**The Role of Prophylactic Antiepileptic Drugs for Seizure Prophylaxis in Meningioma Surgery: A Systematic Review**

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The authors have no relationships that might lead to a perceived conflict of interest.

**Abstract**

Meningiomas are the commonest type of primary brain tumours. Whilst most patients are seizure-free prior to surgery, antiepileptic drugs are frequently administered to reduce the risk of developing post-operative seizures. However, evidence to support their efficacy in providing this outcome is sparse. To this end, we performed a systematic review to assess the impact of prophylactic antiepileptic drugs on post-operative epilepsy rates in seizure-naïve patients undergoing craniotomy for resection of meningiomas. The literature search was performed using PubMed for studies published between January 1990 and November 2016. The total number of patients in each study was extracted and divided into cohorts according to administration of prophylactic antiepileptic drugs. Clinical characteristics, study type and post-operative epilepsy rates were recorded. A total of 11 studies involving 1,143 patients met the selection criteria. There was no statistically significant difference in the number of patients who developed post-operative epilepsy in the cohort that received prophylactic antiepileptic drugs (20 of 766; 2.6%) and the cohort that did not (10 of 377; 2.7%) (Chi-square test; P = 0.96). A detailed meta-analysis could not be performed due to the insufficiency in data reported. Based on the results of this systematic review, the routine use of antiepileptic drugs for seizure prophylaxis in seizure-naïve patients undergoing meningioma resection could not be substantiated. However, limitations of a systematic review should be considered on interpretation. High quality prospective randomised controlled trials are required to definitively answer this important clinical question.

**Keywords**

Antiepileptic drugs; craniotomy; meningioma; post-operative seizure; prophylaxis.

**Introduction**

Meningiomas are the most common primary brain tumours, accounting for approximately a third of all intracranial neoplasms and with an estimated incidence rate of 5 per 100,000 person-years in the UK.**1,2** The World Health Organisation (WHO) classifies these tumours into three groups: benign meningioma (grade I), atypical meningioma (grade II) and anaplastic meningioma (grade III).**3** Approximately 90% of meningiomas discovered are benign and asymptomatic; the remainder go unnoticed until they clinically manifest in the form of headaches, seizures or other neurological problems.**4** This indicates that the majority of patients are free of seizures at the time of diagnosis and remain so up until the time of surgery.**5** Despite this, antiepileptic drugs (AEDs) are frequently prescribed peri-operatively in an attempt to reduce the risk of seizures post-craniotomy albeit being rather evidently unfounded. Furthermore, a recent Cochrane review on the routine administration of AEDs post-operatively for brain tumours, including meningiomas, concluded there was little evidence to recommend routine use.**6** In addition to the risk of acute adverse drug reactions, recent studies have suggested that AEDs may also limit neurological recovery due to their effects on cognitive function.**7** Nonetheless, the consequences of post-operative seizures include major morbidity from cerebral oedema, reduced quality of life,**8** cognitive issues and loss of driving licence, but the rate at which new seizures develop in patients undergoing meningioma surgery has been inconsistently and variably reported over the last four decades and ranges from 0.5-22%.**9–11** When all of the aforementioned factors are taken into consideration, they present a challenge to the clinician whose responsibility is to measure the potential benefits of AED prophylaxis against the adverse effects. Several reviews have previously addressed this issue, however, these include older studies that pre-date more modern micro-neurosurgical practice.**12–14** The role of prophylactic AEDs in meningioma surgery has also been the topic of regular editorials and opinion pieces that highlight the unresolved clinical dilemma.**15,16** The aim of this study was to perform a systematic literature review to determine the association between prophylactic AEDs and the risk of post-operative epilepsy in seizure-naïve patients undergoing meningioma resection.

