Childhood Ca Survivors Risk Later Brain Tumors

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Los Angeles — Malignant and benign secondary brain tumors are a significant problem in childhood cancer survivors, especially those surviving leukemia and brain tumors, according to findings from the Childhood Cancer Survivor Study.

Exposure to cranial radiation increases the risk of these secondary tumors, which may arise years after treatment for the initial cancer, Joseph P. Neglia, M.D., reported at the annual meeting of the Child Neurology Society.

Of 14,327 survivors of childhood cancer—defined as those diagnosed with cancer before the age of 20—in the Childhood Cancer Survivor Study, 116 developed secondary brain tumors between 5 and 28 years after initial diagnosis. The tumors included 66 meningiomas, 40 gliomas, 6 primitive neuroectodermal tumors, 1 lymphoma, and 3 tumors for which the histology could not be determined. A total of 33 of the tumors—30 of the gliomas and 3 of the meningiomas—were malignant. The gliomas occurred sooner after the initial diagnosis (median 9 years) than the meningiomas (median 17 years) and were more common after primary leukemia, while meningiomas occurred more frequently after primary brain tumors, said Dr. Neglia of the University of Minnesota in Minneapolis.

"Radiation therapy exposure was associated with significant increased risks for the development of gliomas, meningiomas, or any central nervous system brain tumors," he said.

Additionally, the study revealed a radiation dose-response relationship with glioma development.

"Patients who received radiotherapy doses between 3,000 and 4,490 cGy had the highest rate of glioma diagnoses," Dr. Neglia said. ■

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Table 1. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body System Preferred term	75 mg/d [N=77] %	150 mg/d [N=212] %	300 mg/d [N=321] %	600 mg/d [N=369] %	All PGB* [N=979] %	Placebo [N=459] %
Body as a whole						
Asthenia	4	2	4	7	5	2
Accidental injury	5	2	2	6	4	3
Back pain	0	2	1	2	2	0
Chest pain	4	1	1	2	2	1
Face edema	0	1	1	2	1	0
Digestive system						
Dry mouth	3	2	5	7	5	1
Constipation	0	2	4	6	4	2
Flatulence	3	0	2	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	4	6	9	12	9	2
Weight gain	0	4	4	6	4	0
Edema	0	2	4	2	2	0
Hypoglycemia	1	3	2	1	2	1
Nervous system						
Dizziness	8	9	23	29	21	5
Somnolence	4	6	13	16	12	3
Neuropathy	9	2	2	5	4	3
Ataxia	6	1	2	4	3	1
Vertigo	1	2	2	4	3	1
Confusion	0	1	2	3	2	1
Euphoria	0	0	3	2	2	0
Incoordination	1	0	2	2	2	0
Thinking abnormal[a]	1	0	1	3	2	0
Tremor	1	1	1	2	1	0
Abnormal gait	1	0	1	3	1	0
Amnesia	3	1	0	2	1	0
Nervousness	0	1	1	1	1	0
Respiratory system						
Dyspnea	3	0	2	2	2	1
Special senses						
Blurry vision[b]	3	1	3	6	4	2
Abnormal vision	1	0	1	1	1	0

*PGB: pregabalin
[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[b] Investigator term; summary level term is amblyopia.

Controlled Studies in Postherpetic Neuralgia: Adverse Events Leading to Discontinuation In clinical trials in patients with postherpetic neuralgia, 14% of patients treated with pregabalin and 7% of patients treated with placebo discontinued prematurely due to adverse events. In the pregabalin treatment group, the most common reasons for discontinuation due to adverse events were dizziness (4%) and somnolence (3%). In comparison, less than 1% of placebo patients withdrew due to dizziness and somnolence. Other reasons for discontinuation from the trials, occurring in greater frequency in the pregabalin group than in the placebo group, were confusion (2%), as well as peripheral edema, asthenia, ataxia, and abnormal gait (1% each). **Most Common Adverse Events** Table 2 lists all adverse events, regardless of causality, occurring in ß1% of patients with neuropathic pain associated with postherpetic neuralgia in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group. In addition, an event is included, even if the incidence in the all pregabalin group is not greater than in the placebo group, if the incidence of the event in the 600 mg/day group is more than twice that in the placebo group. A majority of pregabalin-treated patients in clinical studies had adverse events with a maximum intensity of "mild" or "moderate."

