Efficacy of perioperative anticonvulsant prophylaxis in seizure-naïve glioma patients: A meta-analysis

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ABSTRACT

The efficacy of perioperative seizure prophylaxis in seizure-naïve glioma patients is still controversial. Thus we conducted this meta-analysis to assess the effectiveness of perioperative prophylactic antiepileptic drugs (AEDs) on postoperative seizures in seizure-naïve glioma for the first time. We systematically searched PubMed, Embase, Weipu (VIP) and Chinese National Knowledge Infrastructure (CNKI) until July 5, 2019 for eligible studies. Fixed or random model was used to calculate the odds ratios in STATA 12.0 software. Subgroup analyses of early postoperative seizure, late postoperative seizure, high-grade glioma (WHOIII-IV) and phenytoin (PHT) or phenobarbital (PB) prophylaxis were conducted. Altogether 1143 seizure-naïve glioma patients from 9 studies were included in this meta-analysis, containing 643 prophylaxed and 503 non-prophylaxed patients. No significant association was detected between perioperative seizure prophylaxis and postoperative seizure occurrence in glioma patients without preoperative seizure history (OR = 0.91, 95% CI = 0.65–1.26, P = 0.56). Perioperative AED prophylaxis showed no significant benefit to postoperative seizures when stratified by early postoperative seizure(within the first postoperative week), late postoperative seizure (after the first postoperative week), high-grade glioma and PHT or PB prophylaxis (all P > 0.05). Current evidence indicated that perioperative seizure prophylaxis did not reduce the occurrence of postoperative seizure in seizure-naïve glioma patients. The pros and cons of perioperative seizure prophylaxis should be considered before the start of perioperative AEDs treatment.

1. Introduction

Approximately 30%–40% of patients with brain tumors have experienced seizures at diagnosis, and more might develop seizures during the progression and end-of-life phase of tumor [1,2]. Seizure is a potentially devastating and common complication of glioma, and the incidence of seizure in low-grade glioma is up to 60–80% [3,4]. Postoperative seizures may result in hypoxemia ictal injury, decreased cognitive function, and even death [5–7]. Besides, epilepsy can seriously reduce the patient functioning and quality of life [7–9].

Consequently, many neurosurgeons administer prophylactic antiepileptic drugs (AEDs) in the perioperative period. The American Academy of Neurology (AAN) recommended against routine seizure prophylaxis, but it is decided by operator whether or not to have prophylactic AEDs within the first postoperative week in seizure-naïve patients with brain tumors [10]. Despite the recommendations on evidence-based practice parameters, AAN found that 73% physicians

continued to prescribe prophylactic AEDs for patients undergoing brain tumor resections [11]. Previously, Joiner et.al performed a meta-analysis and demonstrated that AED prophylaxis provides a statistically and clinically significant reduction in early seizures (within the first week) following brain tumor surgery [12]. Nevertheless, the efficacy of perioperative seizure prophylaxis in seizure-naïve glioma patients is still controversial [13–15]. Most trials indicated that anticonvulsant prophylaxis did not reduce the risk of postoperative seizure of patients with glioma, but increased adverse events [13–21].

Thus, it is currently disputed whether perioperative AEDs should be routinely administered to seizure-naïve patients with glioma. Given the high rate of seizure prophylaxis in glioma and controversial conclusion, we conducted this meta-analysis to evaluate the impact of perioperative antiepileptic drug prophylaxis on postoperative seizure in seizure-naïve glioma patients.

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2. Methods

2.1. Search strategy

We performed a systematic search in PubMed, Embase, Wanfang, Weipu (VIP) and Chinese National Knowledge Infrastructure (CNKI) with no language limits (until July 5, 2019) for studies regarding the efficacy of perioperative AED prophylaxis in seizure-naïve glioma patients undergoing craniotomy. The following search terms were used: ('glioma', 'GBM', 'glioblastoma', 'astroblastoma', 'oligodendroglioma', 'oligoastrocytoma'), ('seizure', 'epilepsy'), and ('antiepileptic', 'AED', 'anticonvulsant', 'prophylaxis'). Furthermore, cited references of relevant review articles were screened for potential studies.