**Methods**

Study selection

A filtered literature search was performed using the US National Library of Medicine PubMed database. Filters applied were Language, which had been set as English, and a date range from 01/01/1990 to 30/11/2016. The search term utilised was *("Meningioma"[Mesh] AND ("Postoperative Period"[Mesh] OR "Postoperative Complications"[Mesh] OR "Treatment Outcome"[Mesh] OR "Epilepsy"[Mesh] OR "Seizures"[Mesh] OR "Risk Assessment"[Mesh])) OR ("Meningioma" AND ("Treatment Outcome" OR "Epilepsy" OR "Seizures*"*))*. This term incorporated Medical Subject Headings (MeSH) in conjunction with their counterpart keywords to ensure that relevant MeSH-unindexed records were included. The titles of all results were screened. Abstracts were reviewed with titles that mentioned intracranial meningiomas or brain tumours in combination with seizure, epilepsy, antiepileptic drugs, surgical outcome or anything of similar construct. Full-text articles were inspected if from the abstracts the number of seizure-naïve meningioma patients could be discerned to be more than 15 and if reported outcomes could have possibly incorporated seizures or epilepsy. For inclusion, full-text articles were subjected to the following selection criteria:

1. The number of seizure-naïve meningioma patients ≥ 15.
2. The duration of follow-up ≥ 1 month.
3. The neurosurgical approach was craniotomy based.
4. Post-operative seizure data was available for seizure-naïve patients.
5. A clear statement on whether prophylactic AEDs had been used or not was present.

Data for patients < 16 years of age was omitted. A reference list search on all relevant papers was also undertaken to identify any further relevant studies. The search was carried out by A.I.I, S.M and T-E.K-O. Articles identified were only included upon mutual agreement. Corresponding authors of articles that created a dispute amongst the authors due to their ambiguity were contacted via e-mail by A.I.I to ascertain additional data that could help resolve such disputes. Articles for whom authors did not provide a response were dismissed. Records supplemented by further communications were reviewed again and included upon mutual agreement. M.D.J verified and approved the final set of papers.

Data extraction

Patient characteristics, study type (retrospective, prospective, randomised controlled trial), AED use and post-operative outcomes were recorded. The outcomes of interest were extent of resection (as defined by each study), occurrence of post-operative seizures, and AED-associated adverse reactions. For each study, patients were divided into two cohorts: patients that received prophylactic AEDs and those who did not. Seizures occurring within one week of surgery were classed as "early”, and "late" if they occurred after one week. Data for all seizure-naïve patients were recorded when available including: age, gender, features of meningioma, and AED used.

Statistical analysis

Due to limitations in the available data and variation in outcome reporting it was not possible to perform a detailed meta-analysis. Descriptive statistics were used. For comparisons between the cohorts receiving AED prophylaxis and those not, Chi-square test was employed. Differences were considered to be statistically significant at P < 0.05. Statistical analyses were conducted using IBM SPSS Version 24.0 (SPSS Inc.).

**Results**

Literature Search

Figure 1 describes the study selection process. The filtered PubMed search identified 2,321 records. The number of abstracts screened was 254, and the full-text articles of 114 of those abstracts were reviewed. The initial number of articles excluded and included was 99 and 8 respectively. The corresponding authors of 7 articles were contacted and only 3 of those articles were included in the final analysis. No additional articles were identified on review of references. The final number of articles included was 11, with an overall population of 1,473 patients.

Study characteristics

The characteristics of the 11 studies are summarised in table 1. Eight papers investigated meningioma resection in patients that received prophylactic AEDs: 3 prospective**10,17,18** and 5 retrospective.**19–23** One prospective study investigated meningioma resection in patients that were not administered AEDs.**24** The remaining 2 papers were retrospective and had mixed cohorts.**11,25** The occurrence of post-operative seizures was the primary investigated outcome in only 4 studies.**10,11,17,25** One study was multi-centred**24** whilst the rest were single-institution studies. There were no prospective randomised controlled trials.

