidence suggesting pediatric cancer survivors may minimize affective distress and present themselves in a more favorable light (Elkin, Phipps, Mulhern, & Fairclough, 1997).

When pediatric cancer survivors were examined four years post diagnosis, results consistently demonstrated that the psychological problems experienced by these children were comparable to rates in the general population. The parents of these children were also examined four years later, and adequate family coping was identified based on the stable marital status reported by these parents (Sawyer et al., 2000).

Ross et al. (2003) investigated whether pediatric cancer survivors were at increased risk for psychiatric hospitalization. This study's sample was a large cohort of 3,710 pediatric cancer survivors with up to 24 years of follow-up. Rates found in this sample were then compared to rates in the general population. Findings demonstrated an overall risk of admission into a psychiatric facility to be significantly increased as compared with the general population. Increased risk, however, was restricted to participants who had previously had brain tumors. Increased rates of psychiatric hospitalizations primarily resulted in diagnoses of psychoses of somatic, cerebral causes. Rates of schizophrenia were also found to be elevated in patients previously treated with radiation therapy. Pediatric cancer survivors were not found to be at higher risk for any other psychiatric disorders, including affective disorders. Overall findings were consistent with previous studies, which indicated comparable rates of depression, anxiety, and overall mood disorder (Ross et al., 2003). Findings specific to brain tumor survivors indicate these individuals may be a population of particular risk. Populations of particular risk will be discussed in greater depth.

Studies examining psychological adjustment in cancer survivors suggest functioning to be within normal limits, although some studies have identified psychosocial difficulties. Selection in measures of psychopathology alone versus

adaptation may contribute to varying results (Madan-Swain, 1994; Meyer & Fuemmeler, 2005). When examining psychosocial functioning it may also be important to include measures of family functioning, as they are integrally related. Global assessments of families suggest adequate adjustment, although few components of adaptation within a family have been examined. Madan-Swain et al. (1994) considered a wide variety of adjustment measures and used multiple informants in an attempt to understand previous discrepancies in the literature. Patients, their families, and their teachers completed measures of adaptation, coping, body image, sexual adjustment and psychopathology. Consistent with the literature, most adolescent cancer survivors demonstrated minimal psychiatric symptomatology, which was corroborated by their teachers. Adolescent cancer survivors did, however, report some adjustment difficulties. Body image disturbances were identified in this study and families reported more rigidity and inflexibility. (Madan-Swain et al., 1994). These findings indicated subtle and specific areas of functioning that may be affected during cancer treatment.

While overall adjustment and psychological functioning have been found to be near normal levels, some evidence suggests that more subtle areas may be adversely affected in long-term cancer survivors. An estimated 25-30% of children and family members have significant personal and social difficulties after childhood cancer treatment. Areas identified as being problematic in this population include impaired and decreased social relationships, self-concept, self-esteem, and academic difficulties, as well as the presence of posttraumatic stress symptoms (Patenaude & Kupst, 2005).

Noll et al. (1991) studied peer relationships in children actively undergoing treatment or those that had recently completed chemotherapy regimen (within the previous 18 months). Comparisons were made between pediatric cancer patients and matched controls on the following dimensions: social reputation, interpersonal acceptance, loneliness, and self-worth. Peer nominations indicated that children with cancer were more often nominated to roles descriptive of sensitivity and isolation. While differences were identified in social reputation, no differences between cancer patients and their peers were found from the sociometric data and self-report measures on self-concept and loneliness (Noll et al., 1991). While many cancer children have maintained good peer relationships throughout the course of treatment, those children and adolescents who seem to be at highest risk for peer difficulties were those who had obvious changes in physical appearance and those whose treatment affected the central nervous system (Kazak, 2005).

