Childhood Cancer Survivor Study
Concept Proposal and Analytic Plan

1. **Study Title**
   Prevalence and Patterns of Prescription Psychoactive Medication Use in Adolescent Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study

2. **Primary Working Group**: Psychology

3. **Investigators**:

Yin Ting Cheung	901-595-7699	YinTing.Cheung@StJude.org
Analyst	(to be confirmed)	
Wendy M. Leisenring	206-667-4374	Wleisenr@fredhutch.org
Tara M. Brinkman	901-595-5683	Tara.Brinkman@StJude.org
Rebecca M. Howell	713-563-2493	Rhowell@mdanderson.org
Nicole J. Ullrich	617-355-0498	Nicole.ullrich@childrens.harvard.edu
Karen M. Lommel	859-323-6021	Kmlomm2@email.uky.edu
Pim Brouwers	301-443-6100	ebrouwer@mail.nih.gov
Allen Eng Juh Yeoh	+65-6772 4406	Allen_Yeoh@nuhs.edu.sg
Todd M. Gibson	901-595-8260	Todd.gibson@StJude.org
Leslie L. Robison	901-595-5817	Les.Robison@StJude.org
Gregory Armstrong	901-595-5892	Greg.Armstrong@StJude.org
Kevin R. Krull	901-595-5891	Kevin.Krull@StJude.org

4. **Background and Rationale**

Long-term survivors of childhood cancer experience a myriad of late-effects from the cancer and/or its treatment, such as neurological complications, pain, psychological distress and sleep problems. In the general population, many of these conditions are managed with psychoactive medications. Previous CCSS publications that examined psychoactive medication use in adult survivors (ie. older than 18 years of age) found that survivors were more likely to report baseline medication (22% vs. 15%, $p<0.001$), new onset medication (31% vs. 25%, $p<0.001$), as well as use of multiple concurrent medications ($p<0.001$) compared to their non-cancer siblings.[1] The use of psychoactive medications was concurrently associated with worse health-related quality of life and with impaired neurocognitive functioning on task efficiency and memory in adult survivors.[2]

Of interest to the current proposal is the pattern of psychoactive medication use in adolescent survivors (ie. less than 18 years of age) of childhood cancers. Within the general population in the United States, approximately 6.0% of adolescents aged 12 to 19 years were reported to have used psychotropic medications (ie. medications for attention deficit hyperactive disorder [ADHD]; anxiolytics, sedatives, and hypnotics) in the past month between 2005 and 2010.[3] Adolescent survivors are particularly vulnerable to psychological distress, neurocognitive impairment and behavioral abnormalities,[4-6] raising the question as to whether the use of psychoactive medication is more prevalent within adolescent survivors of childhood cancer compared to adolescent siblings. Previous CCSS reports demonstrated that adolescent survivors of childhood cancer, especially those with a history of leukemia, CNS tumors, or neuroblastoma, were at increased risk for more severe depression/anxiety, attention deficit, externalizing behavior and social withdrawal compared to sibling controls.[5,6] Use of stimulant medication during adolescence was associated with adult obesity (OR=1.9,

1.1 – 3.2), while antidepressant use was associated with physical inactivity (OR=3.2, 1.2 – 8.3).

To date, evidence on the prevalence and predictors of use of psychoactive medications in adolescent survivors of childhood cancer is lacking. Moreover, little is known about the impact of psychoactive medication use in adolescence on long-term consequences such as poor health status, education attainment and employment status in later life. With these research gaps in mind, we propose to examine the prevalence and patterns of psychoactive medication use in adolescent survivors of childhood cancer within the combined CCSS cohort. We are particularly interested in whether use has increased or decreased over the decades from the 1990's to the early 2000's, and factors associated with psychoactive medication use. For a subset of the population with longitudinal data, we will also examine the impact of medication use at baseline on their adult emotional, neurocognitive and functional outcomes, as well as health-related quality of life during adulthood. It is anticipated that upon the completion of this project, findings from this study may potentially guide the development of guidelines for appropriate provision of psychoactive medications for adolescent cancer survivors, and monitoring of adverse behavioral and social outcomes of medication use in these survivors.

5. Specific Aims and Primary Hypotheses

Aim 1.1: To estimate the prevalence of psychoactive medication use in a large and geographically diverse cohort of adolescent survivors of childhood cancer and compare the prevalence of psychoactive medication use at baseline in adolescent survivors against adolescent siblings. Both survivors and adolescent siblings of the Expansion Cohort will also be utilized in the analyses.

> Hypothesis 1.1: The use of psychoactive medications will be more prevalent among adolescent survivors of childhood cancer, as compared to their siblings and population estimates.

Aim 1.2: To describe the trends over time of psychoactive medication use among adolescent survivors and siblings who were surveyed in the 1990s and 2000s.

> Hypothesis 1.2: In both survivors and siblings, medication use will be more common in those who are surveyed in more recent years.

