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Prevalence and predictors of prescription psychoactive medication use in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study

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Abstract
Purpose Childhood cancer survivors are at risk for late effects which may be managed pharmacologically. The purposes of this study were to estimate and compare the prevalence of psychoactive medication use of adult survivors of childhood cancer and sibling controls, identify predictors of medication use in survivors, and investigate associations between psychoactive medications and health-related quality of life (HRQOL).
Methods Psychoactive medication use from 1994 to 2010 was evaluated in 10,378 adult survivors from the Childhood Cancer Survivor Study. A randomly selected subset of 3,206 siblings served as a comparison group. Multivariable logistic regression models were used to calculate odds ratios (OR) for baseline and new onset of self-reported psychoactive medication use and HRQOL.
Results Survivors were significantly more likely to report baseline (22 vs. 15 %, $p<0.001$) and new onset (31 vs. 25 %, $p<0.001$) psychoactive medication use compared to siblings, as well as use of multiple medications ($p<0.001$). In multivariable models, controlling for pain and psychological distress, female survivors were significantly more likely to report baseline and new onset use of antidepressants (OR=2.66, 95 % CI=2.01–3.52; OR=2.02, 95 % CI=1.72–2.38, respectively) and multiple medications (OR=1.80, 95 % CI=1.48–2.19; OR=1.77, 95 % CI=1.48–2.13, respectively). Non-cranial radiation and amputation predicted incident use of analgesics >15 years following diagnosis. Antidepressants

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were associated with impairment across all domains of HRQOL, with the exception of physical function.
Conclusions Prevalence of psychoactive medication use was higher among survivors for most medication classes, as was the use of multiple medications. Clinicians should be aware of the possible contribution of psychoactive medications to HRQOL.
Implications for Cancer Survivors Survivors of childhood cancer are more likely to be prescribed psychoactive medication than their sibling counterparts, though use of such medication does not appear to normalize quality of life. Survivors are encouraged to consider additional interventions, including psychosocial support and physical exercise.

Keywords Psychoactive medication · Quality of life · Survivorship

Introduction

Over 80 % of children diagnosed with cancer will become long-term survivors of their disease [1], and three fourths of survivors will develop a chronic health condition within 30 years of diagnosis [2]. Psychoactive medications are one method by which certain late effects may be managed; however, little is known about the prevalence and predictors of use of these medications in adult survivors of childhood cancer.

The pattern and severity of late effects experienced by survivors may result in different rates of psychoactive medication use, and several classes of medications may have particular import in cancer survivors. Osteosarcoma survivors report persistent pain secondary to amputation [3], which may explain their increased use of prescription analgesics compared with leukemia survivors [4]. Brain tumor survivors are at risk for neurologic sequelae [5, 6], which may lead to higher rates of anticonvulsant use. Subgroups of survivors experience psychological distress [7, 8], which may be associated with increased use of antidepressants or anxiolytics.

Research regarding the impact of psychoactive medications on health-related quality of life (HRQOL) has demonstrated inconsistent effects. Short-term treatment with antidepressant medications may reduce depressive symptoms and improve HRQOL in patients with depression [9] and anxiety disorders [10], although these drugs have side effects such as decreased libido and weight gain. In addition, anticonvulsants are used for mood stabilization but can be associated with diminished cognition [11–13] and reduced quality of life [12]. Such risks may be exacerbated in survivors of childhood cancer who may have changes in metabolism, cardiopulmonary and renal function, and central nervous system integrity following cancer-directed therapies [5, 6, 14–16].

The purposes of this study were to: (1) estimate and compare the prevalence of psychoactive medication use in a large and geographically diverse cohort of adult survivors of childhood cancer and a sibling control group, (2) identify predictors of psychoactive medication use in these survivors, and (3) investigate the impact of psychoactive medications on HRQOL in adult survivors of childhood cancer.

Methods

Childhood Cancer Survivor Study

The Childhood Cancer Survivor Study (CCSS) cohort consists of survivors of one of eight childhood cancers diagnosed ≤21 years of age and treated at 1 of 26 institutions between 1970 and 1986. All survivors were ≥5 years from their original diagnosis upon study enrollment. Sibling controls were recruited from a randomly selected subset of survivors. The study was approved by the institutional review board at each collaborating institution, and informed consent was obtained from each participant. Study participants completed a baseline questionnaire beginning in 1994 and subsequent follow-up questionnaires initiated in 2000, 2003, and 2007. Additional descriptions of the CCSS methodology and participants have been published elsewhere [17, 18].

The current study population is shown in Fig. 1 and included (1) all cancer survivors and siblings ≥18 years of age who completed the baseline survey and (2) survivors and siblings who completed the 2000, 2003, or 2007 follow-up survey as of February 2011. Because HRQOL was last assessed during the 2003 follow-up survey, only participants who completed baseline and the 2003 follow-up were included in the analysis of HRQOL.

Primary outcomes

Baseline and new onset psychoactive medication use were the primary study outcomes. Each survey instructed participants to report prescription drugs taken consistently for more than 1 month or ≥30 days in 1 year during the previous 2-year period. Participants were instructed to report medications prescribed by a physician and dispensed by a pharmacist and not report over-the-counter medications. Medications were classified using the American Hospital Formulary Service Drug Information database (AHFS) [19]. Eight therapeutic drug categories believed to include psychoactive properties were identified: (1) antidepressants, (2) anxiolytics/sedatives/hypnotics, (3) anticonvulsants, (4) non-opioid analgesics, (5) opioids, (6) muscle relaxants, (7) neuroleptics, and (8) stimulants. A list of the AHFS drug classes and codes comprising each medication category is provided in Online resource 1.

