1. STUDY TITLE: Prevalence and Treatment-Related Predictors of Psychoactive Medication Use in Adult Survivors of Childhood Cancer

2. WORKING GROUP AND INVESTIGATORS:

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3. BACKGROUND AND RATIONALE:

Psychological late effects following treatment of childhood cancer are relatively common sequelae which negatively affect survivors' quality of life.[1-5] Several studies, including those by Zebrack et al.,[4-6] have detailed the prevalence of reported psychosocial distress in the Childhood Cancer Survivor Study (CCSS) cohort. Psychological disorders such as anxiety and depression are often treated with psychoactive medications.[7, 8] Research has demonstrated that treatment with antidepressant medication and anxiolytic medication results in reduced symptoms and improved Health-related Quality of Life (HRQOL) in patients diagnosed with depression or Generalized Anxiety Disorder. Specifically, a study of patients with moderate depression found that symptoms of depression decreased and patients reported experiencing better quality of life following a two month trial of antidepressant medication.[9] Another study found that treatment of patients with Generalized Anxiety Disorder using a selective serotonin reuptake inhibitor (SSRI), a class of medications often used to treat depression and/or anxiety, was associated with a significant improvement in HRQOL following a short-term medication trial.[10] Unfortunately, there is a dearth of information regarding the prevalence of psychoactive medication use in survivors of childhood cancer, and research aimed at identifying whether HRQOL improves in cancer survivors treated with psychoactive medications is lacking. Such research is important to determine if there is an association between treatment with psychoactive medications and improved HRQOL.

Some survivors of childhood cancer may be more likely to use of psychoactive medications. Osteosarcoma survivors report increased rates of pain secondary to amputation. Greenberg et al. found that survivors of osteosarcoma experience mild ongoing pain and that the experience of phantom pain and neuralgia was common.[11] This pain may lead to increased use of analgesics, with corresponding effects on arousal.[12] There are increased rates of

seizures among children and adults diagnosed with and treated for brain tumors.[13, 14] Packer et al. found that 25% of CCSS participants experience seizures.[15] These survivors are more likely than other groups of adult survivors to take antiepileptics secondary to ongoing medication maintenance following a history of seizure disorder. Sex may also be a predictor of psychoactive medication use; in a community-based sample of adults in Ontario, women reported more use of sedatives, anxiolytics, and antidepressants, compared to men.[16]

In addition to potential positive impact on HRQOL, there is a need to better understand the individual and compound factors that contribute to use of psychoactive medication in cancer survivors as there may be adverse side effects (e.g., weight gain, type 2 diabetes, movement disorders) associated with use of some of these medications (e.g., antidepressants, antiepileptics, and neuroleptics).[17-20] Otto et al. found that HRQOL may predict response to analgesic treatment in patients with painful polyneuropathy and that various aspects of HRQOL improved with treatment for pain.[21] Krull et al. found that use of antidepressant medication among adolescents in the CCSS cohort was associated with physical inactivity and that use of stimulant medication during adolescence was associated with adult obesity.[22] This suggests that the side effect profile may be different in survivors of childhood cancer.

It is important to note that although there is the potential for positive benefits from taking psychoactive medications, some survivors may avoid taking these medications due to feelings of trepidation concerning medication use following treatment for cancer or worry about adverse side effects. It is also important for practitioners to be aware of the side effects so as to effectively counsel their patients regarding the benefits of psychoactive medcation. For some individuals it may be the initiation of taking a medication such as an antidepressant which enables them to re-engage in their environment and participate in physical exercise which, in turn, will activate endorphins that result in positive rather than negative feelings. Over time, the ability to re-engage in activities could lead to a behavioral method by which to treat a disorder such as depression and the potential to discontinue treatment with medication.

The information gained by identifying predictors of psychoactive medication use among adult survivors of pediatric cancer, will better inform screening and intervention practices for children, adolescents, and young adults who are at risk for psychosocial difficulties following treatment for cancer.

4. SPECIFIC AIMS/OBJECTIVES/RESEARCH HYPOTHESES:

4.1. Primary Aims:

- 4.1.1. To estimate the prevalence of psychoactive medication use among CCSS survivors and the CCSS sibling control group.
- 4.1.2. To identify predictors of psychoactive medication use among CCSS survivors.

4.2. Secondary Aim:

- 4.2.1. To evaluate HRQOL outcomes (i.e., Performance Function, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, Mental

Health) among survivors as a function of recent psychoactive medication use while controlling for cancer diagnosis or cancer therapy.