Patient characteristics

The total number of patients was 1,473, with a mean age of 56.8 years (range 18-95 years). The follow-up period ranged from 1 to 222 months. For the purpose of this systematic review, only seizure-naïve patients were included (n = 1,143). A total of 766 patients who received prophylaxis constituted the AED cohort. The remaining 377 patients formed the No-AED cohort. The differences in proportions of non-skull base (% of valid cases = 29.5; 100% vs 46.9%; P < 0.05) and WHO grade I (% of valid cases = 64.8; 85.7% vs 75.2%; P < 0.05) meningiomas amongst the two cohorts were statistically significant. The remaining characteristics, detailed in table 2, were either balanced or incomparable.

Antiepileptic drug characteristics

The AEDs that were utilised in seizure-naïve patients are detailed in table 3. Selected doses for AEDs were not reported. Duration of AED administration was only described in 1 study, where patients received a one week treatment course post-operatively.**11** No studies reported whether pre-operative AEDs were switched post-operatively in peri-operative prophylaxis. The discontinuation or withdrawal process was not outlined in any of the studies.

Post-operative outcomes

**Extent of resection**

Extent of resection was reported for seizure-naïve patients in 6 of the 11 studies.**10,11,18,19,23,25** In the AED cohort, gross total resection (GTR) was achieved in 86.5% (410 of 474) patients. In the no-AED cohort, GTR was achieved in 76.3% (261 of 342) patients. The difference in the proportions of GTR between the two cohorts was statistically significant (table 4; P < 0.05).

**Antiepileptic drug use and post-operative seizures**

Out of 1,143 seizure-naïve patients, 766 received prophylactic AEDs peri or post-operatively. Early post-operative seizures occurred in 2.6% of patients (20 of 766). In the no-AED cohort of 377 patients, early post-operative seizures occurred in 2.7% of patients (10 of 377). The occurrence of late post-operative seizures was similarly low in the prophylactic AED group; 52 of 766 patients (6.8%) and the no-AED group; 29 of 377 patients (7.7%). There was no statistically significant difference in early seizure rates (P = 0.96), late seizure rates (P = 0.58) and the overall seizure rates (P = 0.62) (table 4).

**Antiepileptic drug-related adverse effects**

The adverse effects of AEDs or possible consequential changes or discontinuations to the AED regimens were not noted in any of the included studies.

**Discussion**

Seizures, as a clinical manifestation of meningiomas, arise in an estimated 14-50% of cases.**26–30**In brain tumour patients, potential neurological sequelae of craniotomy include seizures, which are associated with secondary morbidities such as cerebral oedema, hypoxia and brain injury, which in turn could have an impact on the long term quality of life and survival rates.**31–33** Whilst older studies suggested a role for AEDs in preventing seizures post-operatively,**34–36** more recent studies have shown similarly low rates of post-operative seizures among the two cohorts of meningioma patients; namely patients administered prophylactic AEDs and patients that have not.**10,11,17–25** Nevertheless, neurosurgeons continue to administer prophylactic AEDs as a preventative measure against post-operative seizures in patients undergoing meningioma surgery despite the lack of evidence to support this practice.**37** Previous recommendations from the American Academy of Neurology (AAN) advised against the routine use of prophylactic AEDs in newly diagnosed brain tumour patients; however, this practice parameter was retired by the AAN Board of Directors on June 4, 2012.

The pathogenesis of post-operative seizures in meningioma patients is not fully understood and is likely to be due to a variety of tumour and surgical factors. Meningiomas are extra-axial tumours and have been hypothesised to distort the peritumoural cortex, release amino acids, alter the acid-base status and disturb the neurotransmitters pathway, particularly of glutamate. All these factors have been shown to contribute to the epileptogenicity of meningiomas.**38,39** Intraoperatively, the surgical resection could contribute to the development of seizures, through a combination of brain retraction, manipulation and cortical irritation. In the post-operative period, complications such as haematoma, infection, hydrocephalus and particularly perifocal cerebral oedema could influence the risk of seizures.**28,40** Such factors are not exclusive to supratentorial lesions and could precipitate seizures in all intracranial meningioma patients. Due to limitations in the reported data, it was not possible to determine whether there was a significant association between the seizures that arose post-operatively in this group of patients and any of the aforementioned factors.