New onset medication use was defined as reported use at the time of any of the three follow-up questionnaires (i.e., 2000, 2003, or 2007) without reported use at the baseline survey. This definition was specific to each medication class (i.e., survivors

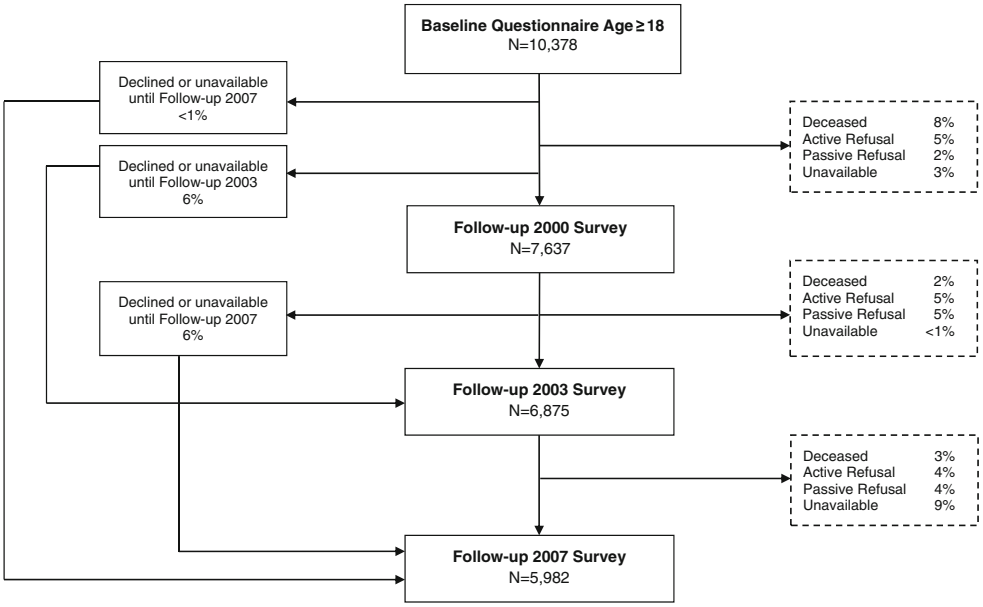

Fig. 1 Flow diagram of study participation of survivors from the Childhood Cancer Survivor Study

reporting baseline use in one class could be included in new onset use for any of the remaining medication classes). The use of multiple medications was defined as reported use of two or more medications at the time of any one survey.

Health-related quality of life was measured using the Medical Outcomes Survey 36-Item Short Form Health Survey (SF-36) [20]. This is a widely used generic health profile that provides subscale scores for eight domains: general health, role physical, physical function, bodily pain, vitality, mental health, social function, and role emotional. The SF-36 provides age and sex-specific norms to generate *T* scores (M=50, SD=10).

Health care utilization was categorized into one of four mutually exclusive groups: (1) no health care, (2) general health care (visits unrelated to previous cancer), (3) general survivor care (visit related to previous cancer, but no information on risk reduction or screening tests), and (4) risk-based survivor care (visit included information about risk reduction or screening test for cancer-specific late effects) (see Krull et al. [21] for additional details regarding health care classification).

Predictor variables and covariates

All predictor variables and covariates were measured beginning at baseline. Demographic and socioeconomic variables considered in the analyses included sex, age at the time of survey completion, race/ethnicity, health insurance, and household income (categorized as <$20,000 or ≥$20,000). Cancer-related variables included age at diagnosis and recurrence or subsequent neoplasm prior to baseline. Treatment variables included radiation therapy, chemotherapy, and amputation. Radiation was categorized as none, cranial radiation, and body radiation, while chemotherapy was categorized into four groups: (1) anthracyclines, (2) vinca alkaloids and/or heavy metals, (3) corticosteroids and/or antimetabolites, and (4) alkylating agents, topisomerase inhibitors, and/or epipodophyllotoxins.

Psychological distress was measured by the Brief Symptom Inventory-18 [22], and subscales for anxiety, depression, and somatization were used as covariates. Sex-specific scores were calculated based on standardized normative values, and scores falling ≥90th percentile were classified as representing a clinical level of acute emotional distress. Neurologic variables included headache, bodily pain, and history of stroke or seizure.

Statistical analysis

Descriptive statistics were calculated for all outcomes, predictors, and covariates used in the analyses. Survivor and sibling medication use was examined through logistic regression modeling with robust variance estimates to account for within-family correlation using SAS version 9.2 PROC Genmod with binomial distribution and logit link (SAS Institute, Cary, NC). Multivariable models for each medication category were adjusted for age, sex, race/ethnicity, health insurance, household income, seizure or stroke history, pain, and psychological distress. Given the small number of survivors and siblings reporting use of neuroleptics or stimulants, these medications were not included in multivariable analyses.

To investigate predictors of baseline and new onset psychoactive medication use in survivors, univariate models were constructed to identify variables contributing to each medication category at $p<0.10$. All variables meeting this significance threshold were included in multivariable logistic regression models. As treatment variables were of primary interest, radiation therapy and chemotherapy were forced into the multivariable models regardless of their statistical

significance. Backward selection was performed for each of the medication models using SAS PROC Logistic. The least significant variables (largest p value) were excluded one at a time until all variables remaining in the model were significant ($p<0.05$). Odds ratios (OR) and 95 % confidence intervals (CI) were calculated for predictors and covariates retained in the final model. To correct for multiple comparisons, a step-down Bonferroni method controlling for familywise error was used to adjust the raw p values in the final models [23].

A parallel statistical approach was employed for each HRQOL outcome. Scores on the SF-36 were classified as impaired based on age-adjusted T scores falling ≤40. Each medication category, as measured at the 2003 follow-up survey, was forced into multivariable regression models regardless of statistical associations with HRQOL outcomes. Similarly, using data only from follow-up 2003, multivariable logistic regression was used to examine associations between health care utilization and psychoactive medication use. For all models, we examined potential collinearity among predictor variables (e.g., antidepressants and depression; analgesics and pain symptoms). Although the predictors were related, the associations were not sufficient to warrant exclusion of any covariates from the models.

Results

At baseline, survivors were statistically significantly (all p values <0.001) younger and more likely to be male, though less likely to be white/non-Hispanic or to have health insurance or a household income above $20,000 compared with siblings (Table 1). Survivors were also significantly more likely to report acute psychological distress and pain, and to have a history of a stroke or seizure relative to siblings.

