Prophylactic antiepileptic drug administration following brain tumor resection: results of a recent AANS/CNS Section on Tumors survey

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OBJECTIVE Antiepileptic drugs (AEDs) are often administered prophylactically following brain tumor resection. With conflicting evidence and unestablished guidelines, however, the nature of this practice among tumor surgeons is unknown.

METHODS On November 24, 2015, a REDCap (Research Electronic Database Capture) survey was sent to members of the AANS/CNS Section on Tumors to query practice patterns.

RESULTS Responses were received from 144 individuals, including 18.8% of board-certified neurosurgeons surveyed (across 86 institutions, 16 countries, and 5 continents). The majority reported practicing in an academic setting (85%) as a tumor specialist (71%). Sixty-three percent reported always or almost always prescribing AED prophylaxis postoperatively in patients with a supratentorial brain tumor without a prior seizure history. Meanwhile, 9% prescribed occasionally and 28% rarely prescribed AED prophylaxis. The most common agent was levetiracetam (85%). The duration of seizure prophylaxis varied widely: 25% of surgeons administered prophylaxis for 7 days, 16% for 2 weeks, 21% for 2 to 6 weeks, and 13% for longer than 6 weeks. Most surgeons (61%) believed that tumor pathology influences epileptogenicity, with high-grade glioma (39%), low-grade glioma (31%), and metastases (24%) carrying the greatest seizure risk. While the majority used prophylaxis, 62% did not believe or were unsure if prophylactic AEDs reduced seizures postoperatively. The vast majority (82%) stated that a well-designed randomized trial would help guide their future clinical decision making.

CONCLUSIONS Wide knowledge and practice gaps exist regarding the frequency, duration, and setting of AED prophylaxis for seizure-naive patients undergoing brain tumor resection. Acceptance of universal practice guidelines on this topic is unlikely until higher-level evidence supporting or refuting the value of modern seizure prophylaxis is demonstrated.

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KEY WORDS brain tumor; epilepsy; levetiracetam; prophylaxis; survey; oncology
AAMS/CNS survey: seizure prophylaxis following tumor resection
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Methods
An email was sent in October and November of 2015 to members of the AANS/CNS Section on Tumors. The email contained a link to an 11-question survey housed within the REDCap (Research Electronic Data Capture) data manager at Vanderbilt University.10 Answers were collected until December 12, 2015.

Survey questions were based largely on controversial facets of perioperative seizure management that have not been adequately addressed via a high-level evidence-based methodology. Participants were asked about their use or nonuse of AED administration in the perioperative period in patients with a brain tumor who have not experienced a seizure. The questions focused on the frequency, duration, and type of AED administered. Tumor-specific factors influencing epileptogenicity, including pathology and location, were also queried. Finally, respondents were asked about their practice setting and diversity, board certification status, and opinion regarding the utility of a clinical trial on the subject. Survey questions were designed such that responses could be used for the concept and design of a potential clinical trial on the subject. A summary of survey questions and answers is contained in the Appendix.

De-identified answers were exported directly to IBM SPSS software (version 23, IBM) for analysis. Responses identified from student members of the Section on Tumors were removed prior to tabulation and analysis. Answers were reported as counts and relative proportions labeled as percentages. Nonparametric data were reported as the median (interquartile range) and compared using the Mann-Whitney U-test. Dichotomous data were compared using the chi-square test. A p value < 0.05 was considered statistically significant.

Results
Study Sample Characteristics
The email listserv included 462 board-certified and 35 board-eligible neurosurgeons, as well as 1481 students, residents, and fellows. Baseline data regarding practice setting (academic vs private) and duration in practice of the members were not available. Among the 1978 individuals contacted electronically, 144 responded with survey answers (7.3% total response rate). Of these 144 respondents, 8 completed less than 25% of the survey, and thus their responses were removed. Ten members submitted incomplete surveys but responded to more than 70% of questions, and these responses were included in the analysis. The answers from 3 student respondents were removed. Among the 133 remaining respondents, 125 self-identified their board certification status (Table 1). Correcting for missing certification data, the response rate among board-certified/board eligible neurosurgeons was 18.8%.