Table 2. Treatment-emergent adverse event incidence in controlled trials in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at least 1% of all LYRICA-treated patients and at least numerically more in all pregabalin than in the placebo group)

Body System Preferred term	75 mg/d [N=84] %	150 mg/d [N=302] %	300 mg/d [N=312] %	600 mg/d [N=154] %	All PGB* [N=852] %	Placebo [N=398] %
Body as a whole						
Infection	14	8	6	3	7	4
Headache	5	9	5	8	7	5
Pain	5	4	5	5	5	4
Accidental injury	4	3	3	5	3	2
Flu syndrome	1	2	2	1	2	1
Face edema	0	2	1	3	2	1
Digestive system						
Dry mouth	7	7	6	15	8	3
Constipation	4	5	5	5	5	2
Flatulence	2	1	2	3	2	1
Vomiting	1	1	3	3	2	1
Metabolic and nutritional disorders						
Peripheral edema	0	8	16	16	12	4
Weight gain	1	2	5	7	4	0
Edema	0	1	2	6	2	1
Musculoskeletal system						
Myasthenia	1	1	1	1	1	0
Nervous system						
Dizziness	11	18	31	37	26	9
Somnolence	8	12	18	25	16	5
Ataxia	1	2	5	9	5	1
Abnormal gait	0	2	4	8	4	1
Confusion	1	2	3	7	3	0
Thinking abnormal[a]	0	2	1	6	2	2
Incoordination	2	2	1	3	2	0
Amnesia	0	1	1	4	2	0
Speech disorder	0	0	1	3	1	0
Respiratory system						
Bronchitis	0	1	1	3	1	1
Special senses						
Blurry vision[b]	1	5	5	9	5	3
Diplopia	0	2	2	4	2	0
Abnormal vision	0	1	2	5	2	0
Eye disorder	0	1	1	2	1	0
Urogenital system						
Urinary incontinence	0	1	1	2	1	0

*PGB: pregabalin
[a] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[b] Investigator term; summary level term is amblyopia.

Controlled Add-on Studies in Epilepsy: Adverse Events Leading to Discontinuation Approximately 15% of patients receiving pregabalin and 6% of patients receiving placebo in add-on epilepsy trials discontinued prematurely due to adverse events. In the pregabalin treatment group, the adverse events most frequently leading to discontinuation were dizziness (6%), ataxia (4%), and somnolence (3%). In comparison, <1% of patients in the placebo group withdrew due to each of these events. Other adverse events that led to discontinuation of at least 1% of patients in the pregabalin group and at least twice as frequently compared to the placebo group were asthenia, diplopia, blurred vision, thinking abnormal, nausea, tremor, vertigo, headache, and confusion (which each led to withdrawal in 2% or less of patients). **Most Common Adverse Events** Table 3 lists all dose-related adverse events, regardless of causality, occurring in at least 2% of all LYRICA-treated patients. Dose-relatedness was defined as the incidence of the adverse event in the 600 mg/day group was at least 2% greater than the rate in both the placebo and 150 mg/day groups. In these studies, 758 patients received pregabalin and 294 patients received placebo for up to 12 weeks. Because patients were also treated with 1 to 3 other AEDs, it is not possible to determine whether the following adverse events can be ascribed to pregabalin alone, or the combination of pregabalin and other AEDs. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of "mild" or "moderate."