2.2. Inclusion and exclusion criteria

Two authors screened the articles independently, and any disagreement was solved by a third author. Articles meeting all of the following criteria were included in this study: (1) estimating the association between perioperative AED prophylaxis and postoperative seizure in seizure-naïve glioma patients; (2) comparative studies (random controlled trial, cohort, case-control or observational studies); (3) sufficient data for odds ratio (OR) with confidence intervals (CIs); and (4) English or Chinese publication. Accordingly, studies meeting any of the following criteria were excluded: (1) patients had preoperative seizure history or did not undergo craniotomy; (2) reviews and conference abstracts; (3) no sufficient data reported; and (4) animal studies or experiments *in vitro*. Moreover, we regarded studies recruiting patients in the same institution during overlapping time periods as duplications and included studies with larger sample sizes.

2.3. Data extraction

The baseline information was extracted from all of the eligible studies by two authors independently and repeatedly, and any controversy was solved by discussion. Items extracted from eligible studies are listed as follows: first author's name, publication year, country, study period, type of study, tumor pathology, resection status, type of AEDs, adverse events, and incidence of postoperative seizure. Early postoperative seizure was defined as seizure incidence within the first postoperative week. Late postoperative seizure was seizure occurred after the first postoperative week.

2.4. Statistical analysis

We used the pooled ORs and corresponding 95%CI to evaluate the strength of the association between perioperative anticonvulsant prophylaxis and risk for postoperative seizure. Furthermore, we performed subgroup analysis for early postoperative seizure, high-grade glioma (WHOIII-IV) and use of phenytoin (PHT) or phenobarbital (PB). We used the Z test to calculate the significance of pooled ORs and considered $P < 0.05$ as statistically significant.

Inter-study heterogeneity in eligible studies was evaluated by a Cochran's Q test and the I^2 statistic. We considered the heterogeneity statistically significant when $I^2 \geq 50\%$, and in that case, we calculated the pooled ORs by the random-effects model; otherwise, the fixed-effects model was used. In addition, publication bias was estimated by a Funnel plot using Begg's test, and visual inspection of the funnel plot was used to evaluate publication bias. All of the statistical analyses were performed using STATA (version 12.0; StataCorp, College Station, Texas).
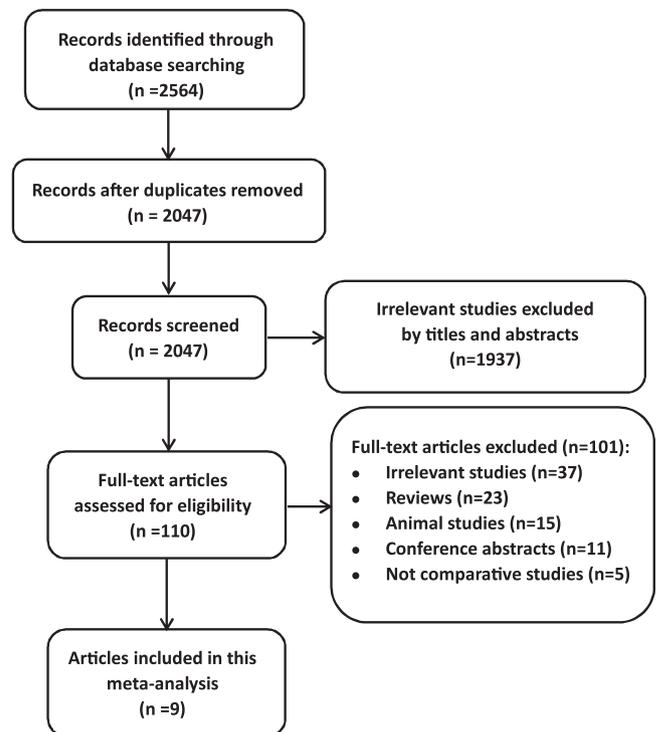

Fig. 1. Flow diagram for study screening.

3. Results

3.1. Characteristics of included studies

We initially identified 2564 potentially relevant records, and exculed 1937 records based on the titles and abstracts (Fig. 1). Altogether 110 articles were considered potentially eligible and retrieved for full-test review. Finally, 9 studies [14–22] met the criteria for qualitative and quantitative synthesis. The basic characteristics of eligible studies are presented in Table 1.

Overall, 643 prophylaxed and 503 non-prophylaxed patients were included to evaluate the effectiveness of perioperative AED prophylaxis on seizure-naïve glioma patients. The rate of AED prophylaxis in the included studies varied from 27 to 82%. Only one study was a randomized controlled trial [20], and the others were observational studies. Occurrences of postoperative seizure in the included studies were summarized in Table S1.