4.2.2. To identify predictors of new onset psychoactive medication use among CCSS survivors.

4.3. Primary Hypotheses:

4.3.1. The prevalence of psychoactive medication use will be higher in survivors compared to siblings.

4.3.2. Cancer characteristics (e.g., Osteosarcoma, CNS tumor diagnosis, amputation, cranial radiation therapy) will be associated with increased use of analgesics and antiepileptic medication in survivors.

4.3.3. Female survivors will demonstrate increased rates of psychoactive medication use in comparison to male survivors or siblings of either sex.

4.4. Secondary Hypotheses:

4.4.1. Survivors who endorsed experiencing psychosocial difficulties on the BSI at the Baseline survey and who were not taking psychoactive medication at the time of the Baseline survey will display increased rates of psychoactive medication use at the 2000 and 2003 Follow-up surveys in comparison to survivors who did not endorse increased rates of psychosocial difficulty on the Baseline survey.

4.4.2. Survivors who are taking psychoactive medications at the 2003 Follow-up will demonstrate more positive functional outcomes than those not taking psychoactive medications (i.e., HRQOL).

Medication use data have been collected at the time of each survey (Baseline, 2000 Follow-up, and 2003 Follow-up). Psychosocial functioning data were collected using the Brief Symptom Inventory (BSI-18) during the Baseline survey and the 2003 Follow-up; we propose to evaluate the effect of psychosocial functioning as assessed with the BSI-18 at the Baseline survey on psychoactive medication use at the time of the 2000 and 2003 Follow-up surveys while controlling for demographic, disease, and treatment-related variables. Additionally, we propose to evaluate HRQOL at the 2003 Follow-up in those survivors who are taking psychoactive medications and those who are not taking psychoactive medications in order to determine whether psychoactive medication use is associated with positive functional outcomes.

5. ANALYSIS FRAMEWORK:

5.1. Population: Cancer survivors who completed the Baseline survey, including the BSI, and who were 18 or older at Baseline. Aim 4.2.1 will require survivors to have completed the 2003 Follow-up survey, while aim 4.2.2. will require the survivors to have completed the Baseline and either the 2000 Follow-up or the 2003 Follow-up.

5.2. Outcomes of interest: The primary outcomes of interest are psychoactive medication use as assessed by survivor and sibling reports of medication use, and HRQOL as reported on the SF-36 at 2003 Follow-up. Psychoactive medications will include the following classes of medications: analgesics, antiepileptics, anxiolytics, mood

stabilizers, and neuroleptics. The content for the medication classes was reached through consensus between Drs. Neelam Jain, Dan Green, Nicole Ullrich, Lonnie Zeltzer, and Kevin Krull. Table 1 contains information detailing the numbers of survivors and siblings who were taking medications within each of the aforementioned classes at the time of the Baseline, 2000 Follow-up, and 2003 Follow-up surveys. We initially considered inclusion of stimulant medications as an additional class but found that there were too few survivors and siblings taking stimulant medications to include in the analysis. This is most likely due to the more recent trend towards prescription of stimulant medications for adults with attention difficulties and for the increasing age of the CCSS survivor and sibling cohort at the time of survey completions. Use of psychoactive medications among the sibling cohort is expected to mimic the general population. The sibling cohort is matched on socio-economic status, is generally healthy, and provided information on medication use at the same time points. Therefore, the sibling cohort can be used as a referent group for the survivor cohort for purposes of analysis.

Table 1: Observed Frequencies of Each Medication Class

	Survivors			Siblings		
	Baseline	2000 FU	2003 FU	Baseline	2000 FU	2003 FU
Analgesics	2375	1517	635	374	248	109
Antiepileptics	1164	939	848	55	52	62
Anxiolytics	369	375	295	39	57	61
Mood Stabilizers	709	1314	1689	165	294	470
Neuroleptics	99	93	120	18	5	20
Stimulants	146	118	96	30	30	31

- Medication information will be obtained from the CCSS Baseline Survey (B8: 1-16), 2000 Follow-up (6 a-q), and 2003 Follow-up (Q 1-9).
- Medication classes (categorized as dichotomous variables: yes/no for use) for the following groups: Analgesics, Antiepileptics, Anxiolytics, Mood Stabilizers, and Neuroleptics.
- HRQOL will be evaluated with SF-36 scores for the following domains: Performance Function, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health with impairment defined as scores falling below a T-score of 40 (1 standard deviation below the mean).

5.3. Primary Predictors:

- BSI (G1-G18) scores for Somatization, Depression, and Anxiety subscales and the composite Global Severity Index (GSI) will be dichotomized (yes/no) based on whether the performance is considered impaired with impairment defined as a performance falling $\leq 10^{th}$ percentile (T-score ≥ 63) based on standardized norms.