Baseline medication use

Twenty-two percent of survivors reported using at least one psychoactive medication compared to 15 % of siblings ($p<0.001$). As shown in Table 2, after adjusting for covariates, survivors were more likely to report use of non-opioid analgesics (OR=1.52; 95 % CI=1.28–1.81), opioids (OR=1.36; 95 % CI=1.15–1.62), and anxiolytics/sedatives/hypnotics (OR=1.64; 95 % CI=1.17–2.28) compared to siblings. Nine percent of survivors reported using multiple medications compared with 4.9 % of siblings (OR=1.49; 95 % CI=1.21–1.83). Among survivors who reported using two medications (n=509), 19 % reported the use of two anticonvulsants, while 16 % reported using one opioid and one non-opioid analgesic. Similarly, among survivors who reported three medications (n=221), 12 % reported taking three different anticonvulsants while 22 % reported varying combinations of three different analgesics.

In multivariable models (Table 3), adjusting for symptoms of pain and psychological distress, female sex was associated with increased use of antidepressants (OR=2.66; 95 % CI=2.01–3.52), analgesics (non-opioids: OR=1.55, 95 % CI=1.32–1.84; opioids: OR=1.49, 95 % CI=1.26–1.76), and multiple psychoactive medications (OR=1.80, 95 % CI=1.48–2.19). Household income <$20,000 was significantly associated with increased use of opioids (OR=1.29, 95 % CI=1.08–1.55), muscle relaxants (OR=1.74, 95 % CI=1.24–2.43), and the use of multiple medications (OR=1.49, 95 % CI=1.21–1.84).

Cranial radiation therapy was associated with increased likelihood of anticonvulsant use (OR=1.92, 95 % CI=1.32–2.80), while no associations emerged with other cancer treatment variables. As expected, history of stroke or seizure was the strongest predictor of anticonvulsant use (OR=50.8, 95 % CI=36.6–70.4) and was significantly associated with the use of multiple medications (OR=6.12, 95 % CI=4.66–8.02). Survivors with history of disease recurrence or subsequent neoplasm prior to baseline were 1.5 times more likely to report use of anxiolytics (OR=1.55, 95 % CI=1.17–2.05).

New onset medication use

Sixty-seven percent of survivors using medication at baseline also reported psychoactive medication use at a subsequent follow-up compared to 59 % of siblings (p=0.001). Thirty-one percent of survivors reported new onset psychoactive medication use compared to 25 % of siblings ($p<0.001$). As shown in Table 2, after adjusting for covariates, survivors were more likely to report use of analgesics (opioids: OR=1.40, 95 % CI=1.14–1.71; non-opioids: OR=1.27, 95 % CI=1.05–1.54), anticonvulsants (OR=1.71, 95 % CI=1.33–1.20), and anxiolytics/sedatives/hypnotics (OR=1.27, 95 % CI=1.03–1.57) compared to siblings. Fifteen percent of survivors reported new onset use of multiple medications compared with 10.4 % of siblings (OR=1.40, 95 % CI=1.20–1.64).

Controlling for pain and psychological distress, female sex was associated with a twofold increased likelihood of new onset antidepressant use (OR=2.02, 95 % CI=1.72–2.38) and 1.8-fold increased likelihood of using multiple medications (OR=1.77, 95 % CI=1.48–2.13). Survivors of older age at diagnosis were significantly more likely to report new onset use of antidepressants and anxiolytics (OR=1.17, 95 % CI=1.15–1.19; OR=1.16, 95 % CI=1.12–1.19, respectively) (see Table 4).

History of amputation was associated with increased likelihood of new onset use of analgesics (opioids OR=3.56, 95 % CI=2.31–5.47; non-opioids OR=3.84, 95 % CI=2.68–5.49). Radiation therapy to non-cranial sites was associated with increased likelihood of new onset medication use across all classes with the exception of anticonvulsants, while cranial radiation was only associated with

Table 1 Baseline characteristics of survivors and siblings

	Baseline survivors (*N*=10,378)		Baseline siblings (*N*=3,206)	
	N	%	*N*	%
Sex				
Male	5,582	53.8	1,519	47.4
Female	4,796	46.2	1,687	52.6
Age at baseline, years				
18–24	4,386	42.3	959	29.9
25–29	2,761	26.6	734	22.9
30–34	1,976	19.0	689	21.5
≥35	1,255	12.1	824	25.7
Race/ethnicity				
White/non-Hispanic	8,693	83.8	2,830	88.3
Other	1,633	15.7	264	8.2
Not specified	52	0.5	112	3.5
Current health insurance				
Yes[a]	8,104	78.1	2,823	88.1
No	1,483	14.3	347	10.8
Not specified	791	7.6	36	1.1
Household income				
<$20,000	2,060	19.9	367	11.5
≥$20,000	6,923	66.7	2,522	78.7
Not specified	1,395	13.4	317	9.9
Pain				
Headache	2,816	27.1	762	23.8
Other bodily pain	662	6.4	97	3.0
No pain	6,871	66.2	2,341	73.0
Not specified	29	0.3	6	0.2
Stroke or seizure				
Yes	942	9.1	82	2.6
No	9,433	90.9	3,124	97.4
Not specified	3	0.03	0	0
Psychological distress				
Somatization	755	7.3	129	4.0
Depression	939	9.1	193	6.0
Anxiety	632	6.1	115	3.6
Global severity index	741	7.1	121	3.8
Age at diagnosis, years				
0–4	2,536	24.4		
5–9	2,487	24.0		
10–14	2,868	27.6		
15–19	2,202	21.2		
≥20	285	2.8		
Time since diagnosis, years				
5–10	1,026	9.9		
11–15	3,042	29.3		
16–20	3,630	35.0		
≥21	2,680	25.8		
Recurrence or new neoplasm				
Yes	2,942	28.4		
No	7,436	71.7		
Amputation				
Yes	755	7.3		
No	9,311	89.7		
Not specified	312	3.0		
Diagnosis				
Leukemia	3,055	29.4		
CNS tumor	1,320	12.7		
Hodgkin lymphoma	1,871	18.0		
Non-Hodgkin lymphoma	924	8.9		
Kidney (Wilms)	670	6.5		
Neuroblastoma	416	4.0		
Soft tissue sarcoma	991	9.6		
Osteosarcoma	1,131	10.9		
Chemotherapy				
Anthracyclines	3,509	33.8		
Vinca alkaloids and heavy metals	6,435	62.0		
Corticosteroids and antimetabolites	5,000	48.2		
Alkylating agents, topoisomerase inhibitors, and epipodophyllotoxins	4,926	47.5		
None	1,930	18.6		
Radiation				
Cranial radiation	2,873	27.7		
Non-cranial radiation	3,320	32.0		
None	2,441	23.5		
Not specified	1,744	16.8		

[a] Includes Canadian citizens

increased likelihood of new onset use of anticonvulsants (OR=1.63, 95 % CI=1.21–2.21).