Several studies have examined self-esteem in survivors of cancer. No major differences have been identified between pediatric cancer survivors and control groups in regards to self-esteem (Langevold, Stam, Grootenhuis, & Last, 2002). Being that adolescence marks a time that is often accompanied by decreased self-esteem and increased social comparisons, self-esteem in cancer patients and survivors in this developmental stage may be of particular importance for researchers. Further, body image has strong implications for self-esteem and social adjustment. Body image may be especially important in adolescents with cancer, as these adolescents must cope with numerous side effects impacting physical appearance (e.g., hair loss). To date, few controlled empirical studies have examined body image issues among adolescent cancer

patients. Pendley, Dahlquist, and Dreyer (1997) found no significant differences between pediatric cancer survivors and healthy peers on either objective ratings of appearance or self-perceptions of attractiveness. The most notable finding in this study was the differences between the two groups in terms of peer activities, with cancer survivors participating in less than half of the activities with peers than was participated in by controls. Despite participating in less peer activities, cancer survivors did not report feeling badly about their lack of participation in peer activities, findings which are consistent with findings reported by Noll and colleagues (1993). Within the cancer sample, loneliness, body image concerns, and social anxiety were associated with time since treatment. These findings suggested differences between peer groups may not develop for several years after treatment. The authors attributed this finding to the possibility of a lag period during which positive physical changes occur and survivors are happy to have successfully completed treatment; however, after several years the positive physical changes slow and comparison groups may shift from other children with cancer to healthy peers (Pendley, Dahlquist, & Dreyer, 1997). The emergence of late effects previously discussed may also contribute to the aforementioned findings.

Kazak and colleagues (1994) examined social adjustment, family environment, support systems, anxiety and hopelessness at several time points in adolescents and pre-adolescents. This age range was chosen due to the processes of differentiation between adolescents and their parents, autonomy, and the increased importance of peer groups. Measures were administered to both the adolescents and their parents. Findings supported the notion that most cancer survivors are psychologically well adjusted overall. Adolescents scored near normative levels with respect to social support, family

functioning, and perceived self-competence. Parents also reported levels of family functioning, psychological distress, and perceptions of their children that were consistent with norms for measures used. There was a subgroup of participants that were found to have increased levels of distress. This study identified participants receiving special education services as experiencing higher levels of anxiety and as being perceived by parents as having greater behavioral difficulties. Findings support the idea that cancer survivors with learning problems may be at a higher risk for poorer adjustment and psychological functioning (Kazak, Chistakis, Alederfer, 1994). The neurocognitive impact of cancer and its treatments may have contributed to this finding.

Being that the pediatric cancer population has been found to be generally well-adjusted but some subtle difficulties have been identified, a post traumatic stress model has been developed to assist with the synthesis and comprehension of such findings (Stuber et al., 1996). A diagnosis of cancer and its treatment may be likened to a trauma with both an acute phase and subsequent chronic stressors, similar to the occurrence of a natural disaster (Barakat et al., 1997). Following the observation of significant heightened arousal and avoidance behaviors in individuals diagnosed with cancer, cancer patients were used in the field trials for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). These trials supported the presence of Post Traumatic Stress Disorder (PTSD) symptoms in cancer patients. As a result, “learning that one/one’s child has a life threatening disease” was added to the DSM-IV as a traumatic event, which could precipitate PTSD (Hobbie et al., 2000).

Stuber et al. (1996) examined 65 families of survivors who had completed treatment a mean of 6.7 years prior. Results indicated a substantial number of childhood cancer survivors and their parents reported symptoms of PTSD. Of the survivors, 12.5% reported symptom levels consistent with a clinical diagnosis of PTSD. Parents, both mothers and fathers, reported levels of symptoms even higher. Findings also revealed time since treatment was not associated with PTSD symptoms, which indicated symptoms may not abate during the first few years post-treatment (Stuber et al., 1996). Similar findings were reported by Barakat et al. (1997), which demonstrated higher rates of PYSD symptoms in cancer survivors and their parents. These researchers also hypothesized the perception of threat involved in the cancer and its treatment may be more influential on child adjustment than the objective characteristics of treatment (Barakat et al., 1997).

Kazak et al. (1997) found similar findings with regards to parents but not children. Findings indicated parents of childhood leukemia survivors had elevated symptoms of PTSD compared to parents of healthy children. Survivors of childhood leukemia themselves, however, were found not to differ from healthy comparison children in level of posttraumatic stress symptoms (Kazak et al., 1997).

