

Analysis of the Adherence to Seizure Prophylaxis Guidelines in Neurosurgery Patients

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ABSTRACT

BACKGROUND: In 2000, the American Academy of Neurology guidelines recommended that long-term seizure prophylaxis should not be routine in patients with newly diagnosed brain tumours and that if anti-epileptic drugs (AEDs) are used, they should be tapered and discontinued after 7 days post-operatively. Recent data shows that most newly diagnosed brain tumour patients continue to receive prophylactic AED.

AIM: This study aimed to examine the seizure prophylaxis practices at Trillium Health Partners – Mississauga Hospital, a regional neurosurgery centre located in Mississauga, Ontario, Canada.

MATERIALS AND METHODS: A retrospective chart review was performed in adult patients with a newly diagnosed brain tumour who underwent neurosurgery between January 2010 and December 2014.

RESULTS: 690 patient charts were screened and 235 patients were

excluded, most commonly due to seizure on admission. Overall, 28% ($n = 129$) of 455 included patients over 5 years received seizure prophylaxis. Phenytoin was the most common prophylactic agent used. The average post-operative length of stay was 7.98 days and the average duration of therapy was 8.73 days. In 61% of patients who received prophylaxis, it was unknown whether the AED was continued in the long-term. The drug cost savings to the organization over 5 years if patients had not received seizure prophylaxis was \$ 4287.52. The patient characteristics most strongly correlated with receiving seizure prophylaxis were increasing tumour size and decreasing number of tumours.

CONCLUSION: 1 in 3 patients at Trillium Health Partners received seizure prophylaxis. Increased awareness of the organization's practice patterns may help prevent unnecessary long-term AED use.

Key words: Seizure; Prophylaxis; Neurosurgery; Adherence; Guidelines; Anti-epileptic Drugs

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INTRODUCTION

In Canada, 55,000 patients live with a brain tumour and an additional 10,000 patients are newly diagnosed with a primary or metastatic brain tumour each year^[1]. Brain tumours are associated with high morbidity and mortality rates, therefore effective treatment is necessary to decrease both morbidity and mortality. However, treatment for brain tumours is complicated by their vast diversity in pathology, location and recurrence rate^[1].

Seizure is a common and debilitating complication for brain

tumour patients, due to physical injury, emotional stress, anxiety, and impaired activities of daily living^[2,3]. Up to half of patients with brain tumours present to hospital with seizure as a manifestation of the disease, and another 10-30% will develop seizures^[4,5]. Seizures resulting from brain tumour significantly decrease patients' quality of life^[6].

Antiepileptic drugs (AEDs) have traditionally been used to both treat and prevent seizures in brain tumour patients. The majority of research conducted supports the usage of AED to prevent seizures in brain tumour patients who have already experienced a seizure^[5-11]. However, the initiation of an AED for seizure prophylaxis in patients without a history of seizures is common, even though evidence does not support this routine practice^[8,12-17].

In 2000, the American Academy of Neurology (AAN) published guidelines recommending against seizure prophylaxis in patients with brain tumours who have not had a first seizure (Appendix 1). Out of 12 randomized controlled trials, only one study showed a significant difference in seizure incidence between patients receiving prophylaxis compared to placebo and the results favoured placebo. In addition, the incidence and severity of AED related side effects were noted to be higher in brain tumour patients compared to a general population of patients receiving AEDs^[7]. Subsequent meta-analyses and systematic reviews conducted after the release of these guidelines further support this recommendation^[5,12,13,18,19]. One of the major limitations in interpreting the available evidence is that many patients who experienced seizures while receiving AED prophylaxis had sub-therapeutic levels. One study looking specifically at this issue, however, demonstrated that re-analysis of data excluding patients with sub-therapeutic blood levels still showed no benefit of AED prophylaxis^[10].