Aim 2: To identify clinical, diagnosis and treatment factors associated with psychoactive medication use in adolescent survivors of childhood cancer.

> Hypothesis 2: Survivors of CNS tumors and those treated with CNS-directed therapies that are known in the literature to be neurotoxic (ie. neurosurgery, cranial radiation therapy, intrathecal (IT) or intravenous (IV) methotrexate) will demonstrate increased use of psychoactive medications, as compared to survivors who did not receive these therapies.

Aim 3: To examine associations between academic functions (as reflected through special education services), parent-reported cognitive and behavioral problems, and psychoactive medication use in adolescent survivors of childhood cancer.

Hypothesis 3: More parent-reported cognitive, behavioral and social functioning problems, as well as special education placement, will be associated with increased use of psychoactive medications in adolescent survivors.

Aim 4.1: In the original cohort who completed the Follow-up 2 survey, to examine the association between psychoactive mediation use during adolescence and emotional, neurocognitive, health-related quality of life and post-traumatic stress symptoms (PTSS) during adulthood. (*Depending on the number of siblings who completed the follow-up survey, these associations will be examined within the adolescent siblings too.)*

Hypothesis 4.1.1: Adolescent survivors who were treated with psychoactive medications will demonstrate worse emotional outcomes (ie. higher levels of self-reported anxiety, depression, somatization and PTSS), neurocognitive outcomes (ie. worse self-reported memory, processing speed and attention problems) and poorer health-related quality of life during adulthood, as compared to those who were not treated with psychoactive medications ie. We do not expect psychoactive medications to normalize their behavioral and emotional outcomes.

Hypothesis 4.1.2 (exploratory): Based on existing literature that an increased risk of suicide ideation and behavior is found in patients on antidepressants and antiepileptic drugs – among adolescent survivors who were treated with psychoactive medications, the risk of endorsing suicide ideation will be higher in adolescent survivors treated with antidepressants and antiepileptic drugs, as compared to those who were not treated with these 2 classes of drugs.

Aim 4.2: In the original cohort who were adolescents at baseline and above 25 years of age when they completed the 2007 Follow-up survey, to examine the association between psychoactive mediation use during adolescence and education attainment and employment status as adults.

Hypothesis 4.2: Adolescent survivors who were treated with psychoactive medications will demonstrate lower education attainment and higher unemployment rates, as compared to those who were not treated with psychoactive medications.

6. Analysis Framework

7.1 **Study Population:** Survivors and siblings enrolled in the combined CCSS cohort.

7.2 **Inclusion criteria:**

- CCSS survivors and siblings ≤18 years of age at baseline survey
- Aim 4 will require the subset of CCSS survivors and siblings from Original Cohort who completed the baseline when ≤18 years of age and also completed a 2003 or 2007 follow-up survey. Aim 4.2 will the subset of the above subjects who completed the 2007 survey when they were over age 25.

7.3 **Outcomes for Aims 1, 2 and 3:**

- Use of psychoactive medications (categorized as dichotomous variables: yes/no for overall use, as well as based on each category of psychoactive medication) [original baseline survey B8; expansion baseline survey B8]. Based on the American Hospital Formulary Service Classification and previous CCSS

publications[1,2], the eight therapeutic drug categories that include psychoactive properties are: (Refer to Appendix 1 for detailed classifications)
(1) antidepressants,
(2) anxiolytics/sedatives/hypnotics,
(3) anticonvulsants,
(4) non-opioid analgesics,
(5) opioids,
(6) muscle relaxants,
(7) neuroleptics,
(8) stimulants

The classification of psychoactive medications was previously conducted on the original adult cohort, based on Dr. Tara Brinkman's study.[1,2] We will use the same classification for the adolescent survivors and siblings, for both the original and expansion cohorts. There may potentially be new drugs that were not previously coded in Dr. Brinkman's study; Drs. Ullrich, Lommel, Brinkman, Cheung and Krull will classify these new drugs based on their clinical expertise.

Outcomes for Aim 4.1:

- **Quality of life outcomes during adulthood** will be assessed using the SF-36 questionnaire. It yields an 8-scale profile of functional health and well-being scores (Performance Function, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health) as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. Impairment is defined as scores falling below a T-score of 40 (1 standard deviation below the mean). [follow up survey E1 to E22, F1 to F14]
- **Emotional distress during adulthood** will be assessed by the Brief Symptom Inventory (BSI-18), a widely used measure of psychological distress including subscales of anxiety, depression and somatization. Distress will be defined as T-scores ≥ 63 (90th percentile) for each subscale. [follow up survey G1 to G18]
    - **Suicide ideation** (for testing hypothesis 4.1.2) will be assessed through a single item: "thoughts of ending your life". Consistent with previous CCSS methods.[7,8] participants who endorsed any suicidal ideation on the item were considered to have suicide ideation.
- **Neurocognitive outcomes during adulthood** will be assessed by the Childhood Cancer Survivor Study- Neurocognitive Questionnaire (CCSS-NCQ). The CCSS-NCQ was developed and validated within the CCSS cohort as a neurocognitive measure specifically designed for cancer survivors. It was constructed to assess skills reported to be sensitive to the effects of radiation and/or antimetabolite chemotherapy and skills included in established measures of executive functioning. Consistent with previous CCSS studies, impaired performance was defined as a score falling ≥90th percentile based on values obtained in the sibling cohort. [follow up survey J1 to J25]
- **Traumatic stress during adulthood** will be assessed by the Posttraumatic Stress Diagnostic Scale (PSD). The PSD is a 17-item self-reported questionnaire to assess symptoms of posttraumatic stress disorder. Each of the 17 items describe PTSS which respondents rate in terms of their frequency or severity using a Likert-type scale ranging from 0 (not at all or only one time) to 3 (almost always or five or more times per week). Ratings on