Hobbie et al. (2000) examined PTSD in young adult survivors of childhood cancer. Results identified one-fifth of childhood cancer survivors as meeting criteria for a diagnosis of PTSD. These rates are comparable to those indicated in the adult cancer survivor research. Young adult survivors who qualified for a PTSD diagnosis were also found to demonstrate higher levels of psychological distress as well (Hobbie et al., 2000). The association between PTSD and psychological distress was explored and supported by

Meeske et al. (2001). Meeske et al (2001) compared childhood cancer survivors with PTSD to survivors without PTSD. Findings indicated psychological distress scores on the Brief Symptom Inventory (BSI) fell in the clinically significant range in the PTSD survivor group. Authors reported that the study sample as a whole appeared no different than its peers until survivors were analyzed by PTSD status, at which time the psychological morbidity of this subset became apparent (Meeske et al., 2001).

Research has identified several factors that may be associated with maladjustment in pediatric cancer survivors. Several studies have examined the relationship between psychological adjustment and disease, treatment and environmental variables (Patenuade & Kupst, 2005).

Diagnosis of a brain tumor may place children at greater risks for psychological maladjustment. Several studies have demonstrated increased risk for children with brain tumors. As previously discussed, Ross et al. (2003) found increased rates of psychiatric hospitalization for survivors of brain tumors only. Another area that is consistently reported to be adversely affected in these children and adolescents is social functioning. Vannatta et al. (1998) examined children who had been previously diagnosed with a brain tumor but were regularly attending school again. Results indicated brain tumor occurrence significantly affected self, peer, and teacher perceptions of social acceptance and reputation. These children were described as being more socially isolated, and based on sociometric nominations, were less often identified by peers as a best friend. Although children with brain tumors were no longer actively receiving treatment, they were still described by peers as being sick and easily fatigued (Vannatta et al. 1998). Other areas of functioning identified as being adversely affected in children with brain

tumors as compared to cancer controls included social competence, participation in activities, and school performance (Carpentieri et al., 1993). Findings also have indicated tumor location may contribute to adjustment and psychosocial functioning. Carpentieri et al. (1993) demonstrated children with non-third ventricle tumor and nonhemispheric tumor exhibited greater social deficits. Abnormal CT-measured brain volume was also found to be associated with a significant increase in internalizing problems (Carpentieri et al., 1993). Results obtained by Radcliffe et al. (1996) challenged the prevailing view that children with brain tumors have poorer psychosocial outcomes. Radcliffe et al. (1996) examined brain tumor survivors two to five years post diagnoses using multi-instrument, multi-respondent methodology. Findings demonstrated equivalent or lower rates of anxiety and depression in brain tumor survivors, as reported by mothers and children. Teachers also identified brain tumor survivors as generally similar to other students (Radcliffe et al., 1996).

In addition to specific diagnoses placing children more at-risk for maladjustment, children and families' reactions to diagnoses has also been linked to psychological functioning. Kupst et al. (1995) demonstrated that those families with the most difficulty at time of diagnosis also experience the greatest distress throughout treatment and even after treatment is completed. Kazak et al. (2003) have demonstrated similar findings by examining psychosocial risks present at time of diagnosis. This study conceptualized a three-tiered psychosocial risk framework based on the Psychosocial Assessment Tool (PAT), a psychosocial screening tool assessing psychosocial risk across ten domains identified as relevant to cancer patients and their families. Data based on the PAT demonstrated 59.2% of families evidenced minimal risk, 33.6% reported several risk

factors, and only 7.2% reported multiple risk factors. Identifying early risk may assist in intervention and prevention of psychological maladjustment later in the treatment process (Kazak et al., 2003). Age of child at time of diagnosis and time since treatment have been indicated as well. For example, older cohorts may have been exposed to more intensive treatment (Elkin, Phipps, Mulhern, & Fairclough, 1997).

As previously indicated, treatment process may also impact psychological functioning. A study which examined children who underwent stem cell transplantations indicated that these children were found to function competently. Previous studies, however, have reported increased levels of anxiety, vulnerability, and emotional sensitivity, as well as fewer peer relationships, in pediatric stem cell transplantation survivors. Results of these studies combined indicate stem cell transplantation may affect psychosocial adaptation without causing or eliciting psychopathology (Simms et al, 2002).