The majority of respondents described practicing in an academic setting (84.7%) as a specialist in tumor surgery (71.2%) (Table 1). Most were board-certified neurosurgeons (65.6%), and current residents or fellows (25.6%) comprised a large proportion. Twenty-seven percent of respondents reported having been in practice for 11 to 20 years and 27% for more than 20 years. Twenty-two percent (22%) of respondents were within their first 10 years of practice, while the remaining respondents were in residency or fellowship positions. Including those who self-reported their institutional affiliation, the respondents represented a total of 86 institutions from 16 countries on 5 continents.

AED Prophylaxis
Eight-five surgeons (63%) reported always or almost always prescribing AED prophylaxis postoperatively in patients with a supratentorial brain tumor without a prior seizure history (Fig. 1). Meanwhile, 12 (8.9%) surgeons reported sometimes prescribing prophylaxis, while 38 (28.1%) reported never or rarely ever prescribing AEDs in such patients. Levetiracetam was the primary agent used by 85% of surgeons, while 14% use phenytoin and a single responder reported using lacosamide. The duration of prophylaxis administration ranged widely from immediately postoperatively to more than 6 weeks after surgery. Among those prescribing prophylaxis, 32% did so for 7 days, 20% for 2 weeks, 27% for 2 to 6 weeks postoperatively, and 16% for more than 6 weeks (Fig. 2).

The majority of respondents (61%) believed that tumor pathology influenced the risk of perioperative seizures, with high-grade glioma (39%), low-grade glioma (31%), and metastases (24%) perceived as carrying the greatest risk (Fig. 3). Eighty-eight percent (88%) of surgeons polled believed that tumor location influenced epileptogenicity. Temporal lobe tumors (79%) were felt to hold the highest seizure risk, followed by cortical-based tumors (47%) and tumors involving the frontal lobe (46%) (Fig. 4).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practice setting</td>
<td>124</td>
</tr>
<tr>
<td>Academic</td>
<td>105 (84.7)</td>
</tr>
<tr>
<td>Private</td>
<td>19 (15.3)</td>
</tr>
<tr>
<td>Practice diversity</td>
<td>125</td>
</tr>
<tr>
<td>Generalist</td>
<td>36 (28.8)</td>
</tr>
<tr>
<td>Specialist</td>
<td>89 (71.2)</td>
</tr>
<tr>
<td>Certification status</td>
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</tr>
<tr>
<td>Board certified</td>
<td>82 (65.6)</td>
</tr>
<tr>
<td>Board eligible</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Not board certified/eligible</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Resident/fellow</td>
<td>32 (25.6)</td>
</tr>
<tr>
<td>Student</td>
<td>3 (2.4)</td>
</tr>
<tr>
<td>No. of years in practice</td>
<td>123</td>
</tr>
<tr>
<td>Resident/fellow</td>
<td>32 (26.0)</td>
</tr>
<tr>
<td>≤5 yrs</td>
<td>9 (7.3)</td>
</tr>
<tr>
<td>6–10 yrs</td>
<td>18 (14.6)</td>
</tr>
<tr>
<td>11–20 yrs</td>
<td>33 (26.8)</td>
</tr>
<tr>
<td>&gt;20 yrs</td>
<td>33 (26.8)</td>
</tr>
</tbody>
</table>
Do you prescribe AEDs post-operatively in patients with a supratentorial tumor who have not experienced a previous seizure?

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes, almost always</td>
<td>63%</td>
</tr>
<tr>
<td>Sometimes</td>
<td>9%</td>
</tr>
<tr>
<td>No, rarely if ever</td>
<td>28%</td>
</tr>
</tbody>
</table>

FIG. 1. Pie chart indicating the general frequency that surgeons report prescribing seizure prophylaxis.

many neurosurgeons held beliefs regarding the risk factors associated with certain tumor types and locations, 24% did not believe and 38% were unsure if prophylactic AED administration reduces the rate of seizures postoperatively (Fig. 5).