items are summed to create three subscales, including re-experiencing, avoidance, and arousal, as well as a total score (that ranges from 0 to 51). Consistent with previous CCSS studies[9,10], an overall positive endorsement of PTSS was defined by the report of at least one re-experiencing symptom, at least three avoidance symptoms and at least two arousal symptoms. [follow up survey K1 to K17]

Outcomes for Aim 4.2:

- **(For the subset of the population who are above 25 years of age at the 2007 follow-up) Functional outcomes during adulthood** will be assessed by their:
  - Highest education attainment [follow up survey A3] (College graduate and above vs below college graduate)
  - Employment status [follow up survey A4] (Full time employment vs others)

6.4 **Predictors:**

Predictors for Aim 2:

- Diagnosis:
  - Type of cancer (categories including leukemia, CNS tumor, Wilms' tumor, neuroblastoma, soft tissue sarcoma)
    - Leukemia vs. CNS turmor vs. others
  - Age at diagnosis (years, continuous)
- Treatment characteristics:
  - Radiation variable
    - CRT vs. non-cranial radiation (ie. body only: Chest, abdomen, pelvis) vs. none
    - For CRT (maximum dose to brain: none vs. < 20 vs. 20-29 Gy, 29-35 Gy, and >36 Gy) Depending on the number of survivors per group, groups may be collapsed to facilitate meaningful analysis and interpretation
  - Chemotherapy variables
    - Anthracyclines (yes/no)
    - Alkylating Agents (yes/no)
    - IV Methotrexate (cumulative)
    - IT Methotrexate (cumulative)
    - Anti-tumor Antibiotics (yes/no)
    - Corticosteroids (yes/no)
    - Enzymes (yes/no)
    - Epipodophyllotoxins (yes/no)
    - Heavy Metals (yes/no)
    - Plant Alkaloids (yes/no)
  - Neurosurgery (yes/no)
- Conditions within the brain and nervous system (yes/no)[original baseline survey J1 to J15; expansion baseline survey J1 to J15]:
  - **Epilepsy** [Original baseline survey J4] and/or repeated seizures, convulsions, or blackouts [original baseline survey J5] [expansion baseline survey J2] (Yes/no)

- **Migraine/headache** [original baseline J6, expansion baseline survey J3] or/and other frequent headaches [original baseline J7, expansion baseline survey J4] (Yes/no)
- **Bodily pain** [original baseline survey J23, expansion baseline survey K10] (none vs mild vs moderate vs severe), where:
  - No: “no pain”
  - Mild: “Small amount of pain”
  - Moderate: “Medium amount of pain”
  - Severe: “A lot of pain” and “Very bad excruciating pain”

Predictors for Aim 3:

- Emotional and social factors:
  - Brief Problem Inventory (BPI): The BPI is a subset of 27 questions from the Child Behavior Checklist and provides scores for five symptom domains: depression/anxiety, headstrong, attention deficit, peer conflict/social withdrawal, and antisocial. Each question is scored on a scale of 1 to 3, where 1 indicates no observation of the behavior and 3 frequent observation of a specific behavior. Impairment within each domain is defined as a score of ≥ 1.3 standard deviations above the sibling group mean for each factor score. [original baseline survey J19 to J21; expansion baseline survey K4 to K6]
  - Social functioning, determined by summing the scores to the 3 questions about friendship and social interactions [original baseline survey J16, J17 and J18b]; expansion baseline survey K1, K2 and K3b]
- Academic functions will be evaluated by assessing previous enrollment into a learning disabled or special education program (categorized as dichotomous variables: yes/no) [original baseline survey O3 and O4; expansion baseline survey R3 to R4]

Predictors for Aim 4:

- Use of psychoactive medications at baseline (categorized as dichotomous variables: yes/no for use) [original baseline survey B8; expansion baseline survey B8].