3.2. Effectiveness of AED prophylaxis on postoperative seizures

In this meta-analysis, AED prophylaxis showed no significant benefit over control in preventing total postoperative seizures (OR = 0.91, 95% CI = 0.65–1.26, P = 0.56; Fig. 2). As for the early postoperative seizure, 67 who received AED prophylaxis and 89 who did not from 2 studies were analyzed. The result showed that AED prophylaxis provided no statistically significant reduction in the risk of early postoperative seizure (OR = 0.49, 95% CI = 0.10–2.38, P = 0.38; Table 3, Fig. 3). Besides, no significant difference was detected between AED prophylaxis and late postoperative seizure (OR = 0.99, 95% CI = 0.61–1.62, P = 0.98; Table 3, Fig. 4).

3.3. Effectiveness of AED prophylaxis on postoperative seizures in high grade glioma

Five hundred fifty patients were evaluated for the outcome of postoperative seizures in high grade glioma. In pooled meta-analysis, compared with control, AED prophylaxis had no significant prevention

Table 1
Basic characteristics of included studies.

Author Publication Year	Country	Study Type	Tumor	Resection Status	Duration of Follow-up	Duration of AED Treatment	Definition of Early Seizure	Prophylaxis Rate (%)
Boarini 1985 [15]	USA	Obs	astrocytoma	biopsy; craniotomy	14m[a]	14 m[a]	NA	46.48 (33/71)
Dewan 2017 [14]	USA	Obs	glioma	craniotomy	2w	1w	2w	82.01 (155/189)
Garbossa 2013 [16]	Italy	Obs	high-grade glioma (WHO II-IV)	craniotomy	6m[a]	6m[a]	1 m	47.25 (43/91)
Lapointe 2015 [17]	Canada	Obs	glioma	biopsy; craniotomy	≥16m	≥3m	2w	62.12 (205/330)
Liang 2016 [18]	China	Obs	Glioblastoma	craniotomy	16.41m[a]	2w-12m[a]	NA	51.77 (73/141)
Lwu 2010 [19]	Canada	Obs	malignant glioma (WHO III-IV)	craniotomy	5.4m[a]	1w-12m	1w	40.00 (44/110)
Mahaley 1981 [22]	USA	Obs	anaplastic glioma	craniotomy	NA	NA	NA	64.41 (38/59)
Wu 2013 [20]	USA	RCT	glioma	craniotomy	12m	1w	1m	50.00 (23/46)
Wychowski 2013 [21]	USA	Obs	glioblastoma	biopsy; craniotomy	11.5m[a]	NA	NA	26.61 (29/109)

Obs: observational study; RCT: Randomized Controlled Trial; w, week; m, month; NA, not available; [a]median of duration of follow-up or AED treatment.
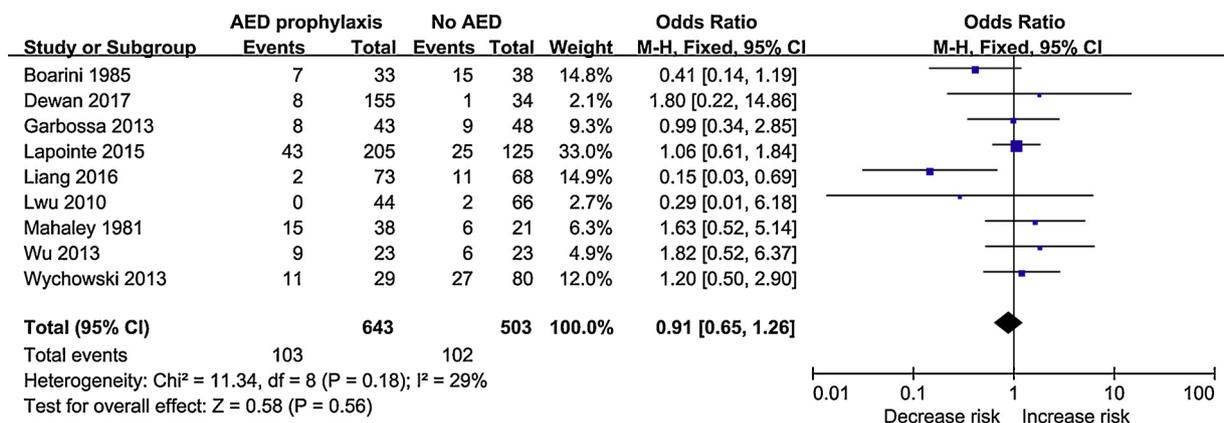