Researchers have hypothesized that cranial radiation therapy places cancer patients at an increased risk for maladjustment. Noll et al. (1997) examined academic and behavioral problems in children with ALL who had received whole brain radiation therapy. These children were not identified as having more academic or behavioral problems than children who did not receive whole brain radiation from the perspective of parents and teachers (Noll et al., 1997). These findings do not support the notion that more intensive treatment leads to greater psychological maladjustment.

Demographic variables have also been associated with treatment outcome and adjustment. As is typical in the general population as well, studies have found behavioral problems in cancer patients and survivors were reported to be higher by parents who

reported more psychological distress themselves. Social class and maternal coping have also both been linked to better adjustment in cancer survivors. Age and gender have not been consistently associated with psychological functioning and adjustment (Eiser, Hill, & Vance, 2000). Some studies have indicated females may be at risk for psychological problems; however, other studies have not supported this finding (Langeveld et al., 2002). Two studies considered minority status as a correlate of psychosocial functioning. Findings indicated minority survivors of ALL showed highest rates of mood disturbance. Black cancer survivors were, however, identified as being more likely to be married in a long-term survivor study (Langeveld et al, 2002). While overall psychological functioning in the pediatric cancer population is believed to be comparable to the general population, there are some subtle differences and numerous variables that contribute to adjustment.

Appendix D

Previous Studies

Since the mid-1980s, the research program in the area of biopsychosocial and neurodevelopmental aspects of pediatric cancer at the University of Miami has explored a number of factors related to neuropsychological functioning, quality of life, and neurodevelopment among children treated for cancer. At the current time, a study funded by the American Cancer Society is being conducted that is evaluating the impact of a school-focused intervention designed to improve neurocognitive functioning and academic achievement in children with brain tumors or leukemia.

Psychological Functioning and Psychopharmacological Use

Over the last five years, a randomized school-focused intervention study for children with leukemia or brain tumors has been conducted. The study examined the utility of different levels of monitoring of Individual Education Plans (IEPs) in the school system for children who have been treated for cancer affecting the CNS and/or requiring CNS-directed treatment. The study has enrolled 65 children with cancer, and will recruit a comparison group of healthy children without cancer during the last year of the study. All of the participants with cancer participate for three years of intervention follow-up and receive a total of four comprehensive neuropsychological evaluations over the course of the study.

This project has provided several innovative and clinically relevant observations. First, an unusually high frequency of characteristics of autism spectrum disorder (ASD) among children who have been treated for leukemia (ALL) has been observed.

Specifically, 7 of 44 (16%) children treated for ALL displayed characteristics of ASD, in contrast to only one of the children treated for brain tumors (Goldman et al., 2008).

Secondly, during the course of this study, a significant number of parents raised questions regarding whether their children should be prescribed psychotropic medications. A review of the sample showed 14 of 65 (21.5%) children treated for ALL or a brain tumor were on a psychotropic medication or had been prescribed psychotropic medications in the past. The majority of these 12 children were taking a stimulant medication; however, other psychotropic medications included antidepressants and antipsychotics (i.e., paroxetine, risperidone, and olanzapine) (Ward et al, 2008).

As part of the protocol for the school-focused intervention study, children were administered repeated neurodevelopmental assessments and recommendations were made based on the evaluations. Of the 57 participants at the time of the last analysis of the data, 38% were recommended for consideration of stimulant medication based on testing results, behavioral observations, and parent/teacher reports from the first neurocognitive evaluation. Few children (n=8), however, were actually subsequently prescribed stimulant medication. It was also found that among the identified participants taking stimulant medication during at least one of their four neurodevelopmental evaluations, changes in performance across time were not observed. Further, no changes were noted in performance when a child began taking stimulant medications from one year to the next. These findings, however, were based on case studies and therefore may not have truly captured the stimulant effects (Snyder et al., 2007).

There are various barriers that may affect whether a parent decides to have their children be prescribed psychotropic medications. These include (a) parent hesitation as

they may be adverse to the continued use of various medications after the intense, long-term chemotherapy regimens their children were exposed to (Butler & Copeland, 2006), (b) the pediatric cancer population is at risk for various health conditions (e.g., cardiac problems) which may interfere with safe psychotropic medication use, and (c) careful monitoring of the dosage of stimulant medications is particularly important for this population as they may be more sensitive to stimulant medications as a result of their treatment (Snyder et al., 2007).

