Anticonvulsant prophylaxis for brain tumor surgery: determining the current best available evidence

A review

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Patients who undergo craniotomy for brain tumor resection are prone to experiencing seizures, which can have debilitating medical, neurological, and psychosocial effects. A controversial issue in neurosurgery is the common practice of administering perioperative anticonvulsant prophylaxis to these patients despite a paucity of supporting data in the literature. The foreseeable benefits of this strategy must be balanced against potential adverse effects and interactions with critical medications such as chemotherapeutic agents and corticosteroids. Multiple disparate meta-analyses have been published on this topic but have not been applied into clinical practice, and, instead, personal preference frequently determines practice patterns in this area of management. Therefore, to select the current best available evidence to guide clinical decision making, the literature was evaluated to identify meta-analyses that investigated the efficacy and/or safety of anticonvulsant prophylaxis in this patient population. Six meta-analyses published between 1996 and 2011 were included in the present study. The Quality of Reporting of Meta-analyses and Oxman-Guyatt methodological quality assessment tools were used to score these meta-analyses, and the Jadad decision algorithm was applied to determine the highest-quality meta-analysis. According to this analysis, 2 meta-analyses were deemed to be the current best available evidence, both of which conclude that prophylactic treatment does not improve seizure control in these patients. Therefore, this management strategy should not be routinely used.

http://thejns.org/doi/abs/10.3171/2014.7.JNS132829

KEY WORDS • anticonvulsant • antiepileptic • prophylaxis • craniotomy • brain tumors • oncology • epilepsy

Abbreviations used in this paper: AED = antiepileptic drug; QUOROM = Quality of Reporting of Meta-analyses; RCT = randomized controlled trial.
postoperatively.50 In a systematic review of supratentorial craniotomies, the first postoperative seizure occurred at means of 2.3 days and 42 months for untreated and AED-treated patients, respectively.26 In another study, the type of epilepsy occurring after brain tumor surgery was generalized, focal, and mixed in 53%, 30%, and 17% of cases, respectively.15 While historical series demonstrated effective seizure prevention using AEDs following craniotomy,32,43 recent data suggest a low baseline incidence of postoperative seizures even in the absence of AED prophylaxis.26,58

The purpose of this study was to critically analyze the literature to select the current best available evidence. Personal preference heavily influences decision making on AED use following brain tumor surgery,58 perhaps an indication that the literature has not been translated into treatment recommendations for clinical practice. While high-quality meta-analyses of randomized controlled trials (RCTs) represent the highest level of evidence available to clinicians,21 methodological differences and discordant results across meta-analyses may complicate their interpretation and clinical application. Thus, published meta-analyses on this topic were assessed using validated methodological quality assessment tools and a decision algorithm, with the intent of selecting the highest-quality meta-analysis to guide clinical decision making.

Methods

In this study, the English-language literature was evaluated to appraise the scientific support for the use of perioperative AED prophylaxis. Published meta-analyses were identified following a PubMed search using the following search terms with Boolean operators: anticonvulsant, antiepileptic, prophylaxis, prophylactic, brain tumor, craniotomy, and neurosurgery. Manual citation cross-referencing of all reviewed articles was also performed. After reviewing study abstracts and procuring full-length papers for potentially eligible studies, the results of eligible meta-analyses were extracted. Meta-analyses were included if they assessed the efficacy and/or safety of AED prophylaxis in patients diagnosed with brain tumors, those undergoing craniotomy, or, optimally, those undergoing craniotomy for brain tumor resection. Systematic reviews that did not perform a meta-analysis using pooled outcome data were excluded. Data were extracted from the selected meta-analyses for the eligible study population and study design; the number of included studies and patients; the search methodology and study selection; follow-up interval; type, timing, and duration of intervention; outcome parameters; performance of statistical heterogeneity analysis and subgroup analyses; and results of pooled analyses with respect to overall, early, and/or late seizures, adverse events, and any secondary outcomes when available.

The methodological quality of the selected meta-analyses was analyzed using the Quality of Reporting of Meta-analyses (QUOROM)39 and Oxman-Guyatt85 scoring systems, which are validated quality assessment tools with increasing application in the broader surgical literature7 for weighing disparate meta-analyses and system-atically determining which meta-analysis should guide clinical decision making. Subsequently, 2 lead authors independently used these scores and other extracted study characteristics to apply the Jadad decision algorithm,23 which aids in the interpretation of meta-analysis quality on the basis of parameters such as the clinical question of interest, inclusion and exclusion criteria, search strategies and study selection, validity assessment, data extraction and pooling, and statistical analysis.