Specific tumour characteristics have been shown to increase the epileptogenic potential of operated meningiomas in seizure-naïve patients. Parietal convexity meningioma, non-skull base location and tumour diameter have all been shown to increase the risk of developing early post-operative seizures.**28,41,42** Late post-operative sequelae including seizures have been previously reported as a result of meningioma regrowth or recurrence.**27** Benign WHO grade I lesions constitute the majority of meningiomas and their recurrence is dependent on the degree of surgical resection,**43,44** whereas atypical and anaplastic meningiomas have an inherently higher recurrence rate regardless of treatment, and therefore could influence seizure rates.**45–47** Similar conclusions on precipitating factors of early and late post-operative seizures could not be drawn using the data in this systematic review and the benefit of prophylactic AEDs in patients included in this review with similar characteristics could not be inferred.

In this systematic review, we restricted the search criteria to 1990 – 2016 in order to examine more modern clinical series. Whilst the pathology and biology of meningiomas have not changed since their early description in 1938,**48** over the last 26 years, imaging and surgical technology have advanced dramatically and these factors may have an impact on the risk of developing seizures following meningioma resection. Indeed, 10 of the 11 papers were published after 2002 and encompass a more ‘modern’ era of neurosurgery. In the AED-cohort, contributed to by 10 of the 11 included papers,**10,11,17–23,25** the incidence rate of early post-operative seizures was only 2.6%. Late post-operative seizures were observed to have affected 6.8% of the patients. In the no-AED cohort, that was comprised of 3 study populations,**11,24,25** the incidence rates of early and late post-operative seizures were 2.7% and 7.7% respectively. These are similar to previously reported reviews.**12–14**

In a recent retrospective single-institution study from Switzerland that attempted to define risk factors for post-operative epilepsy amongst meningioma patients,**25** the rate of new-onset seizures among patients administered prophylactic AEDs and patients who were not was measured; overall, there were more early and late post-operative seizures in the AED cohort (27.0% vs. 13.1%) (Wirsching H-G, personal communication, April 14, 2016), however, the baseline characteristics between the two groups were not matched. In the AED cohort, there were more patients with WHO grades II and III meningiomas who exhibited active electroencephalograms pre-operatively and experienced more post-operative complications. On the other hand, more patients in the no-AED cohort underwent subtotal resection (STR). The study showed these preceding factors, in addition to tumour progression and the convexity location, to be associated with de novo epilepsy post-operatively. However, it failed to demonstrate whether such groups of meningioma benefited from prophylactic AEDs. Such differences in key clinical factors between the two AED cohorts are likely to have an impact on seizure rates and future studies should be designed to compare matched cohorts. In marked contrast, Sughrue et al. compared patients administered 1 week of prophylactic AEDs to patients with no AED therapy following resection of convexity meningiomas.**11** Demographic and clinical characteristics between the two cohorts were balanced. There was only one reported early post-operative seizure in the entire study population (n=180) and that patient had not received an AED.

Details surrounding the prophylactic administration of AEDs lacked across all studies; doses were not specified in any of the studies and in only one of them was the duration noted.11 Moreover, the withdrawal process in patients subjected to prophylaxis was not depicted in any of them. Such information is fundamental to a neurosurgeon’s clinical practice and future meningioma and brain tumour studies should take that into account.

None of the studies included reported the adverse of effects of AEDs. However, AEDs are well known to have a poor adverse event profile. Older drugs such as phenytoin cause skin rashes and deranged liver function and 18-43% of patients experience at least one adverse effect.4**9–52** Newer drugs including levetiracetam are better tolerated, but can still cause side effects such as lethargy, rash and mood changes.**50,52** The systematic under-reporting of adverse events from AEDs in meningioma series makes it impossible to determine whether the potential benefits outweigh the risks and these factors should be considered in all future studies.