The finding that 21.5% of children enrolled in a clinical trial are prescribed a psychotropic medication suggests that children treated for cancer may be more commonly prescribed psychotropic medication than children in the general population. Rates of psychotropic medication use in the general population range from one to six percent depending on the type of medication (Portteus et al., 2006; CDC, 2007). As the rates of psychological illness (i.e., depression and anxiety) have not consistently been found to be higher in this specific population, this raises many important questions.

Neurodevelopmental Model

Cancer, infection with the human immunodeficiency virus, and sickle cell disease have all been found to have adverse effects on the central nervous system. These chronic illnesses and their adverse effects provide models for a better understanding of the relationship between brain development and neuropsychological abilities. Functional deficits are a result of complex determinants, and the emergence of such deficits is impacted by the nature of brain involvement and the timing of such involvement. Investigators at the University of Miami Miller School of Medicine have described a neurodevelopmental model that integrates (a) the understanding of the biologic

mechanisms associated with these deficits, (b) ameliorating factors, and (c) the pattern of deficits that can be expected as part of disease and treatment to describe current deficits and predict future challenges for children treated for various chronic illnesses (Armstrong, 2007; Armstrong & Briery, 2004; Armstrong & Horn, 1995).

This neurodevelopmental model is based on several key components. First, it suggests the specific functional abilities that may be impaired are clearly associated with the age of the child at the time brain injury or the time alteration in brain development occurred. It is at this point that the normal developmental course observed in healthy children is disrupted. The earlier in the developmental sequence, the more neurodevelopmental functions are likely to be disrupted, and the severity of the disruption is likely to be greater. Second, the model suggests that the specific functions that are impaired will depend on the age of the child at the time of current assessment. The amount of time elapsed between when brain injury occurred and the time of testing may also have a significant impact on the child's functioning. While illness may have immediate physical effects, it may also have cognitive effects that reveal themselves over time. These cognitive effects evolve over time as a result of several factors, including interruption of myelin development, failure of connections to develop, and increasing complexity of material in school based on typical brain maturation. If not treated, developmental and neurocognitive difficulties may be noted in infancy, appear subtly during the school-age years, or become evident during the teenage years. It is possible for the adverse effects of the illness on cognitive functioning to appear immediately at the time of brain injury; however, the course varies greatly between children. Deficits in neurocognitive functioning may be global, affecting multiple areas of functioning, or

specific, impeding only one or two areas of functioning. (Armstrong,2007 ; Armstrong & Horn, 1995; Armstrong, Willen, & Sorgen, 2003; Cousens et al, 1992;). The neurodevelopmental model has typically been applied to the arena of cognitive deficits; however, the model may also be applicable to the development of psychological difficulties.

Appendix E

Psychopharmacological Use

Research in the general area of psychological functioning in pediatric cancer survivors is sparse; however, knowledge and research in the area of psychopharmaceutical use in this population is practically nonexistent. In fact, research is scarce regarding the use of psychopharmacological medication in the general child population.

In the general child and adolescent population there has been a marked expansion in the use of psychotropic medication, primarily stimulant medication and antidepressants (Olfson et al., 2002). Research has consistently reported an increase in psychotropic drug use in school-aged children and preschool-aged children, with a rapid increase after 1991. Adolescent use had historically been lower; however, recent reports have suggested adolescents have the highest rates of increase in psychotropic medication use (Thomas et al., 2006).

Thomas et al. (2006) examined psychotropic use in adolescents, aged 14 to 18 years. Findings indicated a 2.5 fold growth between 1994 and 2001, with prescription rates rising from 3.4% in 1994-1995 to 8.3% in 2000-2001. Approximately, one-third were being treated for a diagnosis of Attention Deficit Hyperactivity Disorder (ADHD); however, between 14 and 26 percent of medication-related office visits in which psychotropics were prescribed were not associated with a mental health diagnosis. Results also indicated high rates of increase in “other” psychotropic medications, which is mainly composed of antipsychotics (Thomas et al., 2006). Despite the use of psychotropic medication being controversial, rates in the pediatric population were

estimated to be approximately six percent. While rates of medication use have increased, little research has been conducted regarding the efficacy, safety and the pharmacokinetics of these medications in children (Pao et al., 2006).