Potential covariates:

- Demographics: [original baseline survey A1, A2, A4; expansion baseline survey A1, A2, A5]
  - Age (years, continuous)
  - Sex (male vs female)
  - Race/ethnicity (White/non-Hispanic vs. others)
- Socioeconomic status:
  - Health insurance status (yes/no) [original baseline survey Q2]
  - Household income (< $20000 vs. ≥$20,000) [original baseline survey Q8]
- (For Aim 4) Baseline psychological distress: anxiety, depression and somatization subscales from BPI (yes vs no) [original baseline survey J19 to J21; expansion baseline survey K4 to K6]

6.5 **Statistical analysis**

- For Aim 1.1, frequency distributions will be used to categorize relevant outcome variables, predictors, and covariates according to reasonable groupings and consistent with previous CCSS manuscripts. Descriptive statistics including means, standard deviations, medians, ranges, frequencies, and percentages will be calculated for the primary outcome of interest (psychoactive medication use – yes/no) as well as for the primary predictors (ie. diagnosis, treatment, BPI etc.) (Tables 1 – 3 and Figure 1). Comparisons of the outcome (any psychoactive medication use and specific classes) will be made between survivors and siblings at baseline using generalized linear models with either a logit or log link, depending on the prevalence of the outcome, adjusting for potential confounders (gender, age, health insurance status, and household income). Odds Ratios (OR) and 95% confidence (CI) intervals will be reported for the comparison between survivors and siblings and will utilize robust sandwich variance estimates to account for intra-family correlation between survivors and siblings (Table 2). For Aim 1.2 we will use similar models that incorporate calendar year, change in prevalence over time will be compared between survivors and siblings by testing for interactions between time and survivor/sibling status. Predicted prevalence estimates for each group will be plotted over time to illustrate the pattern in prevalence over time.
- For Aim 2, within the survivors, logistic or log linear regression analyses will be conducted to identify clinical and treatment factors associated with the outcome (any psychoactive medication use and specific classes), using the predictors described above, adjusting for potential covariates: age, sex, race/ethnicity and socioeconomic status. Adjusted OR and 95% CI will be reported. A separate model will be fit with diagnosis category (Table 4) from the model containing treatment variables (Table 5) due to collinearity of those variables.
- For Aim 3, within the survivors, logistic or log linear regression analyses will be conducted to examine the association of parent-reported cognitive, behavioral and social problems and special education placement, with the outcome (any psychoactive medication use and specific classes), including covariates as appropriate. Adjusted OR and 95% CI will be reported. (Table 6). Note: Due to potential collinearities between the key predictor variables, separate adjusted models will be run for each predictor.
- For Aim 4.1, analyses will only be performed on the subset of survivors with 2003 follow up data. Logistic or log linear regression analyses will be conducted for each outcome variable as described above, ie. SF-36 (Table 7), BSI and PTSS (Table 8), NCQ (Table 9) using both the overall use of psychoactive medication and medication class as the primary predictors, each in separate models, adjusting for potential covariates, to generate adjusted OR and 95% CI for each predictor and outcome combination.
- For Aim 4.2, analyses will only be performed on the subset of survivors with 2007 follow up data and older than 25 years of age. Logistic or log linear regression analyses will be conducted for each outcome variable as described above, ie.

highest education attainment and employment status (Table 10), using both the overall use of psychoactive medication and medication class as the primary predictors and controlling for potential covariates, to create adjusted OR and 95% CI for each outcome as for Aim 4.1.

- For all regression analyses, potential collinearity among predictor variables will be examined.

Reference

1. Brinkman TM, Ullrich NJ, Zhang N, et al. Prevalence and predictors of prescription psychoactive medication use in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Journal of Cancer Survivorship.* 2013;7(1):104-114.

2. Brinkman TM, Zhang N, Ullrich NJ, et al. Psychoactive medication use and neurocognitive function in adult survivors of childhood cancer: A report from the childhood cancer survivor study. *Pediatric Blood and Cancer.* 2013;60(3):486-493.

3. Jonas BS, Gu Q, Albertorio-Diaz JR. Psychotropic medication use among adolescents: United States, 2005-2010. *NCHS data brief.* 2013(135):1-8.

4. Gianinazzi ME, Rueegg CS, Wengenroth L, et al. Adolescent survivors of childhood cancer: Are they vulnerable for psychological distress? *Psycho-Oncology.* 2013;22(9):2051-2058.

5. Krull KR, Huang S, Gurney JG, et al. Adolescent behavior and adult health status in childhood cancer survivors. *Journal of Cancer Survivorship.* 2010;4(3):210-217.

6. Schultz KAP, Ness KK, Whitton J, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: A report from the childhood cancer survivor study. *Journal of Clinical Oncology.* 2007;25(24):3649-3656.

7. Brinkman TM, Zhang N, Recklitis CJ, et al. Suicide ideation and associated mortality in adult survivors of childhood cancer. *Cancer.* 2014;120(2):271-277.