Health-related quality of life

Multivariable logistic regression models adjusting for covariates revealed associations between psychoactive medication use and impaired HRQOL (Table 5). Antidepressant use was associated with impairment across all domains, with the exception of physical function (e.g., vitality OR=2.13, 95 % CI=1.75–2.60; social functioning OR=1.98, 95 % CI=1.58–2.48). Anticonvulsant use was associated with impaired social function (OR=1.84, 95 % CI=1.30–2.60) and physical function (OR=2.27, 95 % CI=1.66–3.11). Use of pain medications was associated with reduced

Table 2 Baseline and new onset medication use among survivors and siblings

Medication class	Baseline			New onset use[a]		
	Survivors, *N*=10,378 *N* (%)	Siblings, *N*=3,206 *N* (%)	OR (95 % CI)	Survivors, *N*=8,277 *N* (%)	Siblings, *N*=2,598 *N* (%)	OR (95 % CI)
Non-opioid analgesics	994 (9.6)	205 (6.4)	**1.52 (1.28–1.81)**	704 (9.4)	174 (6.9)	**1.27 (1.05–1.54)**
Opioids	1,103 (10.6)	221 (6.9)	**1.36 (1.15–1.62)**	664 (8.9)	152 (6.0)	**1.40 (1.14–1.71)**
Antidepressants	421 (4.1)	116 (3.6)	0.96 (0.75–1.22)	1,527 (19.1)	464 (17.7)	1.10 (0.96–1.25)
Anticonvulsants	536 (5.2)	48 (1.5)	1.41 (0.97–2.06)	531 (6.7)	94 (3.5)	**1.71 (1.33–2.20)**
Anxiolytics/sedatives/hypnotics	409 (3.9)	50 (1.6)	**1.64 (1.17–2.28)**	575 (7.1)	140 (5.2)	**1.27 (1.03–1.57)**
Muscle relaxants	231 (2.2)	57 (1.8)	1.10 (0.80–1.52)	263 (3.2)	49 (1.8)	**1.59 (1.13–2.25)**
Stimulants[b]	52 (0.5)	25 (0.8)	0.64 (0.39–1.03)	128 (1.5)	32 (1.2)	1.30 (0.88–1.93)
Neuroleptics[b]	63 (0.6)	16 (0.5)	1.20 (0.70–2.07)	146 (1.8)	32 (1.2)	1.50 (1.01–2.20)
Multiple medications[c]	934 (9.0)	158 (4.9)	**1.49 (1.21–1.83)**	1,158 (15.2)	268 (10.4)	**1.40 (1.20–1.64)**

ORs adjusted for current age, sex, race/ethnicity, household income, health insurance, stroke or seizure, pain, and psychological distress. Statistically significant results are in bold

[a] Percent based on the number reporting medication use for each category at either 2000, 2003, or 2007 follow-up with no reported baseline medication use

[b] Unadjusted ORs reported for stimulants and neuroleptics

[c] Defined as use of ≥2 psychoactive medications at the time of one survey

functioning across all domains of physical HRQOL, and opioids were associated with impaired social function (OR=1.88, 95 % CI=1.26–2.80).

Health care utilization

Survivors who reported receiving general health care, general survivor care, or risk-based survivor care were significantly more likely to report use of all psychoactive medication classes compared to survivors who reported no health care in the preceding 2 years (all p values <0.001; see Online resource 2), with the exception of muscle relaxants and opioid analgesics. General survivor care and risk-based survivor care were associated with a threefold increased likelihood of opioid use (OR=3.84, 95 % CI=2.09–7.06; OR=3.06, 95 % CI=1.67–5.59, respectively), whereas survivors who received general health care were not more likely to use opioids compared to survivors who did not receive health care.

Discussion

To our knowledge, this is the first study to examine psychoactive medication use in a large cohort of adult survivors of childhood cancer. Overall, 42 % of survivors reported using at least one psychoactive medication between 1994 and 2010 compared with 33 % of siblings. The prevalence of psychoactive medication use was higher among survivors compared to siblings for most medication classes, as was the practice of using multiple medications. After controlling for symptoms of pain and psychological distress, medication use was predicted by demographic factors, although several disease and treatment-specific factors also emerged as important predictors.

Antidepressants evidenced the highest rate of incident use, representing a fourfold increase among survivors from 1994 to 2010 (4.1 to 17.4 %). Importantly, a parallel pattern of increased antidepressant use emerged for siblings. Data from Medical Expenditure Panel Surveys reflect a similar trend for antidepressant medication use in the general population with a reported increase from 5.8 % in 1996 to 10.1 % in 2005[24]. Although methodological differences limit our ability to make direct comparisons across studies, our findings are consistent with reports of increasing antidepressant use over time and that antidepressants are among the most commonly used prescription drugs in adults [25]. Moreover, after adjusting for the presence of pain and psychological distress, we found that females were more likely to report use of antidepressant medications. Similar trends for female sex have been observed in the general population [24].