Rationale for Anticonvulsant Prophylaxis

The occurrence of seizures after craniotomy obfuscates the postoperative evaluation of the patient’s mental status, immediate postsurgical status, and possible evolving complications such as cerebral edema.10 In turn, the seizures can cause intracranial hypertension, leading to neurological deficits and delayed postoperative recovery.33 Seizures cause functional impairment, societal stigmatization (e.g., the ability to work and drive), and psychological distress to the patient and family. They are also associated with secondary morbidities such as aspiration, brain hypoxia and edema, consequent neurotoxicity, and falls.25,26 Strikingly, the seizure incidence has been associated with increased brain tumor progression and poorer overall survival.13 These patients are also predisposed to neurological impairment11 and higher rates of depression, anxiety, and suicidality.68 Rarely, seizure episodes can provoke potentially fatal status epilepticus or acute intracranial herniation syndromes.26,35 Speculative benefits of AED prophylaxis include not only the prevention of early postoperative seizures, but also long-term epilepsy.49 It is unclear whether AEDs have a disease-modifying effect by preventing postoperative epileptogenesis7,51,59 or merely suppress the clinical manifestations of seizures.1,26 Proponents of prophylactic treatment cite the kindling model of epilepsy, yet to be proven in humans, which suggests that postoperative seizures generate and/or sustain secondary epileptogenic foci in the brain.27,42

Overview and Pharmacology of Anticonvulsants in Use

The most commonly used AED for perioperative prophylaxis after brain tumor surgery is phenytoin.71 Other preferred AEDs include valproic acid, carbamazepine, lamotrigine, and levetiracetam.28 AEDs tend to have multiple mechanisms of action.34 AEDs can be straightforwardly characterized as being broad-spectrum (e.g., valproic acid, lamotrigine, and levetiracetam), which refers to their suitability for all types of seizures, or narrow-spectrum (e.g., phenytoin, carbamazepine, phenobarbital, primidone, and gabapentin), indicating utility for simple partial, complex partial, and secondarily generalized seizures. Older AEDs such as phenytoin, carbamazepine, phenobarbital, and primidone are hepatically degraded by the cytochrome P450 (CYP450) system.35 The same is true for lamotrigine and topiramate, albeit to a lesser degree.66 Valproic acid exhibits hepatic metabolism but is not enzyme-inducing.70

When AEDs are used, it is critical to attain adequate serum levels, as subtherapeutic dosing may be the most commonly implicated factor in treatment-resistant post-
operative seizures.6–28 With certain AEDs, especially phenytoin, clinicians should ensure timely quantitation and calibration of serum drug levels to avoid subtherapeutic levels or toxicities.7 Phenytoin has been historically favored in neurosurgery because it does not impair the level of consciousness29 and has a well-established therapeutic serum concentration range,10,20,42 although a disadvantage is its unpredictable nonlinear pharmacokinetics requiring up to 1 week before the steady-state serum concentration is achieved,6,10,27,30 which may be too late relative to the peak epileptic period.27 Newer AEDs generally allow for shorter loading periods,27 and later-generation AEDs such as levetiracetam have increasingly gained favor in neurosurgery. Another complicating factor with perioperative AED prophylaxis is that operative blood loss, which can be sizable with tumors such as meningiomas, can delay postoperative equilibration of the AED level with the neural tissue.27

Risks of Anticonvulsant Prophylaxis

Most early-generation AEDs are hepatically metabolized and thus either activate or inhibit cytochrome P450 enzymes. As a result, AEDs frequently interact with chemotherapeutic agents and corticosteroids, along with several other medications that patients admitted for brain tumor surgery may require, such as proton pump inhibitors, histamine H2-blockers, macrolide antibiotics, antidepressants, benzodiazepines, and typical antipsychotics.46,47 Interactions have been identified between enzyme-inducing AEDs and nitrosoureas, paclitaxel, 9-aminocamptothecin, thiopeta, topotecan, and irinotecan.8,65 Specifically, phenytoin, phenobarbital, and carbamazepine blunt the efficacy of corticosteroids.8,12,17,69 Strikingly, patients undergoing chemotherapy for glioblastoma exhibited significantly poorer overall survival when treated with enzyme-inducing versus non–enzyme inducing AEDs (10.8 vs 13.9 months), attributed to altered efficacy of chemotherapeutic agents.44 Importantly, AEDs such as phenytoin, carbamazepine, and valproic acid commonly interact with other AEDs, which may complicate the use of polytherapy, as can become necessary after tumor progression or increased brain edema.44 Lastly, patients with brain tumors have increased susceptibility to characteristic AED-related adverse effects.31