Table 3. Dose-related treatment-emergent adverse event incidence in controlled trials in Epilepsy (Events in at least 2% of all LYRICA-treated patients and the adverse event in the 600 mg/day group was ≥2% the rate in both the placebo and 150 mg/day groups)

Body System Preferred term	150 mg/d [N=185] %	300 mg/d [N=90] %	600 mg/d [N=395] %	All PGB* [N=670][a] %	Placebo [N=294] %
Body as a whole					
Accidental injury	7	11	10	9	5
Pain	3	2	5	4	3
Digestive system					
Increased appetite	2	3	6	5	1
Dry mouth	1	2	6	4	1
Constipation	1	1	7	4	2
Metabolic and nutritional disorders					
Weight gain	5	7	16	12	1
Peripheral edema	3	3	6	5	2
Nervous system					
Dizziness	18	31	38	32	11
Somnolence	11	18	28	22	11
Ataxia	6	10	20	15	4
Tremor	3	7	11	8	4
Thinking abnormal[b]	4	8	9	8	2
Amnesia	3	2	6	5	2
Speech disorder	1	2	7	5	1
Incoordination	1	3	6	4	1
Abnormal gait	1	3	5	4	0
Twitching	0	4	5	4	1
Confusion	1	2	5	4	2
Myoclonus	1	0	4	2	0
Special senses					
Blurred vision[c]	5	8	12	10	4
Diplopia	5	7	12	9	4
Abnormal vision	3	1	5	4	1

*PGB: pregabalin
[a] Excludes patients who received the 50 mg dose in Study E1 (included in full prescribing information).
[b] Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slowed thinking.
[c] Investigator term; summary level term is amblyopia.

Adverse events occurring in ß2% of patients with partial onset seizures in the combined pregabalin group for which the incidence was greater in this combined pregabalin group than in the placebo group, but did not show dose-relatedness, include the following: asthenia, infection, chest pain, vomiting, nervousness, nystagmus, paresthesias, visual field defect. **Other Adverse Events Observed During the Clinical Studies of LYRICA (pregabalin)** Following is a list of treatment-emergent adverse events reported by patients treated with LYRICA during all clinical trials. The listing does not include those events already listed in the previous tables or elsewhere in labeling, those events for which a drug cause was remote, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life-threatening. Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: **frequent** adverse events are those occurring on one or more occasions in at least 1/100 patients; **infrequent** adverse events are those occurring in 1/100 to 1/1000 patients; **rare** events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are described in the **WARNINGS** and **PRECAUTIONS** sections. **Body as a Whole**–*Frequent:* Abdominal pain, Allergic reaction, Fever; *Infrequent:* Abscess, Cellulitis, Chills, Malaise, Neck rigidity, Overdose, Pelvic pain, Photosensitivity reaction, Suicide attempt; *Rare:* Anaphylactoid reaction, Ascites, Granuloma, Hangover effect, Intentional injury, Retroperitoneal fibrosis, Shock, Suicide **Cardiovascular System**–*Infrequent:* Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare:* ST depressed, Ventricular fibrillation **Digestive System**–*Frequent:* Gastroenteritis, Increased appetite; *Infrequent:* Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare:* Aphthous stomatitis, Esophageal ulcer **Hemic and Lymphatic System**–*Frequent:* Ecchymosis; *Infrequent:* Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare:* Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocythemia **Metabolic and Nutritional Disorders**–*Rare:* Glucose tolerance decreased, Urate crystalluria **Musculoskeletal System**–*Frequent:* Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent:* Arthrosis; *Rare:* Generalized spasm **Nervous System**–*Frequent:* Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent:* Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia; *Rare:* Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Psychotic depression, Schizophrenic reaction, Torticollis, Trismus **Respiratory System**–*Rare:* Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn **Skin and Appendages**–*Frequent:* Pruritus; *Infrequent:* Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare:* Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Petechial rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule **Special Senses**–*Frequent:* Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent:* Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare:* Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis **Urogenital System**–*Frequent:* Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent:* Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention; *Rare:* Acute kidney failure, Balanitis, Bladder neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis **Comparison of Gender and Race** The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: LYRICA is a Schedule V controlled substance. In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated subjects and 1% of placebo-treated patients overall reported euphoria as an adverse event, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea (see **PRECAUTIONS**, Abrupt Discontinuation), suggestive of physical dependence. Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans There is limited experience with overdose of pregabalin. The highest reported accidental overdose of pregabalin during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse events experienced by patients exposed to higher doses (ß900 mg) were not clinically different from those of patients administered recommended doses of pregabalin. **Treatment or Management of Overdose** There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patients clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

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