One reason that many brain tumour patients receive prophylactic AEDs is because they have undergone craniotomy, which is associated with higher seizure risk^[20]. However, the evidence for seizure prophylaxis in neurosurgery patients is conflicting as well. Temkin and colleagues analyzed six prospective controlled trials in a meta-analysis that involved 2,152 patients undergoing neurosurgery and found that AED prophylaxis reduced the incidence of seizures (RR 0.42; CI 0.25-0.71) in the first post-operative week, but did not reduce the incidence of late seizures. Phenytoin was the only AED that significantly reduced seizures, with a NNT of 26 when patients were treated with an average duration of one week post-operatively. However, this study had limited generalizability as it included both brain tumour and traumatic brain injury patients^[21-23].

In a meta-analysis published in 2004 by Sirven *et al.*, five randomized controlled trials were evaluated, three of which included patients with primary and secondary brain lesions who underwent surgical debulking or resection. Four of the five trials showed no benefit of seizure prophylaxis^[19]. More recently, a 2011 meta-analysis concluded that their review did not support the routine use of prophylactic AEDs in patients undergoing supratentorial meningioma resection^[12]. Despite lack of evidence showing AED are beneficial, agreement is seen among neurosurgeons with the use of AEDs during the peri- and post-operative period (within 7-14 days of the surgery) as the risk of seizures is the highest during this timeframe^[6]. Indeed, this does not contradict the AAN guidelines as they recommend an AED, if started, to be discontinued after 7 days post-surgery if the patient is medically stable and has not experienced a seizure^[7].

Overall, the current body of literature does not support the routine use of seizure prophylaxis in patients with primary or secondary brain lesions, whether they undergo neurosurgery or not. However, research of practice patterns show that clinicians are still routinely prescribing

AEDs for seizure prophylaxis. In a 2005 survey of all members of the American Association of Neurological Surgeons, 70% of responders revealed that their practice does not follow the guidelines^[14]. However, peri-operative administration of AEDs may be appropriate because liver enzyme induction (common cause of drug interactions) occurs after the first 2 weeks of therapy and adverse events are less likely with short-term use^[8]. Therefore, a practitioner who is making a clinical judgment must decide if the benefits of prophylaxis really outweigh the risks in an individual patient.

Rationale for study

The American Academy of Neurology published their practice recommendations in 2000. However, recent literature suggests that adherence to guidelines is low^[14,15,24]. Moreover, the majority of research on this topic is done in the United States of America.

This study is the first to investigate seizure prophylaxis rates in neurosurgery patients at a single site in Ontario, Canada. In addition, no previous studies in the available literature have evaluated the financial impact on an organization by initiating therapy that may not be indicated. Therefore, this study aimed to examine Trillium Health Partners - Mississauga Hospital's practice patterns in neurosurgery.

METHODS

Study Design

The research questions were addressed using a retrospective chart review of electronic charts to identify patients who underwent neurosurgery for brain tumours at Trillium Health Partners - Mississauga Hospital from January 1st 2010 to December 31st 2014. Approval by a research ethics board was granted and the need for informed consent was waived. This research was conducted in accordance with the ethical standards of the responsible committee(s) on human experimentation (institutional and national) and the Helsinki Declaration.

Study Population

Inclusion Criteria: (1) Newly diagnosed (< 1 month prior to hospital admission) brain tumour patients undergoing neurosurgery/tumour resection or biopsy; (2) Age \geq 18 years old.

Exclusion Criteria: (1) History of seizures or seizure disorder; (2) Use of AED prior to admission.

As per the AAN guidelines, only newly diagnosed adult brain tumour patients without a history of seizures, undergoing neurosurgery/ tumour resection or biopsy, were included in this study. The timeframe of 5 years was chosen as electronic patient records started becoming available towards the end of 2009 at Trillium Health Partners. In the literature, limited studies have included patients receiving biopsy. This study has included these patients to provide a more comprehensive description of Trillium Health Partner's current practice patterns.

Patients using AED prior to admission were excluded as this may alter seizure incidence post-surgery. Comorbidities such as electrolyte disturbance may be associated with a higher risk of seizure onset, however, there is no concrete evidence associating concurrent disease states, other than existing seizure disorder, with initiation of seizure prophylaxis^[25]. Therefore, patients' comorbidities were not included as they do not directly impact seizure prophylaxis initiation. Although there are certain medications that may decrease seizure threshold, there is no evidence to support initiation of seizure prophylaxis due to concurrent medications^[25]. Thus, patients' current drugs were not included in the analysis.