The New Generation of Antiepileptic Drugs: Levetiracetam

Later-generation AEDs, such as levetiracetam46 and gabapentin,9 are excreted without significant hepatic processing, lessening their risk of pharmacological interactions. As levetiracetam and gabapentin circulate in free form, they have a minimal effect on the protein binding and bioavailability of other drugs.46 Levetiracetam, a novel AED, is an increasingly favored agent with primarily renal metabolism and an improved risk profile relative to traditional AEDs.24 In 1 study, only 2.4% of 82 patients treated with this AED experienced adverse effects requiring treatment cessation, and no laboratory abnormalities were detected when given alongside chemotherapy.52 A large number of smaller studies have also shown levetiracetam to be well tolerated in brain tumor patients, with somnolence or other behavioral side effects being the most common adverse events,31,37,40,41,55,64 with adverse effects being mostly reversible with dose reduction or displacement.31,34,67

Levetiracetam demonstrated significantly fewer adverse effects than phenytoin when AED prophylaxis was given for supratentorial surgery, along with statistically equal efficacy (1% vs 4.3% early seizure incidence).31 In contrast, patients given phenytoin were more likely to experience adverse effects than a seizure (18% vs 4%), and were much less likely to remain on the medication 1 year after surgery than with levetiracetam (26% vs 64%).35 Usery et al. reported that 92 potential drug interactions were avoided by using levetiracetam instead of phenytoin, based on their analysis of the CYP450-processed medications their cohort of 17 patients had received.64 Lim et al. showed in their Phase II pilot study that conversion of phenytoin to levetiracetam following craniotomy was safe and feasible in glioma patients, along with a slightly higher rate of seizure control at 6 months with levetiracetam (87% vs 75%).31 Among 281 patients undergoing craniotomy for a supratentorial brain tumor, long-term complications were significantly less likely after perioperative prophylaxis with levetiracetam (9.8%) versus valproic acid (26.8%), as was the need for polytherapy (17.6% vs 38.5%).30