8. Recklitis CJ, Diller LR, Li X, Najita J, Robison LL, Zeltzer L. Suicide ideation in adult survivors of childhood cancer: A report from the childhood cancer survivor study. *Journal of Clinical Oncology.* 2010;28(4):655-661.

9. Stuber ML, Meeske KA, Krull KR, et al. Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. *Pediatrics.* 2010;125(5):e1124-e1134.

10. Stuber ML, Meeske KA, Leisenring W, et al. Defining medical posttraumatic stress among young adult survivors in the Childhood Cancer Survivor Study. *General Hospital Psychiatry.* 2011;33(4):347-353.

Table 1: Survivor Descriptive Statistics (Baseline)

	Siblings (N=)	All survivors (N=)	Survivors with psychoactive medication (N=)	Survivors without psychoactive medication (N=)
		n (%)	n (%)	n (%)
Year of completion				
1992 - 1999	-	3955		
2000 - 2009	798	980		
2010 - 2015	19	500		
Sex				
Male				
Female				
Race				
White/non-Hispanic				
Others				
Not specified				
Age at assessment* (years)				
Health Insurance				
Yes				
No				
Not specified				
Household Income				
< $20000				
≥$20,000				
Not specified				
History of epilepsy				
No				
Yes				
Not specified				
History of migraine/headache				
No				
Yes				
Not specified				
Bodily pain				
No				
Mild				
Moderate				
Severe				
Not specified				
Diagnosis				
Leukemia				
CNS tumor				
Wilms' tumor				
Neuroblastoma				
Soft Tissue Sarcoma				
Others				
Age at Diagnosis (years)				
Chemotherapy				
Anthracycline				

Alkylating Agent			
IV Methotrexate* (cumulative)			
IT Methotrexate* (cumulative)			
Anti-tumor Antibiotic			
Corticosteroids			
Enzymes			
Epipodophyllotoxins			
Heavy Metals			
Plant Alkaloids			
Radiation			
None			
Brain <20 Gy			
Brain 20-29 Gy			
Brain 29-35 Gy			
Brain > 36 Gy			
Body only (Chest, abdomen, pelvis)			
Surgery			
Neurosurgery			

*Presented as a continuous variable: mean (standard deviation)

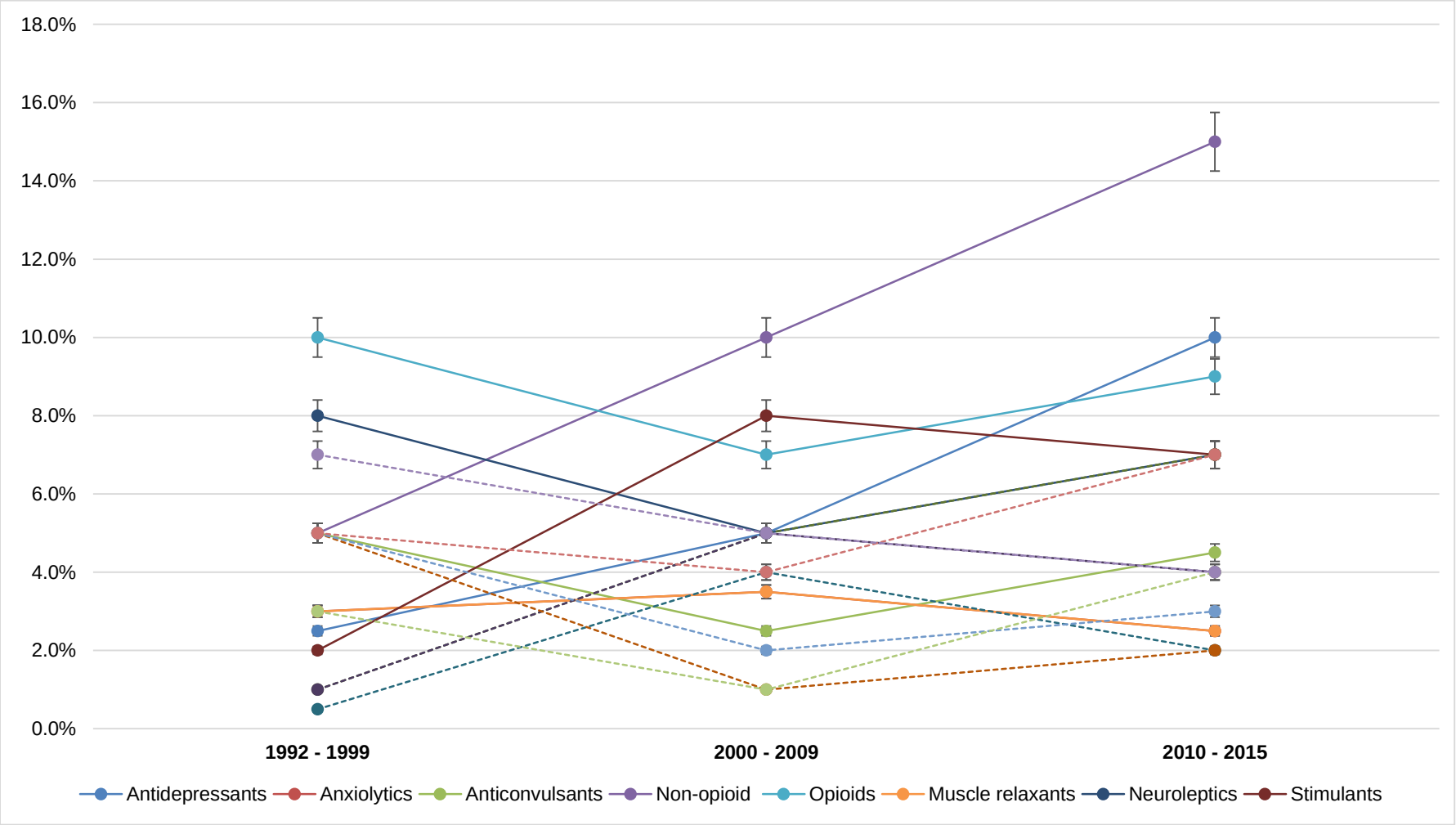
Preliminary numbers for adolescent siblings from expansion cohort are not available.