- Cancer Diagnosis (eight categories including leukemia, CNS tumor, Hodgkin, Non-Hodgkin lymphoma, Wilms' tumor, Neuroblastoma, soft tissue sarcoma, and Osteosarcoma)
- Chemotherapy Variables (Data categorized as cut-points, tertile scores, continuous variables, or dichotomous variables: yes/no) for Anthracyclines (yes/no), Alkylating Agents (tertile score), Antimetabolites including Methotrexate (continuous variable for IV, high dose IV, and IT Methotrexate), Anti-tumor Antibiotics (yes/no), Corticosteroids (yes/no), Enzymes (yes/no), Epipodophyllotoxins (yes/no), Heavy Metals (yes/no), Plant Alkaloids (yes/no)
- Radiation Variables (Data categorized as dichotomous variables: yes/no) for brain, chest, abdomen, and pelvis; no further localization required.
- Surgery Variables during treatment (Data categorized as dichotomous variables: yes/no) Amputation, single or multiple, no localization required. Appropriate ICD-9 codes including 84.0, 84.1: 84.10-84.19, will be used when reviewing surgical procedures for inclusion. Amputation data will also be taken from the Baseline questionnaire (B.9).

5.4. Covariates:

- Sex (A2 – Baseline survey)
- Age/Time Variables (Continuous, modeled 2 at a time)
  - Baseline Age (A1)
  - Age at Diagnosis
  - Age at 2000 Follow-up
  - Age at 2003 Follow-up
  - Time Since Diagnosis
- History of seizures (J5 on Baseline survey)
- History of stroke (F9 on Baseline survey)
- Pain (J36 on Baseline survey)
- Health Insurance Status (Q2 - Baseline survey)
- Household income (Q8 - Baseline survey)

5.5 Statistical Modeling

5.5.1. Frequency distributions will be used to categorize relevant outcome variables, predictors, and covariates according to reasonable groupings and consistent with previous CCSS manuscripts.

5.5.2. Descriptive statistics including means, standard deviations, medians, ranges, frequencies, and percents will be calculated for the primary outcome of interest (psychoactive medication use – yes/no) at each questionnaire as well as for the primary predictors (BSI, diagnosis, and treatment) and all covariates for both survivors and siblings (Tables I-III).

5.5.3. Comparisons of the primary outcome variables (any psychoactive medication use and specific classes) will be made between survivors and siblings at baseline using logistic regression models with robust variance estimates to account for within subject correlation (Table IV). A multivariable model adjusted for sex,

history of seizures, stroke, pain, health insurance status, and household income, will be fit and Odds Ratios (OR) and 95% confidence intervals will be reported for the comparison between survivors and siblings. This analysis will address Hypothesis 1 from the Primary Aim. In addition, we will evaluate both main effects and two-way interactions between sex and survivor/sibling status to determine whether female survivors are more likely to use psychoactive medications than female siblings or male survivors or siblings. This will address hypothesis 3 from the Primary Aim.

5.5.4. Among survivors, logistic regression analyses will be conducted for each outcome variable medication class (described in 5.2) using the diagnosis or treatment as a covariate (in separate models, as the two are confounded) and controlling for sex, age at diagnosis, current age, seizure history, stroke history, reported pain, health insurance status, and household income to create Odds ratios for use in each medication class (See Table V). If the rate of occurrence exceeds 10% we will evaluate relative risk ratios. These analyses will enable us to address hypotheses 2 from the Primary Aim.

5.5.5. Among survivors, logistic regression analyses will be conducted for each outcome variable medication class (described in 5.2) using the BSI outcomes from Baseline and controlling for sex, age at diagnosis, current age, seizures history, stroke history, reported pain, health insurance status, and household income to create Odds ratios for new onset medication use in each medication class (See Tables VI). This analysis will address hypothesis 1 from the Secondary Aim.

5.5.6. Among survivors who responded to the 2003 Follow-up, logistic regression analyses will be conducted for each outcome variable HRQOL (described in 5.2) using medication class as the primary predictor and controlling for sex, age at diagnosis, age at the 2003 Follow-up, health insurance status, and household income, to create Odds ratios for SF-36 outcomes (See Table VII). Separate analyses will be conducted to include diagnosis or treatment as a covariate. If the rate of occurrence exceeds 10% we will also evaluate relative risk. This will enable us to address hypothesis 2 from the Secondary Aim.

5.5.7. For all regression analyses, univariable analyses will be conducted first to identify variables contributing to each outcome at $p<0.10$. All variables meeting this riteria will be included in the multi-variable analyses for each outcome.