Stimulants have been the most researched and prescribed medication in children and adolescents in the area of mental health, typically for the management of ADHD. Stimulant use has increased drastically for children of all ages, including preschoolers. Few studies have researched long-term effects of stimulant use in children; however, a recent clinical trial has indicated efficacy and safety of stimulant medication over the course of 14 months. Some concerns have been raised regarding the impact of stimulant medication on cardiovascular functioning, as a result of increased heart rate, respiration, and blood pressure (Brown & Sammons, 2002). Concerns have also been raised regarding stimulant use and sudden death; however, this concern has been based on spontaneously reported post-marketing information (Vitiello, 2007). Stimulant use may be of particular interest with regard to pediatric cancer patients and survivors. Neurocognitive deficits due to impaired frontal lobe functioning/development may place cancer survivors at an increased risk for needing stimulant medication (Butler & Mulhern, 2005).

Aside from common diagnoses of ADHD, major depressive disorder (MDD) is also a disorder seen in the pediatric population, affecting approximately 2% of children and 6% of adolescents (Boylan, Romero, & Birmaher, 2006). Typically antidepressants are used to treat target symptoms of depression (e.g., depressed mood, anhedonia, anergia, appetite change, and decreased concentration) (Brown & Sammons, 2002). Efficacy in children and adolescents has been demonstrated for several antidepressants;

however, few have been approved by the Food and Drug Administration (FDA). Therefore, many children and adolescents are being treated off-label (Boylan, Romero, & Birmaher, 2006). It has been estimated that up to 60% of all medication prescriptions written over the course of one year are off label, and a large number of these target the pediatric population (Spetie & Arnold, 2007). To date, no dose-response studies of selective serotonin reuptake inhibitors (SSRIs) have been conducted, thereby leaving physicians to the dosing approach of “start low and go slow” (Boylan, Romero, & Birmaher, 2006). Practitioners have generally tried to extrapolate findings of adult research in psychopharmacology to children (Vitiello, 2007).

While efficacy continues to be explored, the issue of safety of antidepressant use in children and adolescents has become a primary focus of research. Increased risk of suicidal ideation and behavior was first reported by the manufacturers of paroxetine, after a study conducted by the manufacturer suggested increased risk of suicide-related adverse events (SREs) (Hammad, Laughren, & Racoosin, 2006). In 2004, the Food and Drug Administration (FDA) instructed manufacturers of all antidepressants to revise their product labeling to include a boxed warning statement, as well as an expanded warning statement, alerting health care providers to an increased risk of suicidality in the pediatric population being treated with antidepressants (FDA, Public Health Advisory). This risk was determined by a meta-analysis of clinical trials of nine antidepressant drugs, and a total of 22 randomized, placebo-controlled trials. Results indicated a total of 108 SREs, 74 on active drug and 34 on placebo. Of the 108 SREs, 75 of the events involved some type of self-injury (Mosholder & Willy, 2006). No completed suicides occurred in any

trials (FDA, Public Health Advisory). Results supported an increased risk of suicidality during the first few months of treatment with antidepressants due to increased suicidal adverse events relative to placebo (Mosholder & Willy, 2006).

Data has also indicated some inconsistency with regard to antidepressant use and suicide in children and adolescents. Studies have suggested rates of antidepressant medication use in the pediatric population have increased, while absolute rate of adolescent suicide has decreased in recent years. Ecologic data has suggested an association between increased antidepressant use in adolescents and decreased adolescent suicide rates. Consistent with the previously discussed association, recent suicide autopsy studies have been unable to find evidence of antidepressant use in most suicide victims (Hammad, Laughren, & Racoosin, 2006).