Table 2: Psychoactive Medication Use at Baseline in Survivors and Siblings

	Survivors (N=)		**Siblings (N=)**		
	N	(%)	N	(%)	OR (95%CI)
Use of psychoactive medication (overall)					
Medication Class					
Antidepressants					
Anxiolytics/sedatives/hypnotics					
Anticonvulsants					
Non-opioid analgesics					
Opioids					
Muscle relaxants					
Neuroleptics					
Stimulants					

ORs and 95% CIs adjusted for potential confounders (e.g., sex, age etc.)

Figure 1: Proportion of Adolescent Survivors and Siblings Treated with Psychoactive Medications by Survey Era



Solid line: Survivors; Dotted line: Siblings; error bars: 95% confidence interval

May consider regrouping the survey era based on the results. May also consider dropping certain medication classes if the rates are too low.

Table 3: Cognitive, Behavioral and Social Problems in Survivors

	All survivors (N=)	**Survivors with psychoactive medications (N=)**	**Survivors with psychoactive medications (N=)**
	*% impaired**	*% impaired**	*% impaired**
Behavior Problems Index			
Depression/Anxiety			
Headstrong Behavior			
Attention Deficit			
Peer Conflict/Social Withdrawal			
Antisocial			
Social Problems			
Social functioning			
Special Education Placement			

**Frequency of participants with scores that are ≥ 1.3 SD above the sibling cohort*

Table 4: Cancer diagnosis as Predictor for Psychoactive Medication Use in CCSS Survivors (multivariable model)

	Psychoactive Medication Use at Baseline (yes/no)																	
	Overall (N=X)		Antidepressant		Anxiolytics/ sedatives/ hypnotics		Anticonvulsants		Non-opioid analgesics		Opioids		Muscle relaxants		Neuroleptics		Stimulants	
	OR	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*
Clinical characteristics																		
Sex																		
Male (referent)	1		1		1		1		1		1		1		1		1	
Female																		
Race																		
White/non-Hispanic (referent)	1		1		1		1		1		1		1		1		1	
Others																		
Age at baseline (years)																		
Age at diagnosis (years)																		
Health insurance																		
Yes (referent)	1		1		1		1		1		1		1		1		1	
No																		
Household income																		
< $20000 (referent)	1		1		1		1		1		1		1		1		1	
≥$20,000																		
Seizures																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Pain																		
Headache/migraine																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Bodily pain																		
No (referent)	1		1		1		1		1		1		1		1		1	
Mild																		
Moderate																		
Severe																		
Cancer diagnosis																		
Leukemia (referent)	1		1		1		1		1		1		1		1		1	
CNS tumor																		
Others																		

Table 5: Treatment Characteristics as Predictor for Psychoactive Medication Use in CCSS Survivors (multivariable model)

	Psychoactive Medication Use at Baseline (yes/no)																	
	Overall (N=X)		Antidepressant		Anxiolytics/ sedatives/ hypnotics		Anticonvulsants		Non-opioid analgesics		Opioids		Muscle relaxants		Neuroleptics		Stimulants	
	OR	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*	*OR*	*(95%CI)*
Clinical characteristics																		
Sex																		
Male (referent)	1		1		1		1		1		1		1		1		1	
Female																		
Race																		
White/non-Hispanic (referent)	1		1		1		1		1		1		1		1		1	
Others																		
Age at baseline (years)																		
Age at diagnosis (years)																		
Health insurance																		
Yes (referent)	1		1		1		1		1		1		1		1		1	
No																		
Household income																		
< $20000 (referent)	1		1		1		1		1		1		1		1		1	
≥$20,000																		
Seizures																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Pain																		
Headache/migraine																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Bodily pain																		
No (referent)	1		1		1		1		1		1		1		1		1	
Mild																		
Moderate																		
Severe																		
Neurosurgery																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Chemotherapy																		
Anthracycline																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Alkylating Agent																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
IV Methotrexate (cumulative doses)																		
IT Methotrexate (cumulative doses)																		
Anti-tumor Antibiotic																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Corticosteroids																		