There are several limitations to this study including those related to the inherent bias in meta-analysis of data from several studies. In ten of the studies, prophylactic AEDs were administered to all patients (n=766), which reflects clinician bias and preference for treatment. Comparisons of clinical characteristics between the AED and no-AED cohorts revealed imbalances; however, the number of cases valid for each characteristic differed and ranged from 129 to 741. This was also observed for outcome comparisons, which exhibited a significant difference in the proportions of GTR amongst the two cohorts. These significant differences in characteristics and outcomes combined with the disproportional cohort sizes (766 vs 377) limit the interpretation of our results. In addition, only four studies addressed post-operative seizures as their primary outcome, of which two directly compared the AED and no-AED cohorts and these had unequal numbers in each group, which is likely to introduce bias into any statistical analysis. Similarly, the number of patients in each study ranged from 20 to 779 and meta-analysis of data will be biased towards the largest of studies,**25** which contributed in total to 46.8% of patients included and 93.7% of seizures reported. These factors limit the quantitative analysis that could be undertaken in our study and subsequent interpretation of results, and ultimately highlight the need for prospective clinical trials. Lastly, there was marked variation in the quality and completeness of the data available reflecting the lack of standardised outcome reporting in neurosurgery studies and the propensity for single institution case-series, which compounds the difficulty in comparing the results of different studies.

**Conclusion**

The results of this systematic review suggest that based on current literature evidence, the routine use of prophylactic AEDs in seizure-naïve patients undergoing craniotomy and resection of meningioma cannot be justified. However, the data used to reach this conclusion is inadequate, with significant methodological shortcomings including a wide variation in the reporting of outcome measures such as AED-related adverse reactions. Despite the lack of evidence to support the routine use of prophylactic AEDs, these drugs continue to be prescribed in clinical practice. Studies suggest that supratentorial location and post-operative perifocal oedema to be the factors associated with early seizures and recurrence to be the sole factor associated with seizures of late-onset. Unfavourable recurrence rates are observed in high-grade meningiomas. Whether prophylactic AEDs affect seizure rates in these groups of meningioma remains unanswered and only a well-designed prospective randomised controlled trial could help resolve this issue.

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**Figure and table legends**

**Figure 1**. Flow diagram of the study selection process

**Table 1.** Study characteristics of meningioma cohorts with and without AED prophylaxis

**Table 2.** Patient characteristics in seizure-naïve meningioma patients

**Table 3.** The specificAEDs used in seizure-naïve meningioma patients

**Table 4.** Extent of resection and seizure outcome in seizure-naïve meningioma patients

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Authors & year** | **Study design** | **Total No. of patients** | **Mean age (yrs.)** | **FU (mos.)** | **No. of seizure-naïve patients** | **AED** | **No-AED** | **Early post-operative seizures** | | **Late post-operative seizures** | |
| **AED** | **No-AED** | **AED** | **No-AED** |
| Tsuji et al., 1993**10** | pros | 20 | 53.7 | 24c | 17 | 17 | 0 | 1 | 0 | 1 | 0 |
| Rothoerl et al., 2002**17** | pros | 102 | 52.6 | 29.6d | 70 | 70 | 0 | 0 | 0 | 0 | 0 |
| Jallo et al., 2002**19** | retro | 23 | 57.7 | 111.6d | 23 | 23 | 0 | 0 | 0 | 0 | 0 |
| Otani et al., 2006**20** | retro | 32 | 53.5 | 38.3d | 30 | 30 | 0 | 0 | 0 | 0 | 0 |
| Margalit et al., 2007**18** | pros | 20 | 58.5 | 3c | 20 | 20 | 0 | 0 | 0 | 0 | 0 |
| Gazzeri et al., 2008**21** | retro | 36 | 56.4 | 111d | 26 | 26 | 0 | 0 | 0 | 0 | 0 |
| Sughrue et al., 2011**11** | retro | 180 | 55.5 | 1c | 180 | 129 | 51 | 0 | 1 | 0 | 0 |
| Konglund et al., 2013**24** | pros | 54 | 70 | 6c | 35 | 0 | 35 | 0 | 0 | 0 | 0 |
| Poon et al., 2013**22a** | retro | 184 | 61.9 | 12c | 166 | 166 | 0 | 1 | 0 | 3 | 0 |
| Della Puppa et al., 2015**23** | retro | 43 | 63 | 24d | 41 | 41 | 0 | 0 | 0 | 0 | 0 |
| Wirsching et al., 2015**25b** | retro | 779 | 57 | 67e | 535 | 244 | 291 | 18 | 9 | 48 | 29 |
| Abbreviations: AED=antiepileptic drug; pros=prospective; retro=retrospective; FU=follow-up.  **a**(Poon MT-C, personal communication, March 12, 2016).  **b**(Wirsching H-G, personal communication, April 14, 2016).  cThe data employed was at this point in time post-operatively.  dMean follow-up time.  eMedian follow-up time. | | | | | | | | | | | |