Practice setting (academic vs private; p = 0.314), practice type (specialist vs generalist; p = 0.158), board certification status (p = 0.870), and practice duration (p = 0.655) were not significantly associated with the rate of AED prophylaxis (Table 2). Lastly, 82% of survey respondents believed that an adequately powered randomized clinical trial evaluating the efficacy of modern seizure prophylaxis would help guide their clinical decision on the matter, while 9% did not and 9% were unsure.

Discussion

This survey of the members of the AANS/CNS Section on Tumors demonstrates wide knowledge and practice gaps regarding the pattern and duration of postoperative AED administration in patients with a brain tumor. While greater than 70% of neurosurgeons sometimes or always prescribe AED prophylaxis, 62% believe either that AED administration does not influence postoperative seizure occurrence or that there is insufficient evidence suggesting that it does. The appropriate duration of prophylactic treatment is also a point of disagreement, wherein the most commonly reported duration of prescription (7 days postoperatively) represents less than a third (32%) of respondents who prescribe. While the majority of tumor neurosurgeons believe that pathology and location influence seizure risk, there is a discrepancy regarding which tumor characteristics are in fact epileptogenic. There were 2 items with strong agreement across respondents: 85% of neurosurgeons prescribe levetiracetam, and 82% would use the results from a well-designed randomized trial to help guide their decision to administer or not administer prophylactic AEDs.

Seizures in brain tumor patients have been shown to increase health care costs, diminish quality of life, and negatively impact survival.\textsuperscript{2,4,7,16} Specifically, immediate postoperative seizures (within 14 days of surgery) have been linked to increased hospital length of stay, increased rates of unplanned readmission, and reduced overall survival.\textsuperscript{4} Prophylactic AEDs are commonly administered in the perioperative period to avoid this postoperative complication, though their efficacy in patients without a seizure history has been disputed.\textsuperscript{1,6,23} Several nonrandomized studies have demonstrated a benefit to this practice, resulting in early postoperative seizure rates as low as 1.4% to 2.5%.\textsuperscript{11,12,18,25} On the other hand, numerous prospective clinical trials\textsuperscript{5,6,9,24} and meta-analyses\textsuperscript{9,14} have
shown no detectable seizure reduction upon the administration of various antiepileptic agents. To date, no study has examined this topic by comparing the most commonly prescribed AED (levetiracetam) to a placebo. The value of modern perioperative seizure prophylaxis is among the many knowledge gaps in clinical neurosurgery.

Citing a lack of therapeutic effect, in 2000 the American Academy of Neurology released a statement recommending against the routine use of AEDs in brain tumor patients without a seizure history. Since then, 2 similar surveys have been published: 1 by Brouwers et al. in 2003 and the other in 2005 by Siomin et al. (Table 3). In the first survey of Canadian neurooncology providers (22% neurosurgeons), 22% felt that AEDs were “always” indicated in this population, and 30% stated they were “never indicated,” while the remainder reported “sometimes” administering. Though most acknowledged the lack of a unified set of guidelines, the majority (72%) were interested in helping to draft a set of practice parameters to guide future management.

The survey by Siomin et al. polled 386 members of the AANS/CNS (one-third of the members of the Section on Tumors) in 2005 and found that more than 70% of respondents routinely prescribe AEDs in this population—a value somewhat higher than what was found in our assessment (63%). Of note, their survey was distributed prior to the popularization of levetiracetam, and almost all participants (> 96%) described using phenytoin as their agent of choice. As with our survey, these authors found wide disparity in the duration of AED prescription: 21% of respondents administered AEDs for \( \leq 7 \) days, 35% for 2 to 6 weeks, and 36% for > 6 weeks (Table 3). Relative to 2005, neurosurgeons today seem to provide AED prophylaxis for a shorter duration. As with our analysis, the type of practice did not influence AED prescribing patterns in their survey. They also showed no difference between members and nonmembers of the Joint Section on Tumors, suggesting that our results may be generalizable to the neurosurgeon population as a whole. Aside from the preferred agent, there were few differences between this survey and the
one conducted in 2005, suggesting that despite 10 years of additional data accumulation and experience, this controversy remains just that—a controversy. Plainly, the use of perioperative seizure prophylaxis represents a major practice gap among neurosurgeons.