Results

Seizure Control

To date, 6 meta-analyses (Table 1),18,26,27,57,61,63 5 of which considered only Level I evidence from RCTs, have analyzed this management strategy. An additional study by Temkin60 presented results from the same meta-analysis,61 but it added information that was not provided in the original study. Five of 6 meta-analyses found no reduction in the overall, early, and/or late seizure risk after AED prophylaxis, while 1 found a reduction in the early seizure risk. There was significant heterogeneity across meta-analyses in the mean follow-up period, particular agents used, timing of the intervention, and duration of the intervention, as outlined in Table 1. Kuijlen et al., who studied AED prophylaxis for supratentorial craniotomy based on 3 trials that met the authors’ threshold of methodological quality,27 found a nonsignificant trend toward reduced postoperative seizures using prophylactic AEDs. Glantz et al., whose meta-analysis was based on 4 RCTs, found that AED prophylaxis did not reduce the overall seizure risk in patients with gliomas, meningiomas, or brain metastases, although their focus was not specific to the perioperative setting.18 Temkin, who performed a meta-analysis of 6 trials of nontraumatic craniotomy, found that phenytoin decreased the risk of early postoperative seizures by 44%.61 Carbamazepine and valproic acid, each tested in one included study, had no significant effect on seizure incidence. Phenytoin, carbamazepine, and phenobarbital did not improve the late seizure risk.61 Sirven et al., who included 5 trials of patients with brain tumors and no history of epilepsy, concluded that AEDs did not reduce the early or late seizure risk.57 Fur-
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<th>Meta-Analysis</th>
<th>Eligible Study Population</th>
<th>Eligible Study Designs</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Agents (no.)</th>
<th>Mean Follow-Up Interval (range)</th>
<th>Timing of Intervention (no.)</th>
<th>Duration of Intervention (no.)</th>
<th>Results of Pooled Analyses</th>
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<tr>
<td>Kuijlen et al., 1996</td>
<td>patients undergoing supratentorial craniotomy</td>
<td>controlled trials meeting methodological quality threshold</td>
<td>3</td>
<td>621</td>
<td>Pht (1), Phb (2), Ph (1), Cbz (1)</td>
<td>22.3 mos (3 days–48 mos)</td>
<td>preop (1), intraop (1), postop (1)</td>
<td>3 days (1), 6 or 24 mos (1), 12 mos (1)</td>
<td>no difference in overall Sz risk</td>
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<td>Glantz et al., 2000</td>
<td>patients diagnosed w/ brain tumors</td>
<td>RCTs</td>
<td>4</td>
<td>318</td>
<td>Pht (3), VPA (1), Phb (1)</td>
<td>9.7 (5.4–12) mos</td>
<td>≤14 days after diagnosis (1), preop (1), postop (1)</td>
<td>12 mos (2)</td>
<td>no difference in overall Sz risk or Sz-free survival</td>
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<tr>
<td>Temkin, 2001/2002†</td>
<td>patients undergoing craniotomy</td>
<td>prospective controlled trials</td>
<td>6</td>
<td>1560</td>
<td>Pht (5), Cbz (1), VPA (1), Phb (1)</td>
<td>9.4 mos (3 days–24 mos)</td>
<td>day of surgery (1), preop or ≤24 hrs after diagnosis, preop (1), intraop (1), postop (2)</td>
<td>3 days (1), 7 days (1), 6 or 24 mos (1), 12 mos (2)</td>
<td>reduction of early Sz risk by 44%; no difference in late Sz risk</td>
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<tr>
<td>Sirven et al., 2004</td>
<td>patients diagnosed w/ brain tumors w/o prior Szs</td>
<td>RCTs</td>
<td>5</td>
<td>403</td>
<td>Phb (2), Pht (4), VPA (1)</td>
<td>6.9 mos (3 days–12 mos)</td>
<td>≤14 days after diagnosis (1), preop (1), intraop (1), postop (1)</td>
<td>3 days (1), 12 mos (2)</td>
<td>no difference in early or late Sz risk</td>
</tr>
<tr>
<td>Tremont-Lukats et al., 2008</td>
<td>patients diagnosed w/ brain tumors</td>
<td>RCTs</td>
<td>5</td>
<td>404</td>
<td>Phb (2), Pht (4), VPA (1)</td>
<td>6.9 mos (3 days–12 mos)</td>
<td>≤14 days after diagnosis (1), preop (1), intraop (1), postop (1)</td>
<td>3 days (1), 12 mos (2)</td>
<td>no difference in overall Sz risk; significantly higher adverse event rate</td>
</tr>
<tr>
<td>Komotar et al., 2011</td>
<td>patients undergoing resection of supratentorial meningioma w/o prior Szs</td>
<td>all studies presenting original data w/ AED administration &amp; outcome data</td>
<td>3 (19)‡</td>
<td>698</td>
<td>Pht, VPA, Cbz, Lam, Lev were most common</td>
<td>36.5 (1–12 mos)</td>
<td>intraop (1), postop (2)</td>
<td>mean 4.2 (range 1–52) wks</td>
<td>no difference in early or late Sz risk, extent of resection, recurrence, or periop mortality</td>
</tr>
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</table>

* Cbz = carbamazepine; Lam = lamotrigine; Lev = levetiracetam; Phb = phenobarbital; Pht = phenytoin; Sz = seizure; VPA = valproate; Zon = zonisamide.
† Both publications present results from the same meta-analysis, but each provides some unique information that the other did not provide.
‡ Komotar et al. included an additional 16 uncontrolled studies in addition to the clinical trials referenced in the table.
thermore, their subgroup analyses found no efficacy for AEDs used for individual tumor pathologies, namely primary glial tumors and cerebral metastases. Komotar et al., whose meta-analysis studied craniotomy for supratentorial meningioma, found no significant differences in seizure incidence prior to and following hospital discharge, perioperative mortality, and recurrence between those treated with and without AED prophylaxis. The treated and untreated groups, respectively, had equal rates of early and late postoperative seizures. Tremont-Lukats et al., who studied patients with brain tumors based on 5 trials, likewise found that prophylactic phenytoin, phenobarbital, or valproic acid did not decrease the incidence of first-time seizures.63