No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Enzymes																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Epipodophyllotoxins																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Heavy Metals																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Plant Alkaloids																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Radiation																		
None (referent)	1		1		1		1		1		1		1		1		1	
Non-CRT (ie body)																		
CRT																		
Cranial radiation																		
None (referent)	1		1		1		1		1		1		1		1		1	
<20 Gy																		
20-34 Gy																		
≥ 35 Gy																		

Table 6: Multivariable Model of Parent-reported Cognitive and Behavioral Problems, Special Education Service and Psychoactive Medication Use at Baseline in CCSS Survivors

	Psychoactive Medication Use at Baseline (yes/no)																	
	Medications (overall)		Antidepressant		Anxiolytics/ sedatives/ hypnotics		Anticonvulsants		Non-opioid analgesics		Opioids		Muscle relaxants		Neuroleptics		Stimulants	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Behavior Problems Index*																		
Depression/Anxiety																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Headstrong Behavior																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Attention Deficit																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Peer Conflict/Social Withdrawal																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Antisocial																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		
Placement in special education																		
No (referent)	1		1		1		1		1		1		1		1		1	
Yes																		

* Impairment within each domain is defined as a score of ≥ 1.3 standard deviations above the sibling group mean for each factor score

ORs and 95% CIs from multivariable models adjusted for potential covariates (e.g., sex, age etc.)

Note: separate models will be run for each predictor.

Table 7: Association between the Use of Psychoactive Medications at Baseline and Health-related Quality of Life during Adulthood in CCSS Survivors

	Impairment in Health-related Quality of Life during Adulthood (yes/no)							
	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)
Use of psychoactive medication (overall)								
No (referent)	1	1	1	1	1	1	1	1
Yes								
By categories:								
Antidepressants								
No (referent)	1	1	1	1	1	1	1	1
Yes								
Anxiolytics/sedatives/ Hypnotics								
No (referent)	1	1	1	1	1	1	1	1
Yes								
Anticonvulsants								
No (referent)	1	1	1	1	1	1	1	1
Yes								
Non-opioid analgesics								
No (referent)	1	1	1	1	1	1	1	1
Yes								
Opioids								
No (referent)	1	1	1	1	1	1	1	1
Yes								
Muscle relaxants								
No (referent)	1	1	1	1	1	1	1	1
Yes								
Neuroleptics								
No (referent)	1	1	1	1	1	1	1	1
Yes								
Stimulants								
No (referent)	1	1	1	1	1	1	1	1
Yes								

* Impairment is defined as scores falling below a T-score of 40 (1 standard deviation below the mean)

ORs and 95% CIs from multivariable models adjusted for potential covariates (e.g., sex, age etc.)

Note: separate models will be run for each predictor.

Table 8: Association between the Use of Psychoactive Medications at Baseline and Emotional Outcomes during Adulthood in CCSS Survivors

	Psychological Symptoms (yes/no)				Post-traumatic Symptoms (yes/no)
	Anxiety*	**Depression***	**Somatization***	**Suicide ideation#**	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Use of psychoactive medication (overall)					
No (referent)	1	1	1		1
Yes					
By categories:					
Antidepressants					
No (referent)	1	1	1	1	1
Yes					
Anxiolytics/sedatives/hypnotics					
No (referent)	1	1	1		1
Yes					
Anticonvulsants					
No (referent)	1	1	1	1	1
Yes					
Non-opioid analgesics					
No (referent)	1	1	1		1
Yes					
Opioids					
No (referent)	1	1	1		1
Yes					
Muscle relaxants					
No (referent)	1	1	1		1
Yes					
Neuroleptics					
No (referent)	1	1	1		1
Yes					
Stimulants					
No (referent)	1	1	1		1
Yes					

* Distress will be defined as T-scores ≥ 63 (*90th percentile*) for each subscale within the Brief Symptom Inventory (BSI)

^ An overall positive endorsement of PTSS was defined by the report of at least one re-experiencing symptom, at least three avoidance symptoms and at least two arousal symptoms

Exploratory subgroup analysis of suicide ideation risk will only be performed on anti-depressants and anticonvulsants. Suicide ideation is defined as endorsement of any suicidal ideation on the item “thoughts of ending your life” within the Brief Symptom Inventory

ORs and 95% CIs from multivariable models adjusted for potential covariates (e.g., sex, age etc.)

Note: separate models will be run for each predictor.