AED levels were not examined as most clinical studies used fixed dosing regimens and did not measure drug levels^[11]. AED prophylaxis in patients who were maintained in therapeutic range does not provide additional benefit in preventing seizures compared to those patients with subtherapeutic levels^[10]. In addition, it is commonplace to not follow AED levels unless patients experience a seizure while on prophylactic therapy, which is also the practice at Trillium Health Partners^[11].

Study Outcomes

Primary Outcome: The percent (%) of brain tumour patients without seizure history undergoing neurosurgery intervention who received primary seizure prophylaxis with an AED.

Secondary Outcomes: (1) In patients who received seizure prophylaxis with an AED and had not experienced a seizure within the first post-operative week (7 days), the percent (%) of patients whose AED was discontinued between 5-16 days post-operatively; (2) In patients who received seizure prophylaxis with an AED and had not experienced a seizure within the first post-operative week (7 days post-op), the financial impact (in terms of drug cost over the study period) on Trillium Health Partners if these patients had not received prophylaxis; (3) In patients who received seizure prophylaxis, the patient characteristics (in terms of number, size, and location of tumours) that were most strongly associated with receiving prophylaxis.

RESULTS

Over the 5 year study period, 690 patient charts were screened and 235 patients were excluded, most commonly due to seizure on admission. 455 patients met inclusion criteria.

More than half the patients were female (56%) with a mean age of 59.4 years old. The most common tumour pathology was glioblastoma (the most common and aggressive type of primary brain tumour), followed by meningioma and metastasis. Most patients had a single lesion (85%) with an average tumour diameter of 4.3 cm. The tumours were most often located in multiple lobes of the brain (32%), followed by the frontal (26%) and temporal lobes (15%). WHO grade 4 describes high-grade tumours that are fast growing, aggressive and invasive. All glioblastoma tumours are of WHO grade 4. Thus, as this is the most common type of tumour pathology, grade 4 was the most common tumour grade (38%). In patients whose brain tumour resulted from metastasis, the primary tumours were often located in the lungs (59%), followed by the breasts (12%) and skin (10%).

Primary Outcome

Overall, 28% (*n* = 129) of included patients received primary seizure prophylaxis. The percent of prophylaxis increased from 2010 to 2013 (28%, 29%, 32%, 36%, respectively) until 2014 where there was a drop in prophylaxis rates (19%).

Secondary Outcomes

For 61% of patients, it was unknown whether they had continued AED beyond hospitalization. Seizure prophylaxis was discontinued in 22% of patients, where the prescribers dictated a plan to taper and discontinue therapy within the defined timeframe of 5-16 days post-operatively in the discharge note, wrote a discharge prescription to taper and discontinue, or tapered and stopped therapy in hospital. Seizure prophylaxis was not discontinued within the defined timeframe for 15% of patients. For very few patients (2%), AED was continued appropriately as these patients experienced post-operative seizures.

Table 1 Patient Demographics (N = 455).

Characteristic	Result
Male (% , N)	44% (N = 202)
Female (% , N)	56% (N = 253)
Mean age at admission, years	59.4 years old
Tumour Pathology	Glioblastoma multiform - 36% (N = 164) Meningioma - 33% (N = 149) Metastasis - 21% (N = 97) Astrocytoma - 2% (N = 9) Oligodendroglioma - 1% (N = 6) Other - 7% (N = 30)
Tumour Location	Multiple - 32% (N = 145) Frontal - 26% (N = 118) Temporal - 15% (N = 70) Parietal - 10% (N = 46) Occipital - 4% (N = 16) Other - 13% (N = 60)
Tumour WHO Grade	I - 24% (N = 110) II - 11% (N = 50) III - 5% (N = 23) IV - 38% (N = 173) N/A (Metastasis) - 22% (N = 99)
Number of Tumours	1 - 85% (N = 386) 2 - 7% (N = 30) 3 - 3% (N = 18) Multiple - 5% (N = 21)
Average Tumour Size	4.3 cm (longest diameter)
For metastases - Primary area of tumour (N=97)	Lungs - 59% (N = 56) Breast - 12% (N = 12) Skin - 10% (N = 10) GI - 7% (N = 7) Other - 12% (N = 12)