5.5. Examples of specific tables:

Table I
Survivor and Sibling Descriptive Statistics

	Survivor		Sibling	
	N	*P*	N	*P*
Sex				
Male				
Female				
Age at Diagnosis				
0-4				
5-9				
10-14				
15-20				
Age at Baseline (categories to be determined)				
Health Insurance				
Yes, Canadian				
No				
Household Income (categories to be determined)				
History of Seizures				
Yes				
No				
History of Stroke				
Yes				
No				
Pain				
Yes				
No				

	Survivor	
	N	%
Diagnosis		
Leukemia		
CNS		
HD		
NHL		
Wilms'		
Neuroblastoma		
Soft Tissue Sarcoma		
Osteosarcoma		
Treatment		
Chemotherapy		
Anthracycline		
Alkylating Agent		
Anti-metabolite		
Anti-tumor Antibiotic		

	Corticosteroids	
	Enzymes	
	Epipodophyllotoxins	
	Heavy Metals	
	Plant Alkaloids	
Radiation		
	Brain	
	Chest	
	Abdomen	
	Pelvis	
Amputation – single		
	Yes	
	No	
Amputation - multiple		
	Yes	
	No	

Table II

Psychoactive Medication Descriptive Statistics at Baseline (B), Follow-Up 1 (FU1), and Follow-Up 2 (FU2)

	Survivors						Siblings					
	B N	B %	FU1 N	FU1 %	FU2 N	FU2 %	B N	B %	FU1 N	FU1 %	FU2 N	FU2 %
Medication Class												
Analgesics												
Antiepileptics												
Anxiolytics												
Mood Stabilizers												
Neuroleptics												

Table III

Psychosocial Functioning at Baseline

	BSI-18			
	Somatization	Depression	Anxiety	Composite
Survivors				
N				
Mean				
SD				
Range				
p-value				
% Impaired $\leq 10^{th}$ %ile				
Siblings				
N				
Mean				
SD				
Range				
p-value				
% Impaired $\leq 10^{th}$ %ile				

Table IV: Multivariate Model of Psychoactive Medication Use in CCSS Survivors and Siblings					
	Analgesics	**Antiepileptics**	**Anxiolytics**	**Mood Stabilizers**	**Neuroleptics**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Siblings (Referent)	1.00	1.00	1.00	1.00	1.00
Survivors					
Sex (F vs. M)					
Pain					
Seizures					
Stroke					
Health Insurance					
Household Income					

Table V: Multivariate Model of Cancer Characteristics and Psychoactive Medication Use in CCSS Survivors

	Analgesics	Antiepileptics	Anxiolytics	Mood Stabilizers	Neuroleptics
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Survivors					
Sex (F vs. M)					
Age at Diagnosis					
Current Age					
Pain					
Stroke					
Seizures					
Health Insurance					
Household Income					
Diagnosis					
Leukemia					
CNS					
HD					
NHL					
Wilms'					
Neuroblastoma					
Soft Tissue Sarcoma					
Osteosarcoma					
Treatment					
Anthracycline					
Alkylating Agent					
Anti-metabolite					
Anti-tumor Antibiotic					
Corticosteroids					
Enzymes					

Epipodophyllotoxins					
Heavy Metals					
Plant Alkaloids					
Brain RT					
Chest RT					
Abdomen RT					
Pelvis RT					
Amputation					

Table VI: Multivariate Model of Psychosocial Status and New Onset Psychoactive Medication Use in CCSS Survivors Compared to Siblings					
	Analgesics	**Antiepileptics**	**Anxiolytics**	**Mood Stabilizers**	**Neuroleptics**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Siblings (Referent)	1.00	1.00	1.00	1.00	1.00
Survivors					
Baseline BSI-18 Impairment Rates (Impaired vs. Unimpaired)					
Anxiety					
Depression					
Somatization					
Composite					
Sex (F vs. M)					
Age at Diagnosis					
Current Age					
Pain					
Seizures					
Stroke					
Health Insurance					
Household Income					

Table VII: Multivariate Model of Functional Outcomes at Follow-Up 2 in Survivors								
	Performance Function	**Role Physical**	**Bodily Pain**	**General Health**	**Vitality**	**Social Functioning**	**Role Emotional**	**Mental Health**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Survivors								
Psychoactive Medications								
Analgesics								
Antiepileptics								
Anxiolytics								
Mood Stabilizers								
Neuroleptics								
Sex (F vs. M)								
Age at Diagnosis								
Current Age								
Pain								
Stroke								
Seizures								
Health Insurance								
Household Income								

6. SPECIAL CONSIDERATION:

Per Dr. Leisenring's recommendation, Dr. Jain will be working with Dr. Srivastava and his group at St. Jude Children's Research Hospital on the statistical analyses. Dr. Kumar Srivastava will have primary responsibility for the analysis at St Jude, with final review done at the statistical center in Seattle.

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