A substantial proportion of survivors reported new onset use of multiple medications, significantly more so than siblings. History of a neurologic event was the strongest predictor of using multiple medications while female sex was associated with an over 1.8-fold increased likelihood of baseline and new onset use of multiple medications. It is important to consider that use of psychoactive medications may increase sensitivity to other medications, potentially leading to adverse side effects in addition to drug–drug interactions. For example, in clinical practice, anticonvulsants are increasingly used in combination with antidepressants or mood-stabilizing

Table 3 Multivariable model predicting baseline psychoactive medication use in survivors

	Non-opioids OR (95 %CI)	Opioids OR (95 %CI)	ATD OR (95 %CI)	AED OR (95 %CI)	ASH OR (95 %CI)	Muscle relaxants OR (95 %CI)	≥2 medications vs. none OR (95 %CI)
Clinical characteristics							
Female sex	1.55 (1.32, 1.84)[a]	1.49 (1.26, 1.76)[a]	2.66 (2.01, 3.52)[a]	–	–	–	1.80 (1.48, 2.19)[a]
White/non-Hispanic (vs. other)	–	–	–	–	–	–	–
Age at diagnosis (years)	–	–	–	–	1.03 (1.01, 1.06)[c]	–	–
Age at baseline (years)	–	–	1.03 (1.01, 1.06)[b]	–	–	–	1.03 (1.01, 1.05)[a]
Health insurance (vs. none)	–	–	–	–	–	–	–
Household income <20,000 vs. ≥20,000	–	1.29 (1.08, 1.55)[c]	–	2.13 (1.52, 2.98)[a]	–	1.74 (1.24, 2.43)[b]	1.49 (1.21, 1.84)[a]
Pain							
Headache (vs. none)	2.33 (1.96, 2.78)[a]	2.22 (1.86, .65)[a]	2.58 (1.97, 3.39)[a]	–	2.87 (2.13, 3.88)[a]	3.22 (2.26, 4.60)[a]	2.59 (2.11, 3.17)[a]
Bodily pain (vs. none)	2.49 (1.85, 3.34)[a]	2.20 (1.63, 2.97)[a]	2.39 (1.50, 3.80)[a]	–	2.24 (1.34, 3.74)[a]	2.58 (1.42, 4.67)[a]	2.84 (2.01, 4.00)[a]
Neurologic event							
Stroke or seizure (vs. none)	–	–	–	50.8 (36.6, 70.4)[a]	4.33 (3.11, 6.02)[a]	–	6.12 (4.66, 8.02)[a]
Cancer event							
Recurrence or neoplasm (vs. none)	–	1.28 (1.08, 1.53)[c]	–	1.62 (1.15, 2.27)[c]	1.55 (1.17, 2.05)[c]	–	1.43 (1.17, 1.75)[b]
Surgery							
Amputation (vs. no)	–	–	–	–	–	–	–
Psychological distress							
Somatization (vs. no)	2.01 (1.59, 2.54)[a]	2.16 (1.71, 2.73)[a]	–	–	2.07 (1.46, 2.93)[a]	2.59 (1.78, 3.76)[a]	2.39 (1.82, 3.14)[a]
Depression (vs. no)	–	–	3.91 (2.86, 5.33)[a]	–	–	–	1.72 (1.30, 2.27)[a]
Anxiety (vs. no)	1.55 (1.19, .02)[b]	1.49 (1.12, 1.97)[c]	1.83 (1.28, 2.61)[b]	–	2.45 (1.70, 3.55)[a]	–	2.00 (1.46, 2.75)[a]
Chemotherapy (vs. other)							
Anthracyclines	1.01 (0.84, 1.21)	1.23 (1.02, 1.48)	0.80 (0.59, 1.08)	0.60 (0.39, 0.93)	0.74 (0.53, 1.02)	0.68 (0.46, 1.01)	0.98 (0.78, 1.22)
Vinca alkaloids and heavy metals	1.08 (0.85, 1.38)	0.96 (0.75, 1.22)	1.09 (0.73, 1.62)	0.65 (0.39, 1.08)	1.10 (0.71, 1.70)	0.91 (0.56, 1.48)	1.00 0.74, 1.34)
Corticosteroids and antimetabolites	0.96 (0.78, 1.19)	0.88 (0.71, 1.09)	1.29 (0.92, 1.81)	0.65 (0.40, 1.06)	0.70 (0.49, 1.01)	1.14 (0.74, 1.75)	0.87 (0.67, 1.14)
Alkylating agents, TOP, EP	1.00 (0.81, 1.22)	1.11 (0.90, 1.37)	1.03 (0.74, 1.42)	0.99 (0.66, 1.51)	1.32 (0.91, 1.91)	1.05 (0.70, 1.59)	1.11 (0.87, 1.41)
Radiation							
Cranial radiation (vs. none)	1.08 (0.87, 1.33)	1.02 (0.83, 1.26)	0.94 (0.66, 1.34)	1.92 (1.32, 2.80)[a]	0.89 (0.62, 1.27)	0.91 (0.59, 1.40)	1.10 (0.90, 1.45)
Other bodily radiation (vs. none)	1.03 (0.84, 1.27)	0.96 (0.78, 1.18)	1.04 (0.74, 1.45)	0.52 (0.31, 0.86)	0.74 (0.52, .05)	0.80 (0.53, .22)	0.67 (0.52, 0.87)

Variables listed were included in the final model; – indicates variables not retained in the final model

ATD antidepressants, *AED* anticonvulsants, *ASH* anxiolytics/sedatives/hypnotics, *TOP* topoisomerase inhibitors, *EP* epipodophyllotoxins

[a] Adjusted $p<0.001$

[b] Adjusted $p<0.01$

[c] Adjusted $p<0.05$

Table 4 Multivariable model predicting new onset psychoactive medication use in survivors