It is interesting that such variability exists among brain tumor experts on such a common topic, and one that affects nearly every patient with an operative brain tumor. Yet while interesting, perhaps it is not surprising, given the paucity of Level I evidence to definitively support or refute this practice. Indeed, the sequelae of a postoperative seizure can be challenging for both the patient and the surgeon to manage. Thus, if even a miniscule benefit is believed to result from a drug with a favorable side-effect profile, some neurosurgeons may—and perhaps do—feel compelled to offer an AED. Therefore, the mismatch between the evidence and the practice pattern seems understandable, even if not scientific.

The findings presented above warrant interpretation in light of several important considerations. As with all surveys, the results provided herein reflect self-reported habits and opinions and not necessarily actual clinical practice. The survey was disbursed electronically to email addresses belonging to all Section on Tumors members, which did not distinguish students and trainees from board-certified surgeons. Respondents identified as students were removed from the analysis, as we believed these few responses would distract from the physician majority. After careful consideration, resident and fellow responses, however, were included. While not independent practitioners, their beliefs and practices were felt to largely reflect the practices of their supervising physicians, many of whom did not return a survey. Including these trainee responses allowed us to capture the practices of many additional institutions, thereby adding power and generalizability to the survey’s results. The low response rate among trainees relative to their majority status resulted in a modest overall response rate (7.2%). But, considering board-certified and board-eligible surgeons only, the response rate was 18.8%, slightly higher than that of the survey by Siomin et al. Since the survey was distributed by the AANS/CNS Section on Tumors, respondents may have felt compelled to answer questions in a way that reflected the position of their expert peers. And, while respondents were permitted to keep their answers confidential, if they expressed a desire to participate in a future trial by including their email address, their answers theoretically could have been identifiable. This may have influenced the responders’ answers, though to what degree—and in which direction—is unclear.

A 2010 systematic review produced Level III evidence recommending against routine AED prophylaxis in patients with brain metastases who have not experienced a seizure. However, specific guidelines for the administration of prophylactic AEDs in patients with a glioma or meningioma have not been formulated by the neurosurgical community. Undoubtedly, low-level evidence precludes the adaptation of an explicit, defensible position on the matter. As a result, one of the most common clinical decisions made by tumor neurosurgeons—to administer or not to administer prophylaxis—represents both a wide knowledge gap and a wide practice gap. The debate surrounding the use of AEDs in the perioperative period will likely persist until an adequately powered trial is conducted by randomizing patients to receive the most commonly prescribed AED. While impactful, such a trial would likely require many centers and resources.

![Pie chart demonstrating the relative proportion of surgeons who believe seizure risk is reduced by the administration of seizure prophylaxis.](image)

**FIG. 5.** Pie chart demonstrating the relative proportion of surgeons who believe seizure risk is reduced by the administration of seizure prophylaxis.
example, assuming a conservative baseline perioperative seizure rate of 6%, nearly 750 patients in each of the 2 arms would be needed to detect an absolute seizure reduction of 3% (relative reduction of 50%) with 80% power. It is left to the neurosurgical community to determine if the time and cost required for such a study are justified to resolve this controversy. However, given the wide range of management strategies for this patient population, in an era of cost containment and evidence-based medicine, it is an intriguing and relevant consideration.

Conclusions

This survey of tumor neurosurgeons demonstrates wide variability in the frequency, duration, and setting of AED prophylaxis for seizure-naive patients undergoing craniotomy for brain tumor resection. Meanwhile, most neurosurgeons prefer levetiracetam, and the majority believes that tumor pathology and location influence epileptogenicity. Acceptance of a universal practice guideline on this topic is unlikely until higher level evidence supporting or refuting the value of modern seizure prophylaxis is demonstrated.

Acknowledgments

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**Disclosures**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

**Author Contributions**

Conception and design: Dewan. Acquisition of data: Dewan. Analysis and interpretation of data: Dewan. Drafting the article: Dewan. 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: Dewan. Statistical analysis: Dewan. Administrative/technical/material support: Thompson, Kalkanis, Barker, Hadjipanayis. Study supervision: Thompson, Kalkanis, Barker, Hadjipanayis.

**Supplemental Information**

**Online-Only Content**

Supplemental material is available with the online version of the article.


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