There is also a scarcity of data regarding antipsychotic medication use in children and adolescents. Haloperidol (Haldol) has been the mainstay in the treatment of childhood-onset schizophrenia (Brown & Sammons, 2002). Atypical antipsychotics have begun to replace some of the more traditional antipsychotics in the treatment of bipolar, childhood-onset schizophrenia, tic disorders, and pervasive developmental disorders (Jefferson, Markowitz, & Brewerton, 1998). Use of antipsychotics has been implicated in health risks for children. Long-term treatment of such disorders has been associated with a risk of inducing tardive dyskinesia. It has also been suggested younger patients were more susceptible to the development of hyperprolactinemia. Recently, the FDA has issued a black-box warning regarding the development of diabetes in individuals treated with antipsychotics (Spetie & Arnold, 2007).

Psychotropics have been consistently used in the treatment of pervasive developmental disorders. A large survey of subjects with autism determined 30.5% of participants were taking one or more psychotropic medication. Neuroleptics and anticonvulsants were identified as the two most frequently used psychotropics (Martin et al., 1999). Martin et al. (1999) examined psychotropic medication use in individuals diagnosed with Asperger Syndrome and high functioning autism. Findings indicated overall 55% of participants were taking psychotropic medication, with the most commonly used being antidepressants (32%), stimulants (20%) and neuroleptics (17%). Lifetime use of psychotropic medication in this population was 69%. General and child psychiatrists, as well as pediatric neurologists, were found to be most commonly the prescribing doctors (Martin et al., 1999).

A limitation in the child psychopharmacology literature is that little is known about possible long-term effects of psychotropics on a child's developing brain. Long-term effects may be especially critical for children under the age of six. The developing brain undergoes dramatic changes involving the neurotransmitter system, which is also the very system upon which psychotropic medications act. Research findings have suggested that early blockade of a neurotransmitter system can cause permanent down-regulation of that neurotransmitter system. Likewise, early stimulation can result in persistent up-regulation (Vitiello, 1998). Concerns regarding psychotropic medication interference with neurotransmitter systems have been identified in animal research and remain unclear in humans (Vitiello, 2007). Preschoolers may be at an increased risk for long-term effects due to their brains having not yet undergone many critical stages of development. Almost no pharmacokinetic studies and few safety and efficacy studies

have been conducted in the preschool population, leaving these children as a vulnerable population (Spetie & Arnold, 2007). Cancer patients also introduce a variety of challenges pharmacologically. For those children actively undergoing cancer treatment, psychotropic medication becomes part of a complex regimen of medication. Pediatric cancer patients may have alterations in body composition, illness affecting cardiac, renal, or hepatic function, and individual variations in drug metabolizing capacity, all of which may increase risk for clinically significant drug interactions (Kalash, 1998). Cancer and its treatment may also place children at risk for permanent alterations in their CNS and neurochemical functioning. These disease and treatment effects may in turn place these children at an increased risk for psychosocial maladaptiveness and long-term cardiomyopathy, leading to more severe side effects and greater negative outcomes resulting from medication use.

To date only two studies have reported on antidepressant use in the pediatric cancer population (Portteus et al. 2006). As previously discussed, rates of psychopathology in the pediatric cancer population have been found to be comparable to rates identified in the general population, despite increased stressors associated with cancer (Patenaude & Kupst, 2005). Portteus et al. (2006) found that 10% of pediatric cancer patients were prescribed antidepressant medication within one year of being diagnosed with cancer. Results also identified the prevalence of antidepressant use in adolescents being treated for cancer to be 23%, and 7% in younger children. Both rates are significantly higher than existing data for same-aged non-cancer controls (Portteus et al., 2006).

Pao et al. (2006) examined medical records of pediatric patients who had entered Pediatric Oncology Branch, National Cancer Institute clinical research trials between 2000 and 2003 in an effort to determine rates of psychotropic medication use among patients diagnosed with cancer. An overall rate of psychotropic use was determined to be 14% among these patients, and the majority of these patients were older than 12 years of age. Anticonvulsants (37%) and antidepressants (35%) were the most common psychotropic medications used by this population (Pao et al., 2006).

These reports indicated psychopharmacological use might be higher in the pediatric cancer population, despite increasing use in the general child population. This area is in need of further exploration, due to the psychopharmacological challenges potentially introduced by the pediatric cancer population.