	Non-opioids OR (95 % CI)	Opioids OR (95 % CI)	ATD OR (95 % CI)	AED OR (95 % CI)	ASH OR (95 % CI)	Muscle relaxants OR (95 % CI)	Multiple medications OR (95 % CI)
Clinical characteristics							
Female sex	–	–	2.02 (1.72, 2.38)[a]	–	1.39 (1.11, 1.74)[c]	–	1.77 (1.48, 2.13)[a]
White non-Hispanic (vs. other)	–	–	–	–	–	–	–
Age at diagnosis (years)	–	–	1.17 (1.15, 1.19)[a]	–	1.16 (1.12, 1.19)[a]	–	–
Age at new onset (years)	0.86 (0.84, 0.87)[a]	0.80 (0.78, 0.82)[a]	0.79 (0.78, 0.81)[a]	0.88 (0.86, 0.90)[a]	0.83 (0.81, 0.85)[a]	0.81 (0.79, 0.84)[a]	0.90 (0.88, 0.91)[a]
Health insurance (vs. none)	–	–	–	–	–	–	–
Household income <20,000 vs. ≥20,000	–	–	–	–	–	–	–
Pain							
Headache (vs. none)	2.20 (1.78, 2.72)[a]	2.13 (1.68, 2.71)[a]	1.70 (1.42, 2.02)[a]	2.01 (1.57, 2.56)[a]	1.97 (1.55, 2.49)[a]	3.23 (2.33, 4.48)[a]	2.08 (1.71, 2.52)[a]
Bodily pain (vs. none)	1.85 (1.23, 2.76)[a]	2.21 (1.44, 3.41)[a]	1.29 (0.92, 1.80)	1.65 (1.05, 2.61)[a]	1.65 (1.08, 2.53)[a]	2.32 (1.29, 4.18)[a]	2.17 (1.53, 3.07)[a]
Neurologic event							
Stroke or seizure (vs. none)	–	–	–	3.68 (2.54, 5.32)[a]	1.80 (1.24, 2.61)[a]	–	2.79 (2.04, 3.82)[a]
Cancer event							
Recurrence or neoplasm (vs. none)	1.62 (1.31, 2.01)[a]	2.11 (1.65, 2.70)[a]	1.73 (1.45, 2.05)[a]	1.86 (1.45, 2.38)[a]	1.82 (1.44, 2.30)[a]	–	1.69 (1.38, 2.05)[b]
Surgery				–			
Amputation (vs. no)	3.84 (2.68, 5.49)[a]	3.56 (2.31, 5.47)[a]	–	–	–	–	–
Psychological distress							
Somatization (vs. no)	–	2.13 (1.48, 3.06)[a]	1.69 (1.27, 2.25)[b]	1.75 (1.23, 2.50)[c]	1.83 (1.31, 2.55)[b]	2.37 (1.58, 3.54)[a]	1.73 (1.27, 2.35)[b]
Depression (vs. no)	–	–	1.60 (1.21, 2.10)[b]	–	1.52 (1.11, 2.07)[c]	–	1.93 (1.47, 2.54)[a]
Anxiety (vs. no)	–	–	1.62 (1.15, 2.26)[c]	–	–	–	–
Chemotherapy (vs. other)							
Anthracyclines	0.94 (0.74, 1.19)	0.67 (0.51, 0.88)	0.70 (0.58, 0.85)	1.12 (0.85, 1.47)	0.76 (0.59, 0.99)	0.89 (0.62, 1.28)	0.93 (0.76, 1.15)
Vinca alkaloids and heavy metals	0.71 (0.53, 0.95)	0.63 (0.45, 0.88)	1.09 (0.85, 1.39)	0.64 (0.46, 0.89)	1.38 (0.97, 1.97)	0.69 (0.44, 1.07)	0.75 (0.58, 0.98)
Corticosteroids and antimetabolites	1.05 (0.81, 1.37)	1.27 (0.95, 1.71)	0.89 (0.72, 1.10)	0.63 (0.46, 0.87)	0.87 (0.65, 1.16)	1.12 (0.74, 1.67)	0.87 (0.68, 1.10)
Alkylating agents, TOP, EP	0.98 (0.77, 1.25)	1.34 (1.01, 1.76)	0.88 (0.72, 1.07)	1.17 (0.88, 1.57)	1.05 (0.78, 1.40)	1.35 (0.92, 1.99)	1.19 (0.95, 1.49)
Radiation							
cranial radiation (vs. none)	1.14 (0.87, 1.50)	0.75 (0.55, 1.03)	0.97 (0.79, 1.19)	1.63 (1.21, 2.21)[c]	0.81 (0.60, 1.09)	0.73 (0.49, 1.11)	1.09 (0.86, 1.39)
Other bodily radiation (vs. none)	1.58 (1.21, 2.07)[c]	1.80 (1.34, 2.42)[a]	1.42 (1.16, 1.74)[b]	1.10 (0.81, 1.51)	1.42 (1.08, 1.87)[b]	1.53 (1.04, 2.26)[c]	1.28 (1.02, 1.62)

Variables listed were included in the final model; – indicates variables not retained in the final model

ATD antidepressants, *AED* anticonvulsants, *ASH* anxiolytics/sedatives/hypnotics, *TOP* topoisomerase inhibitors, *EP* epipodophyllotoxins

[a] Adjusted $p<0.001$

[b] Adjusted $p<0.01$

[c] Adjusted $p<0.05$

Table 5 Psychoactive medication use and reduced HRQOL in survivors at 2003 follow-up

	Physical function OR (95 % CI)	Role physical OR (95 % CI)	Bodily pain OR (95 % CI)	General health OR (95 % CI)	Vitality OR (95 % CI)	Social function OR (95 % CI)	Role emotional OR (95 % CI)	Mental health OR (95 % CI)
Non-opioids	1.59 (1.10, 2.30)[c]	2.17 (1.53, 3.08)[a]	1.90 (1.32, 2.72)[b]	1.92 (1.35, 2.73)[b]	1.39 (1.00, 1.93)	1.55 (1.05, 2.29)	0.84 (0.57, 1.25)	1.05 (0.60, 1.82)
Opioids	1.86 (1.29, 2.69)[b]	2.66 (1.82, 3.88)[a]	4.19 (2.91, 6.01)[a]	1.35 (0.92, 1.98)	1.50 (1.03, 2.19)	1.88 (1.26, 2.80)[b]	1.29 (0.87, 1.90)	1.05 (0.61, 1.80)
Antidepressants	0.89 (0.69, 1.15)	1.47 (1.18, 1.83)[b]	1.52 (1.21, 1.92)[b]	1.46 (1.18, 1.82)[b]	2.13 (1.75, 2.60)[a]	1.98 (1.58, 2.48)[a]	2.57 (2.09, 3.17)[a]	2.12 (1.57, 2.86)[a]
Anticonvulsants	2.27 (1.66, 3.11)[a]	1.75 (1.27, 2.40)[b]	1.33 (0.94, 1.87)	1.29 (0.93, 1.80)	1.20 (0.89, 1.61)	1.84 (1.30, 2.60)[b]	0.90 (0.63, 1.27)	0.75 (0.47, 1.22)
Anxiolytics/sedatives/hypnotics	1.20 (0.83, 1.75)	1.09 (0.75, 1.59)	0.93 (0.63, 1.37)	1.25 (0.86, 1.81)	1.09 (0.76, 1.56)	1.13 (0.76, 1.68)	1.46 (1.01, 2.11)	2.11 (1.31, 3.38)[c]
Muscle relaxants	2.85 (1.50, 5.41)[b]	1.97 (0.97, 4.03)	2.54 (1.28, 5.03)[c]	2.03 (1.02, 4.05)	1.29 (0.63, 2.63)	1.61 (0.78, 3.33)	1.39 (0.70, 2.74)	1.16 (0.47, 2.83)