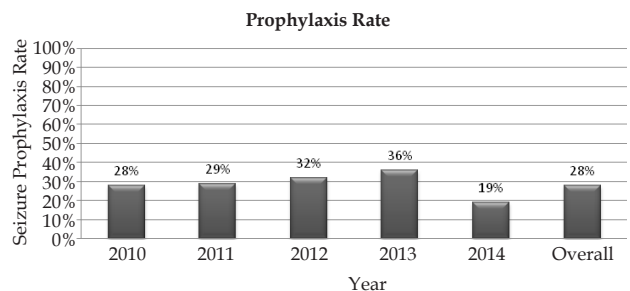


Figure 1 Primary Outcome of Seizure Prophylaxis Rates by Year.

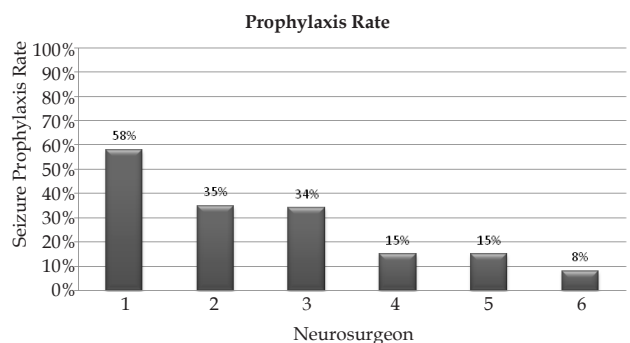


Figure 2 Differences among prescribers in initiating seizure prophylaxis..

The cost savings to Trillium Health Partners over 5 years of the study period if patients had not received seizure prophylaxis was \$4287.52 in terms of drug cost. The majority of patients received phenytoin, intravenously for the first 1-2 days and were stepped down to oral formulation. The main cost driver was intravenous phenytoin which cost \$5.20 per 100 mg dose compared to \$0.06 per 100 mg of an oral dose.

To investigate the association between tumour, patient characteristics and the odds of being prescribed prophylaxis, a logistic regression model was conducted. This analysis revealed a significant association between prophylaxis and size of tumour ($p = 0.0002$). For each centimetre increase in size, the odds of prophylactic prescription increased by 25%. Logistic regression did not indicate an association between prophylaxis and the number of tumours ($p = 0.13$). However, there was a threshold beyond which prophylactic prescribing was significantly reduced. A binary variable study indicated that patients with fewer than or equal to two tumours (≤ 2) were significantly more likely to receive prophylaxis ($p = 0.007$) and those who had more than two (> 2) tumours were less likely to receive prophylaxis. Tumour location (e.g. frontal, temporal, parietal lobes) was not associated with prophylaxis either on their own or analyzed together with tumour size and number of tumours. Therefore, the patient characteristics most significantly associated with prophylaxis initiation were increasing tumour size and fewer number of tumours (≤ 2).

Additional Factors of Interest

The post-operative average length of stay was 7.98 days which relate well with the average duration of therapy of 8.73 days as most prophylaxis regimens started the day prior to surgery.

Phenytoin was the AED used in 92% of patients, followed by levetiracetam at 5% and clobazamat 3%. For phenytoin, the most common prophylaxis regimen was a loading dose of 500-1500 mg IV the day prior to neurosurgery or in the operating room, followed by 100 mg PO or IV q8h for the first 1 to 2 days. Then, patients were switched to 300 mg PO qHS as an oral maintenance dose. The tapering regimen most commonly observed was decreasing the phenytoin dose by 100 mg every 2-3 days, with an average tapering duration between 6-10 days. For levetiracetam, the most common prophylaxis dosing was 500 mg PO twice daily and discontinuation after 5-7 days without tapering. For clobazam, the dosing was 10 mg PO qHS and no tapering regimen was noted.