Adverse Events

Two of the 6 meta-analyses performed a pooled analysis of adverse events associated with AED prophylaxis. The majority of reported adverse effects were not severe. The meta-analysis of Glantz et al. documented an AED-related adverse event rate of 23.8% using pooled data from 3 RCTs and 4 retrospective studies with historical controls. The most common adverse events were rash (14%), nausea or vomiting (5%), encephalopathy (5%), myelosuppression (3%), and ataxia, transaminitis, or gingival pain (5%). The meta-analysis of Tremont-Lukats et al. found an adverse event rate of 15% after AED prophylaxis, which was significantly higher than 0.9% in the control group, resulting in a number needed to harm of 3.13,19 The most common adverse events were rash and nausea, while tremor, vertigo and blurred vision, gait ataxia, gingival pain, myelosuppression, and increased lactate dehydrogenase were noted in 1 case each. The occurrence of these adverse events in relation to short-versus long-term AED use was not clearly indicated. In the meta-analysis of Glantz et al., adverse event data were derived from 2 RCTs, of which one employed long-term treatment for 12 months, while the other did not indicate the treatment duration, although data from an additional 4 uncontrolled studies were used for this analysis. In the meta-analysis of Tremont-Lukas et al., adverse event data were derived from 4 RCTs, of which 2 employed long-term treatment for 12 months, while the other 2 did not indicate the treatment duration.13,16

Determining the Current Best Available Evidence

Search Methodology and Meta-Analysis Design. A total of 10 RCTs were included among the 6 meta-analyses (Table 2), with each meta-analysis including between 3 and 6 of these primary studies. All but one meta-analysis limited the inclusion criteria for study design to RCTs. These meta-analyses differed in the comprehensiveness of their search strategies according to their use of the PubMed/Medline, Excerpta Medica Database (EMBASE), Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and other databases (Table 3). Various outcome measures were analyzed for AED-treated versus untreated patients using pooled data, chiefly overall seizure risk, early seizure risk, late seizure risk, and mortality. These analyses indicated that AED prophylaxis is safe and effective in reducing the risk of postoperative seizures, particularly early postoperative seizures. The evidence supports the use of AED prophylaxis for brain tumor surgery, providing a clinically meaningful benefit to patients with brain tumors.
risk, and/or adverse events (Table 4). Only 2 and 3 meta-analyses performed a statistical heterogeneity analysis and subgroup and/or sensitivity analyses, respectively, for specifically assessing variables such as the AED or the type of brain tumor pathology.

**Validity Assessment.** The QUOROM score varied widely across the 6 meta-analyses (range 7–15; maximum possible score, 18), with 3 achieving scores of 15 and thus exhibiting better methodological quality than the other 3. The Oxman-Guyatt score also varied widely across these meta-analyses (range 1–6; maximum possible score 7), with all meta-analyses demonstrating major flaws due to a score of 3 or lower, except for those of Sirven et al.57 and Tremont-Lukats et al.63

**Application of Jadad Decision Algorithm.** After scoring of these meta-analyses using these 2 indices was completed, the Jadad algorithm was applied. It was first noted that 3 of the meta-analyses are limited by the clinical question they ask (Steps A and B). Tremont-Lukats et al.63 and Glantz et al.18 studied prophylaxis for brain tumors in general, not necessarily in the perioperative setting, while Temkin61 analyzed prophylaxis for all craniotomies, including but not limited to brain tumors. The 2 meta-analyses by Sirven et al.57 and Tremont-Lukats et al.63 were favored over the other 4 meta-analyses due to clear differences in methodological and/or scientific quality according to the QUOROM and Oxman and Guyatt indices (Step D). Furthermore, the selection criteria of the other 4 meta-analyses were less optimal (Step G), namely their use of narrower search strategies and/or inclusion of uncontrolled trials or respective studies subject to greater bias (Steps H and I). The meta-analysis of Temkin was eliminated from consideration due to the performance of data extraction by a single reviewer (Step E) and lack of validity assessment (Step I). With only the 2 meta-analyses of Sirven et al. and Tremont-Lukats et al. remaining, both were noted to include the same 5 RCTs (Step C), be of similar quality (Step D), and exercise appropriate data extraction, heterogeneity testing, and quantitative data synthesis (Step E). Therefore, application of the Jadad algorithm confirmed that the meta-analyses by Sirven et al. and Tremont-Lukats et al. represent the current best available evidence for clinicians considering whether to use this management strategy. Neither of these 2 meta-analyses demonstrated an improvement in seizure control with the use of AED prophylaxis.