Models adjusted for sex, race/ethnicity, current age, health insurance, household income, pain, neurologic event, radiation, and psychological distress. Reduced HRQOL defined as *T* score ≤40

[a] Adjusted $p<0.001$

[b] Adjusted $p<0.01$

[c] Adjusted $p<0.05$

medications, and some combinations therein have been reported to lead to increased neurotoxicity [26]. Our data show 15 % of survivors reported new onset use of multiple medications. There is a need to better understand the concomitant use of psychoactive agents in cancer survivors, as this practice may heighten the risk for adverse drug events in a medically vulnerable population. Specifically, potential underlying cardiac and/or neurological toxicity following cancer therapies may increase vulnerability to adverse effects from psychoactive medications [5, 6, 27–29].

Cancer treatment variables maintained significant associations with reported medication use, even after controlling for the observed effects of demographic factors and symptoms of pain and distress. Cranial radiation therapy was significantly associated with anticonvulsant use, while radiation to other areas of the body was associated with increased likelihood of new onset use for all other medication classes, including antidepressants, analgesics, and muscle relaxants. These findings suggest, at least in part, that post-radiation-related pain may develop or persist decades after treatment completion [30]. Amputation also was associated with a greater than threefold increased likelihood of new onset analgesic use, in sharp contrast to the nonsignificant association between amputation and baseline analgesic use, which suggests the emergence or worsening of pain for these patients over time. The majority of amputations occur in patients diagnosed with osteosarcoma, and our findings are consistent with reports that long-term osteosarcoma survivors are more likely to report pain compared to survivors of other childhood malignancies [4, 31].

Survivors reported significantly higher rates of baseline and new onset analgesic use compared to siblings. Psychological distress was strongly associated with increased use of pain medications, and pain symptoms were associated with use of medications for psychiatric conditions (e.g., depression, anxiety). These findings likely reflect high levels of comorbidity between pain and emotional distress, consistent with reports that individuals with depression are four times more likely to have a chronic painful physical condition than nondepressed patients [32]. Furthermore, patients with pain symptoms are more likely to experience depression than those without pain [33]. We found rates of psychoactive medication use to be higher in survivors with comorbid pain and psychological distress (55 %) compared to survivors reporting either pain (31 %) or psychological distress (33 %) alone. These data suggest that general practitioners need to be aware of potential comorbidities between pain and psychological distress when prescribing psychoactive medications to cancer survivors, and may necessitate screening for psychological comorbidities, such as depression, in patients presenting with pain symptoms. It is important to note that antidepressants may be used for direct management of pain. Specifically, tricyclic antidepressants

are commonly used for treatment of neuropathic pain as well as headache prophylaxis.

Health-related quality of life may provide an important index of functional outcomes in response to medication treatment. Our findings revealed significant associations between several medication classes and reduced physical and mental HRQOL, independent of established predictors of impaired functional outcomes, including pain and psychological distress. Previous studies have reported improved quality of life in patients following short-term treatment with antidepressants [9, 10], yet these improvements are often directly associated with symptom reduction and reflect initial response to treatment. Quality of life can be negatively impacted by drug-induced side effects and subjective tolerability. For example, weight gain [34], sexual dysfunction [35], and cognitive impairment [12, 36] are well-documented side effects of psychopharmacologic treatment and have the potential to negatively impact quality of life. It is important to note that survivors may be at risk for poor quality of life due to underlying mental health and/or medical conditions, including depression, chronic pain, and epilepsy, and that survivors may use psychoactive medications to treat such conditions [37, 38].

Despite the many strengths of our study, including an extensive follow-up period and use of sibling controls, these findings should be considered in the context of several limitations. Our study relied exclusively on self-reported medication use. As such, we cannot verify use of reported medications nor do we have information regarding indication for medication prescription. It is important to consider that medications may have multiple indications. For example, antidepressants may be prescribed for the management of mood symptoms, neuropathic pain, migraine prophylaxis, and smoking cessation among other conditions. Although survivors reported all medications taken over a specified time period, we cannot verify that multiple medications were taken concurrently. Given the retrospective nature of the study, we are also unable to establish temporal relationships between reported medication use and functional outcomes. This limits our ability to discuss potential changes in HRQOL as a direct result of psychoactive medication treatment.

These findings, however, underscore the need for future research on the psychopharmacologic treatment of survivors of childhood cancer. Enhanced characterization of medication utilization, including indication for use, dose, and polypharmacy, will be important for future studies to consider. Additionally, randomized placebo-controlled trials are necessary to evaluate both the short- and long-term safety and efficacy of psychoactive medications in this at-risk population. As a part of these clinical trials, patient-reported functional outcomes, including HRQOL, will be important to assess and monitor in direct response to treatment. Understanding predictors of psychoactive medication use among adult survivors of pediatric cancer has the potential to inform screening and intervention practices affecting many childhood cancer survivors.