Only 1 physician documented once that the reason for prophylaxis was due to the location of tumour being in the temporal lobe, which increased the risk of seizures.

Among the 6 neurosurgeons currently performing surgeries at Trillium Health Partners, the seizure prophylaxis initiation rates ranged from 8% to 58%.

DISCUSSION

Despite compelling evidence that long-term prophylactic AED does not provide significant benefit in seizure-naive brain tumour patients, data from the Glioma Outcomes Project (a prospective outcome study in brain tumour patients involving 55 academic and private practice centers) indicated that 57% of North American patients received prophylactic AED^[17]. In addition, in a 2010 single center teaching hospital in Alberta, Lwu *et al* found the rate of seizure prophylaxis to be 27%^[15]. Deviation from the guideline recommendations may be attributed to the perceived harms of seizures on the patients' psychosocial and physical well-being, especially during the immediate post-operative period where the risk of seizures is known to be higher^[6,18,20].

Our center revealed a 28% prophylaxis rate overall, which is similar to the prophylaxis rate found by Lwu and colleagues in Alberta. Prophylaxis rates trended upwards before coming down to the lowest rate at 19% in 2014. Many factors could have influenced the prophylaxis rates as there were changes in neurosurgeon, pharmacy, and allied health staffing during the 2013-2014 period. In 2014, the lowest

seizure prophylaxis rate was observed, which could indicate an overall shift in practice, or be simply due to chance. In general, newer staff at Trillium did not routinely initiate seizure prophylaxis in seizure-naive patients. Once initiated, they were also more vigilant on tapering and discontinuing AEDs within the recommended timeframe.

Earlier studies have found that the highest incidence of seizures in the peri-operative period occurs within the first 7 days^[20]. During this short timeframe, drug interactions and adverse events are less likely to occur as drug-induced hepatic enzyme induction generally requires 2 weeks of treatment^[26]. Therefore, prescribing prophylactic AED for up to 1-2 weeks after surgery may be reasonable as long as patients are not maintained on AEDs in the long-term^[20]. Lwu *et al* expressed concern that most patients in their study (30 out of 44 patients) received prophylactic AED beyond the first post-operative week and in some cases, continued for the rest of the patients' lives^[15]. Unfortunately, for most patients examined in this study, it was unknown whether they continued prophylaxis beyond hospitalization. The main reason for the unavailable data was that many patients were repatriated to other care facilities after the neurosurgery procedure. Trillium is a regional neurosurgery centre and receives many referrals from nearby hospitals. Therefore, discharge prescriptions were not written for these patients. In addition, physicians did not often dictate their discharge plan regarding AED use. Without a dictated plan to taper from the neurosurgeon, physicians who likely do not specialize in brain tumours, at the receiving hospitals or in the communities must decide whether to taper and stop the AED.

There are many consequences to continuing AEDs in the long-term. Not only is there no evidence that long-term prophylactic AED administration will significantly reduce the risk of seizures, brain tumour patients are more prone to experience serious side effects, especially with older AEDs^[27]. Phenytoin, for example, has many adverse effects, such as rash, nausea or vomiting, encephalopathy, myelosuppression, ataxia, hepatic toxicity, and gingival hyperplasia, which can impact patients significantly^[20]. In addition, use of AEDs may interact with other important therapeutic medications needed to manage these patients' conditions. It is not uncommon for brain tumour patients to be receiving AED, corticosteroids, and chemotherapeutic agents simultaneously post-neurosurgery, leading to multiple undesirable interactions that can affect treatment efficacy and toxicity, resulting in increased requirement for therapeutic monitoring^[16]. In a study of patients undergoing chemotherapy for glioblastoma, those who received an enzyme-inducing AED (phenytoin, carbamazepine, and valproic acid) had significantly poorer overall survival^[20]. Thus, long-term AEDs use can have a substantial impact on patients' quality of life and their disease control.