Fig. 2. Forest plot for the efficacy of perioperative AED prophylaxis on postoperative seizure.
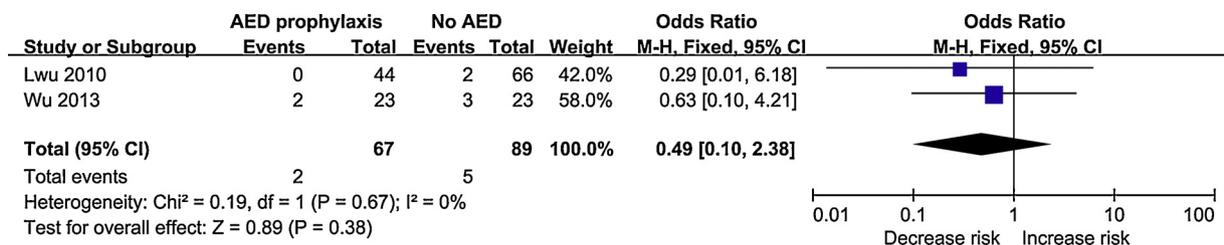

Fig. 3. Forest plot for the efficacy of perioperative AED prophylaxis on early postoperative seizure. Early postoperative seizure was defined as seizure incidence within the first postoperative week.
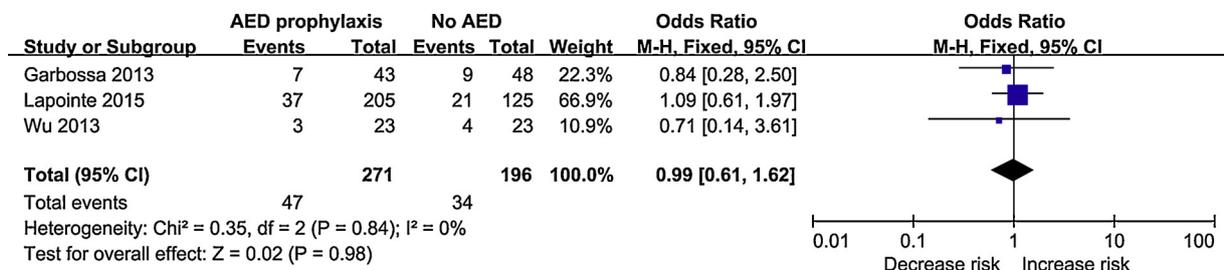

Fig. 4. Forest plot for the efficacy of perioperative AED prophylaxis on late postoperative seizure. Late postoperative seizure was seizure occurred after the first postoperative week.

of postoperative seizures in patients with high grade glioma (OR = 0.82, 95% CI = 0.49–1.35, P = 0.43; Table 3, Fig. S1). Subgroup analysis in low grade glioma was not conducted for the lack of data.

3.4. Effectiveness of PHT or PB prophylaxis on postoperative seizures

In subgroup analysis regarding the types of AEDs, 281 patients were evaluated for the effectiveness of PHT or PB in prevention of

Table 2

Adverse events of prophylactic AEDs in seizure-naïve glioma patients.

Author, Publication Year	AEDs Types	AED Prophylaxis		No AED		Patients with AR (%)	Adverse Events (No. of events)[b]
		n	Seizure (%)	n	Seizure (%)		
Boarini 1985 [15] [a]	PHT,PB	33	7 (21.2)	38	15 (39.5)	NA	–
Dewan 2017 [14]	LEV,PHT OXC	155	8 (5.2)	34	1 (2.9)	24 (5.2)	dermatologic reaction (14) decreased level of consciousness (41) electrolyte imbalance (1) other (5)
Garbossa 2013 [16] [a]	LEV	43	8 (18.6)	48	9 (18.8)	NA	–
Lapointe 2015 [17] [a]	LEV,PHT	205	43 (21.0)	125	25 (20.0)	NA	–
Liang 2016 [18] [a]	VPA,LEVOXC	73	2 (27.4)	68	11 (16.2)	NA	–
Lwu 2010 [19]	PHT	44	0 (0.0)	66	2 (3.0)	1(2.3)	rash necessitating (1)
Mahaley 1981 [22]	PHT,PB	38	15 (39.5)	21	6 (28.6)	11(29.0)	dermatologic reaction (11)
Wu 2013 [20]	PHT	23	6 (26.1)	23	9 (39.1)	4(17.3)	dermatologic reaction, liver toxcity, thrombocytopenia, decreased level of consciousness, aphasia, ataxia, photophobia
Wychowski 2013 [21]	LEV,PHTVPA,CBZ	29	11(37.9)	80	27 (33.8)	10(34.5)	PHT: rash, gait instability (2), toxic epidermal necrolysis (1), unkown cause (1) LEV: depression (1)