Table 9: Association between the Use of Psychoactive Medications at Baseline and Neurocognitive Outcomes during Adulthood in CCSS Survivors

	Task Efficiency*	Emotional Regulation*	Organization*	Memory*
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Use of psychoactive medication (overall)				
No (referent)	1	1	1	1
Yes				
By categories:				
Antidepressants				
No (referent)	1	1	1	1
Yes				
Anxiolytics/sedatives/hypnotics				
No (referent)	1	1	1	1
Yes				
Anticonvulsants				
No (referent)	1	1	1	1
Yes				
Non-opioid analgesics				
No (referent)	1	1	1	1
Yes				
Opioids				
No (referent)	1	1	1	1
Yes				
Muscle relaxants				
No (referent)	1	1	1	1
Yes				
Neuroleptics				
No (referent)	1	1	1	1
Yes				
Stimulants				
No (referent)	1	1	1	1
Yes				

*Impaired performance was defined as a score falling ≥90th percentile based on values obtained in the sibling cohort

ORs and 95% CIs from multivariable models adjusted for potential covariates (e.g., sex, age etc.)

Note: separate models will be run for each predictor.

Table 10: Association between the Use of Psychoactive Medications at Baseline and Functional Outcomes during Adulthood in CCSS Survivors

	Education attainment		**Employment status**	
	College Graduate		**< Full-time**	
	OR	95% CI	OR	95% CI
Use of psychoactive medication (overall)				
No (referent)	1	1	1	1
Yes				
By categories: Antidepressants				
No (referent)	1	1	1	1
Yes				
Anxiolytics/sedatives/hypnotics				
No (referent)	1	1	1	1
Yes				
Anticonvulsants				
No (referent)	1	1	1	1
Yes				
Non-opioid analgesics				
No (referent)	1	1	1	1
Yes				
Opioids				
No (referent)	1	1	1	1
Yes				
Muscle relaxants				
No (referent)	1	1	1	1
Yes				
Neuroleptics				
No (referent)	1	1	1	1
Yes				
Stimulants				
No (referent)	1	1	1	1
Yes				

ORs and 95% CIs from multivariable models adjusted for potential covariates (e.g., sex, age etc.)

Note: separate models will be run for each predictor.

Appendix: Medication Categories by AHFS Drug Classes

Antidepressants
- 28:16.04.12 Monoamine Oxidase Inhibitors
- 28:16.04.16 Selective Serotonin and Norepinephrine Reuptake Inhibitors
- 28:16.04.20 Selective-Serotonin Reuptake Inhibitors
- 28:16.04.24 Serotonin Modulators
- 28:16.04.28 Tricyclics and Other Norepinephrine-Reuptake Inhibitors
- 28:16.04.92 Antidepressants, Miscellaneous

Anxiolytics, Sedatives, Hypnotics
- 28:12.04 Barbiturates, Anticonvulsants
- 28:12.08 Benzodiazepines, Anticonvulsants
- 28:24.04 Barbiturates
- 28:24.08 Benzodiazepines
- 28:24.92 Anxiolytics, Sedatives, and Hypnotics, Miscellaneous

Anticonvulsants
- 28:12.04 Barbiturates, Anticonvulsants
- 28:12.08 Benzodiazepines, Anticonvulsants
- 28:12.92 Anticonvulsants, Miscellaneous
- 28:12.20 Succinimides
- 28:12.12 Hydantoins

Non-Opioid Analgesics
- 28:08.04.08 Cyclooxygenase-2 [COX-2) Inhibitors
- 28:08.04.92 Other Nonsteroidal Anti-inflammatory Agents
- 28:08.04.24 Salicylates
- 28:08.92 Analgesics and Antipyretics, Miscellaneous
- 28:32.28 Selective Serotonin Agonists

Opioids
- 28:08.08 Opiate Agonists
- 28:08.12 Opiate Partial Agonists
- 28:10 Opiate Antagonists

Muscle Relaxants
- 12:20.04 Centrally Acting Skeletal Muscle Relaxants
- 12:20.08 Direct-acting Skeletal Muscle Relaxants
- 12:20.12 GABA-derivative Skeletal Muscle Relaxants
- 12:20.20 Neuromuscular Blocking Agents
- 12:20.92 Skeletal Muscle Relaxants, Miscellaneous

Neuroleptics
- 28:16.08.04 Atypical Antipsychotics
- 28:16.08.08 Butyrophenones
- 28:16.08.24 Phenothiazines
- 28:16.08.32 Thioxanthenes
- 28:16.08.92 Antipsychotics, Miscellaneous
- 28:28 Antimanic Agents

Stimulants
- 28:20.92 Anorexigenic Agents and Respiratory and Cerebral Stimulants, Miscellaneous
- 28:20.04 Amphetamines
- 28:92 Central Nervous System Agents, Miscellaneous

American Society of Health System Pharmacists: AHFS Drug Information. Bethesda, MD, 2011

Brinkman TM, Ullrich NJ, Zhang N, et al. Prevalence and predictors of prescription psychoactive medication use in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Journal of Cancer Survivorship.* 2013;7(1):104-114.