The potential drug cost savings for Trillium if AED had not been prescribed was \$4287.52 CAN over the 5 years studied. Although it may not be a significant part of the neurosurgery drug budget, it is resources that could be reallocated more optimally. In addition, time in prescribing, screening, dispensing, administering and reviewing AEDs could have been put towards other endeavours. This is especially important in a healthcare system with limited resources. Trillium's strategic plan is to ensure quality healthcare, accessibility and sustainability^[24]. Therefore, the optimal use of resources by strategically allocating opportunity costs is a fundamental practice to enhance patient care. Reducing the use of unnecessary expenditures that may cause long-term patient morbidity can contribute towards the organization's goals of ensuring better accessibility for other healthcare services and improve sustainability of the system.

The most common documented reasons for initiating peri-operative prophylaxis are related to tumour size, number of tumours, and

location^[25]. Tumours located in the frontal and temporal lobes are associated with higher seizure incidence. In some studies, a higher number of tumours and larger tumour size also increase seizure probability^[16]. However, the literature is inconclusive as to whether any of these high risk characteristics alone or in combination would warrant the initiation of seizure prophylaxis in seizure naive patients. In this study, the data showed that increasing tumour size and patients with ≤ 2 tumours were significantly correlated with receiving seizure prophylaxis. Tumour location was not a significant factor in initiating prophylaxis. The study findings of tumour burden were not congruent with the literature as fewer tumours were associated with a higher likelihood of prophylaxis. The mismatch between literature findings and the results of this study may be attributed to differences in practice between prescribers.

It is important to note that the retrospective design of this study is a limitation, as confounding factors could not be controlled. Another limitation is that there may have been incomplete documentation of rationale for using prophylaxis, therefore provider justifications for AED use could not be thoroughly determined by review of medical records. This study had limited external validity as it was single sited. In addition, only patient's in-hospital data were analyzed and use of AED beyond hospitalization was unknown.

Future directions

This study outlined the practice patterns of seizure prophylaxis at Trillium HealthPartners in Mississauga, Ontario, Canada. Further research can explore the decision making process for the initiation of prophylaxis to clarify how patient specific factors, such as tumour location, size, and number of tumours, may affect epileptogenesis and whether high risk patients will benefit from prophylaxis. Once such factors are identified, aperi-operative AED prophylaxis protocol can be developed to best optimize care for selected, high risk patients. This protocol will also ensure the appropriate tapering and discontinuation of AEDs post-operatively.

Newer AEDs such as levetiracetam offer an improved safety profile, linear pharmacokinetics, and limited drug interactions. Since the meta-analyses and guidelines were published, a number of new AEDs have been introduced into clinical practice. However, there is no evidence that they are more effective in preventing seizures in patients with brain tumours^[20]. Currently, the published literature is predominantly on the use of traditional AEDs, and the newer AEDs require further study and could be the primary focus in future randomized control trials^[27].

In addition, further research should elucidate how the timing, duration, and tapering method of prophylactic AED administration, which varied across studies, influence its efficacy^[16]. Finally, as the lowest trend of seizure prophylaxis is observed in 2014, it will be interesting to observe Trillium's prophylaxis rates in future years.

CONCLUSION

1 in 3 newly diagnosed brain tumour patients at Trillium Health Partners received prophylactic AED peri-operatively. By itself this practice pattern does not directly contradict the AAN practice guidelines as long as AED prophylaxis is discontinued 1 week after surgery and not used long-term. However, for the majority of studied patients, it was unknown if their AED was continued long-term and this would require additional investigation. Increased awareness of Trillium's practice patterns may help increase communication between neurosurgeons, the allied health team and community healthcare providers. This report may serve to further guide the shift in neurosurgery practice and prevent unnecessary long-term AED use.

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APPENDICES

APPENDIX 1 - American Academy of Neurology Guidelines (2000)

1. In patients with newly diagnosed brain tumours, AED medications are not effective in preventing first seizures. Because of their lack of efficacy and their potential side effects, prophylactic AEDs should not be used routinely in patients with newly diagnosed brain tumours (Level I evidence)
2. In patients with brain tumours who have not had a seizure, tapering and discontinuing AEDs after the first postoperative week is appropriate, particularly in those patients who are medically stable and who are experiencing AED-related side effects (Level II evidence).

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