AR: adverse events; PHT: phenytoin; PB: Phenobarbital;LEV: levetiracetam; OXC: oxcarbazepine ; VPA: valproate; CBZ: carbamazepine.

[a] details of adverse events not available.

[b] adverse events were not presented by the type of AED in some studies due to lack of specific data.

Table 3

Subgroup analysis between AED prophylaxis and postoperative seizure in seizure-naïve glioma patients.

Outcome	Included studies	AED prophylaxis	no AED	OR	95%CI	P_{het}
Total postoperative seizure	9	643	503	0.91	0.65-1.26	0.18
Early postoperative seizure	2	67	89	0.49	0.10-2.38	0.67
Late postoperative seizure	3	271	196	0.99	0.61-1.62	0.84
High grade glioma	5	227	283	0.82	0.49-1.35	0.11
PHT or PB prophylaxis	4	133	148	0.97	0.53-1.80	0.13

PHT: phenytoin; PB: Phenobarbital.
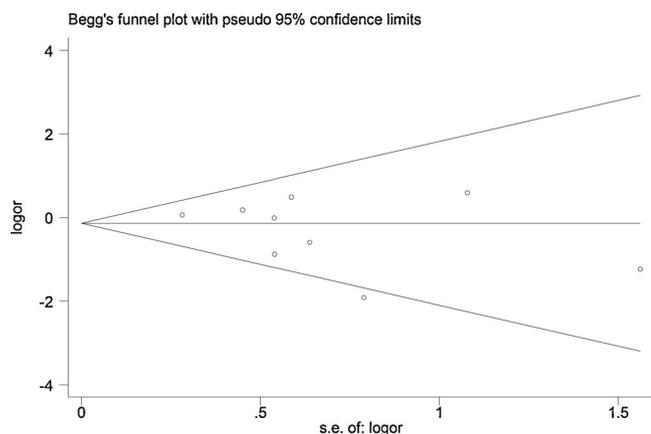
Fig. 5. Begg's funnel plot on publication bias for included studies on the association of between perioperative AED prophylaxis and postoperative seizure.

postoperative seizures. In pooled meta-analysis, PHT or PB prophylaxis did not remarkably alter the incidence rate of postoperative seizures (OR = 0.97, 95% CI = 0.53–1.80, P = 0.93; Table 3, Fig S2).

3.5. The adverse effects of AED prophylaxis

Altogether 5 studies reported adverse events caused by prophylactic AEDs, with the rate of adverse events varied from 2 to 34%. PHT, PB, levetiracetam (LEV), and valproate (VPA) were commonly administered for perioperative prophylaxis. As shown in Table 2, dermatologic reaction and decreased level of consciousness were common adverse events caused by postoperative AEDs. Notably, serious adverse events such as toxic epidermal necrolysis was reported.

3.6. Publication bias

Begg's funnel plot seemed symmetrical, suggesting that no publication bias was detected (Fig. 5). No significant evidence of publication bias was detected by the Egger's test (t= -1.17, P = 0.279).

4. Discussion

The effect of perioperative seizure prophylaxis in glioma without preoperative seizure history is still confusing. For the first time, we conducted this meta-analysis and demonstrated that no significant association between perioperative seizure prophylaxis and postoperative seizure occurrence in seizure-naïve glioma patients. Similar results were detected in subgroup analysis for early postoperative seizure, high-grade glioma and PHT or PB.