**Table 1.** Study characteristics of meningioma cohorts with and without AED prophylaxis

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Characteristics** | | **Studies included (N.)** | **N. of valid cases (%)** | **AED** | **No-AED** | **P-value** |
| **Total No. of Patients (%)** |  | 10, 11, 17–25 (11) | 1143 (100) | 766 (67.0) | 377 (33.0) | N/A |
| **Mean Age** |  | 10, 11, 18, 19 (4) | 240 (20.1) | 54.0 | 58.0 | N/A |
| **Sex (F/M)** | 143/46 | 37/14 | 0.649 |
| **Location (%)** | Non-Skull base | 10, 11, 18-21, 23 (7) | 337 (29.5) | 134 (46.9) | 51(100) | <0.05 |
| Skull base | 152 (53.1) | 0.00 |
| **WHO Grade (%)** | I | 11, 21, 25 (3) | 741 (64.8) | 300 (75.2) | 293 (85.7) | <0.05 |
| II/III | 99 (24.8) | 49 (14.3) |
| **Mean Maximal Tumour Diameter (cm)** |  | 10, 18-20, 24 (5) | 129 (11.3) | 2.81 | N/A | N/A |
| Abbreviations: AED=antiepileptic drug; GTR=gross total resection; STR=subtotal resection; WHO=World Health Organisation. | | | | | | |

**Table 2.** Patient characteristics in seizure-naïve meningioma patients

**Table 3.** The specificAEDs used in seizure-naïve meningioma patients

|  |  |  |
| --- | --- | --- |
| **AED** | **Studies included (N.)** | **N. of cases (%)** |
| Phenytoin | 17 ,25 (2) | 256 (33.4) |
| Levetiracetam | 23, 25 (2) | 55 (7.18) |
| Sodium valproate | 11, 25 (2) | 28 (3.66) |
| Carbamazepine | 25 (1) | 15 (1.96) |
| Phenytoin/ levetiracetam\* | 11 (1) | 129 (16.8) |
| \*This group of patients were described to have received either phenytoin or levetiracetam with no detailed breakdown | | |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Variable** | | **Studies included (N.)** | **AED** | | **No-AED** | | **p-value** |
| **Occurrence/ total No. of patients** | **%** | **Occurrence/ total No. of patients** | **%** |
| Extent of resection | GTR | 10, 11, 18, 19, 23, 25 (6) | 410/474 | 86.5 | 261/342 | 76.3 | <0.05 |
| STR | 64/474 | 13.5 | 81/342 | 23.7 |
| Post-operative seizures | Early | 10, 11, 17–25 (11) | 20/766 | 2.6 | 10/377 | 2.7 | 0.96 |
| Late | 52/766 | 6.8 | 29/377 | 7.7 | 0.58 |
| Overall | 72/766 | 9.4 | 39/377 | 10.4 | 0.62 |
| Abbreviations: AED=antiepileptic drug; GTR=gross total resection; STR=subtotal resection. | | | | | | | |

**Table 4.** Extent of resection and seizure outcome in seizure-naïve meningioma patients