References

1. Howlader N, Noone A, Krapcho M, Neyman N, Aminou R, Waldron W. SEER cancer statistics review, 1975–2008. Bethesda: National Cancer Institute; 2011.
2. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Engl J Med. 2006;355:1572–82.
3. Greenberg DB, Goorin A, Gebhardt MC, Gupta L, Stier N, Harmon D, et al. Quality of life in osteosarcoma survivors. Oncology (Williston Park). 1994;8:19–25.
4. Lu Q, Krull KR, Leisenring W, Owen JE, Kawashima T, Tsao JC, et al. Pain in long-term adult survivors of childhood cancers and their siblings: a report from the Childhood Cancer Survivor Study. Pain. 2011;152:2616–24.
5. Bowers DC, Liu Y, Leisenring W, McNeil E, Stovall M, Gurney JG, et al. Late-occurring stroke among long-term survivors of childhood leukemia and brain tumors: a report from the Childhood Cancer Survivor Study. J Clin Oncol. 2006;24:5277–82.
6. Packer RJ, Gurney JG, Punyko JA, Donaldson SS, Inskip PD, Stovall M, et al. Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study. J Clin Oncol. 2003;21:3255–61.
7. Zeltzer LK, Lu Q, Leisenring W, Tsao JC, Recklitis C, Armstrong G, et al. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev. 2008;17:435–46.
8. Stuber ML, Meeske KA, Krull KR, Leisenring W, Stratton K, Kazak AE, et al. Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer. Pediatrics. 2010;125:e1124–34.
9. Skevington SM, Wright A. Changes in the quality of life of patients receiving antidepressant medication in primary care: validation of the WHOQOL-100. Br J Psychiatry. 2001;178:261–7.
10. Allgulander C, Jorgensen T, Wade A, Francois C, Despiegel N, Auquier P, et al. Health-related quality of life (HRQOL) among patients with generalised anxiety disorder: evaluation conducted alongside an escitalopram relapse prevention trial. Curr Med Res Opin. 2007;23:2543–9.
11. Meador KJ, Loring DW, Hulihan JF, Kamin M, Karim R. Differential cognitive and behavioral effects of topiramate and valproate. Neurology. 2003;60(9):1483–8.
12. Meador KJ, Loring DW, Vahle VJ, Ray PG, Werz MA, Fessler AJ, et al. Cognitive and behavioral effects of lamotrigine and topiramate in healthy volunteers. Neurology. 2005;64(12):2108–14.
13. Meador KJ, Loring DW, Ray PG, Murro AM, King DW, Perrine KR, et al. Differential cognitive and behavioral effects of carbamazepine and lamotrigine. Neurology. 2001;56(9):1177–82.
14. Reddick WE, Laningham FH, Glass JO, Pui CH. Quantitative morphologic evaluation of magnetic resonance imaging during and after treatment of childhood leukemia. Neuroradiology. 2007;49(11):889–904. doi:10.1007/s00234-007-0262-9.
15. Porto L, Preibisch C, Hattingen E, Bartels M, Lehrnbecher T, Dewitz R, et al. Voxel-based morphometry and diffusion-tensor MR imaging of the brain in long-term survivors of childhood leukemia. Eur Radiol. 2008;18(11):2691–700. doi:10.1007/s00330-008-1038-2.

16. Lew SM, Morgan JN, Psaty E, Lefton DR, Allen JC, Abbott R. Cumulative incidence of radiation-induced cavernomas in long-term survivors of medulloblastoma. J Neurosurg. 2006;104:103–7.
17. Leisenring WM, Mertens AC, Armstrong GT, Stovall MA, Neglia JP, Lanctot JQ, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. J Clin Oncol. 2009;27:2319–27.
18. Robison LL, Armstrong GT, Boice JD, Chow EJ, Davies SM, Donaldson SS, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol. 2009;27:2308–18.
19. American Society of Health-System Pharmacists. AHFS Drug Information. 2011. http://www.ahfsdruginformation.com/. Accessed 10 June 2011.
20. McHorney CA, Ware Jr JE, Rogers W, Raczek AE, Lu JF. The validity and relative precision of MOS short- and long-form health status scales and Dartmouth COOP charts. Results from the Medical Outcomes Study. Med Care. 1992;30:MS253–65.
21. Krull KR, Annett RD, Pan Z, Ness KK, Nathan PC, Srivastava DK, et al. Neurocognitive functioning and health-related behaviours in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Eur J Cancer. 2011;47:1380–8.
22. Derogatis L. Brief Symptom Inventory (BSI): administration, scoring, and procedures manual. Minneapolis: NCS Pearson; 2000.
23. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat. 1979;6:65–70.
24. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatry. 2009;66:848–56.
25. Gu Q, Dillon CF, Burt VL. Prescription drug use continues to increase: U.S. prescription drug data for 2007–2008. NCHS Data Brief. 2010;(42):1–8.
26. Freeman MP, Stoll AL. Mood stabilizer combinations: a review of safety and efficacy. Am J Psychiatry. 1998;155(1):12–21.
27. van der Pal HJ, van Dalen EC, Hauptmann M, Kok WE, Caron HN, van den Bos C, et al. Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. Arch Intern Med. 2010;170:1247–55.
28. Armstrong GT, Stovall M, Robison LL. Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the childhood cancer survivor study. Radiat Res. 2010;174:840–50.
29. Brouwer CA, Postma A, Vonk JM, Zwart N, van den Berg MP, Bink-Boelkens MT, et al. Systolic and diastolic dysfunction in long-term adult survivors of childhood cancer. Eur J Cancer. 2011;47:2453–62.
30. Burton AW, Fanciullo GJ, Beasley RD, Fisch MJ. Chronic pain in the cancer survivor: a new frontier. Pain Med. 2007;8:189–98.
31. Nagarajan R, Kamruzzaman A, Ness KK, Marchese VG, Sklar C, Mertens A, et al. Twenty years of follow-up of survivors of childhood osteosarcoma: a report from the Childhood Cancer Survivor Study. Cancer. 2011;117:625–34.
32. Ohayon MM, Schatzberg AF. Using chronic pain to predict depressive morbidity in the general population. Arch Gen Psychiatry. 2003;60:39–47.
33. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. Arch Intern Med. 2003;163:2433–45.
34. McCloughen A, Foster K. Weight gain associated with taking psychotropic medication: an integrative review. Int J Ment Health Nurs. 2011;20:202–22.
35. Serretti A, Chiesa A. Sexual side effects of pharmacological treatment of psychiatric diseases. Clin Pharmacol Ther. 2011;89:142–7.
36. Loring DW, Williamson DJ, Meador KJ, Wiegand F, Hulihan J. Topiramate dose effects on cognition: a randomized double-blind study. Neurology. 2011;76:131–7.
37. Elliott TE, Renier CM, Palcher JA. Chronic pain, depression, and quality of life: correlations and predictive value of the SF-36. Pain Med. 2003;4:331–9.
38. Kobau R, Zahran H, Grant D, Thurman DJ, Price PH, Zack MM. Prevalence of active epilepsy and health-related quality of life among adults with self-reported epilepsy in California: California Health Interview Survey, 2003. Epilepsia. 2007;48:1904–13.