**Discussion**

**Implications for Clinical Practice**

The current best available evidence, from the meta-analyses of RCTs conducted by Sirven et al.57 and Tremont-Lukats et al.63 suggests that AED prophylaxis for brain tumor surgery should not be routinely used due to a lack of significant improvement in seizure control and a potential increase in adverse events. However, as later-generation AEDs such as levetiracetam offer an improved safety profile over older AEDs, clinicians who wish to use prophylaxis should use these newer agents.
Limitations of Current Evidence

Limitations of the existing literature include significant heterogeneity within and across cohorts in drug dosing, the route and timing of administration, the use of drug level monitoring, and outcome parameters. For instance, the trials included in the 6 meta-analyses treated patients with AEDs for as long as 3 days to 24 months. Further methodological variation was present in drug level monitoring and the route and timing of administration. Furthermore, many studies did not differentiate between early and late postoperative seizures or report auxiliary outcomes such as adverse events, functional disability (i.e., in relation to seizure severity), and mortality. Some studies also intermixed brain tumors with other nontraumatic and nontraumatic neurosurgical pathologies, such as traumatic brain injury, which is amenable to perioperative AED prophylaxis, and subarachnoid hemorrhage, for which such treatment strikingly impedes functional recovery.

Future Directions

More research is needed to clarify how patient-specific factors, such as tumor location and histological type, tumor size, type of retraction and surgical technique required for resection, and residual tumor after craniotomy affect epileptic susceptibility and, perhaps, consideration of AED prophylaxis in selected, high-risk patients. In addition, further research should elucidate how the timing and duration of prophylactic AED administration, which varied significantly across the analyzed studies, influence its efficacy. Prophylaxis may be commenced preoperatively, intraoperatively, or postoperatively, and recommendations variably recommend treatment cessation after 1 week, as per the 2000 American Academy of Neurology guidelines, to 6 months after surgery. Future meta-analyses must consistently differentiate between early and postoperative seizures, as the former are of particular concern during neurosurgical care. Lastly, as newer-generation AEDs such as levetiracetam become increasingly favored by neurosurgeons in modern antiepileptic regimens, they should be the primary focus of any future RCTs and meta-analyses.

Conclusions

The management approach to seizures after brain tumor surgery is challenging. Although routinely employed at many neurosurgical centers, the current best available evidence on perioperative AED prophylaxis for brain tumor surgery, according to validated quality assessment indices and the Jadad decision algorithm for interpreting meta-analyses, indicates that this strategy should not be routinely employed due to a lack of improvement in seizure control and an appreciable adverse event rate. A limitation of the published literature is the predominant use of traditional AEDs in studies, which does not account for contemporary regimens that increasingly favor levetiracetam and other later-generation AEDs.

Disclosure

The authors report no conflict of interest concerning the

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<th>Outcome Reported</th>
<th>Meta-Analysis</th>
<th>Overall Sz Risk</th>
<th>Early Sz Risk</th>
<th>Late Sz Risk</th>
<th>Adverse Events</th>
<th>Extent of Resection</th>
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<th>Extent of Resection</th>
<th>Sz-Free Survival</th>
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* All outcomes pertain to the comparison of patients treated with AED prophylaxis versus without it. OS = overall survival; PFS = progression-free survival.
materials or methods used in this study or the findings specified in this paper. This work was supported by grants from the Howard Hughes Medical Institute (E.T.S.), the Reza and Georgianna Khatib Endowed Professor at Northwestern University (O.B.), and the Michael J. Marchese Professor and Chair at Northwestern University (A.T.P.).

Author contributions to the study and manuscript preparation include the following. Conception and design: Sayegh. Acquisition of data: Sayegh. Analysis and interpretation of data: Sayegh. Drafting the article: Sayegh, Fakurnejad. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Parsa. Study supervision: Parsa.

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Manuscript submitted December 21, 2013. Accepted July 17, 2014. Please include this information when citing this paper: published online August 29, 2014; DOI: 10.3171/2014.7.JNS132829. Address correspondence to: Andrew T. Parsa, M.D., Ph.D., Department of Neurological Surgery, Northwestern University Feinberg School of Medicine, 676 N. St. Clair St., Ste. 2210, Chicago, IL 60611. email: aparsa@nmff.org.