The administration of prophylactic AEDs needs comprehensive evaluation. The rate of seizure prophylaxis was comparatively high, deviating from the guidelines of AAN [10]. Our meta-analysis demonstrated that perioperative anticonvulsant prophylaxis did not reduce the incidence of postoperative seizure in seizure-naïve glioma patients. Accordingly, in a previous meta-analysis regarding seizure-naïve patients undergoing craniotomy, no significant effect of prophylactic AED was detected for postcraniotomy seizures [23]. However, the results should be carefully interpreted. The risk of postoperative seizure in glioma was elevated by temporal tumor location, low-grade glioma and subtotal resection [24,25]. The complex pathologic mechanisms and various predisposing factors make it difficult to determine whether

seizure prophylaxis is effective to prevent postoperative seizure occurrence in patients with glioma [26,27]. Regrettably, the benefit of AED prophylaxis to high-risk glioma patients was not further pooled-analyzed due to insufficient data in this study. Thus risk stratification may be essential for further investigating the effectiveness of seizure prophylaxis.

The rate of adverse events caused by prophylactic AEDs was relatively high (up to 17–34%) in several included studies. Notably, severe adverse events such as toxic epidermal necrolysis and decreased level of consciousness were reported [14,21], making it more intractable to determine the use of prophylactic AEDs. Therefore, surgeons should weigh the pros and cons before the start of seizure prophylaxis. Additionally, traditional AEDs, including PHT, CBZ, VPA and PB were commonly used for perioperative prophylaxis. As a new generation AED, levetiracetam has been reported to reduce postoperative seizures and increase the sensitivity of glioblastoma to chemotherapy with well tolerance [28,29]. Besides, Yuan's meta-analysis suggested that VPA administration prolonged the survival of glioblastoma patients [30]. Further investigation focused on the benefit of AED to glioma is still needed.

Several limitations should be stated in this meta-analysis. First, the evidence is of low quality since only one RCT was included and the sample sizes of eligible studies were relatively small in this study. Besides, seizure prophylaxis differed in the timing, duration and types of AEDs, which may also bias the results. Finally, further assessments for types of AED, site of glioma, specific pathology and the extent of resection were limited due to insufficient data.

4.1. Conclusions

In conclusion, perioperative seizure prophylaxis did not reduce the occurrence of postoperative seizure in seizure-naïve glioma patients based on present studies. Further high-quality RCT is essential to assess the effectiveness of perioperative seizure prophylaxis. The administration of prophylactic AEDs needs comprehensive evaluation.

Funding information

Declaration of Competing Interest

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

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2019.105529.

References

[1] M. Weller, R. Stupp, W. Wick, Epilepsy meets cancer: when, why, and what to do about it? Lancet Oncol. 13 (2012) e375–382.

[2] E.K. Avila, M. Chamberlain, D. Schiff, J.C. Reijneveld, T.S. Armstrong, R. Ruda, P.Y. Wen, M. Weller, J.A. Koekkoek, S. Mittal, Y. Arakawa, A. Choucair, J. Gonzalez-Martinez, D.R. MacDonald, R. Nishikawa, A. Shah, C.J. Vecht, P. Warren, M.J. van den Bent, L.M. DeAngelis, Seizure control as a new metric in assessing efficacy of tumor treatment in low-grade glioma trials, Neurooncology 19 (2017) 12–21.

[3] D.A. Kvam, C.M. Loftus, B. Copeland, D.O. Quest, Seizures during the immediate postoperative period, Neurosurgery 12 (1983) 14–17.

[4] T.S. Armstrong, R. Grant, M.R. Gilbert, J.W. Lee, A.D. Norden, Epilepsy in glioma patients: mechanisms, management, and impact of anticonvulsant therapy, Neurooncology 18 (2016) 779–789.

[5] A. Neal, A. Morokoff, T.J. O'Brien, P. Kwan, Postoperative seizure control in patients with tumor-associated epilepsy, Epilepsia 57 (2016) 1779–1788.

[6] M. Klein, N.H. Engelberts, H.M. van der Ploeg, D.G. Kasteleijn-Nolst Trenite, N.K. Aaronson, M.J. Taphoorn, H. Baaijen, W.P. Vandertop, M. Muller, T.J. Postma, J.J. Heimans, Epilepsy in low-grade gliomas: the impact on cognitive function and quality of life, Ann. Neurol. 54 (2003) 514–520.

[7] A. Jacoby, C. Gamble, J. Doughty, A. Marson, D. Chadwick, Medical Research Council MSG. Quality of life outcomes of immediate or delayed treatment of early epilepsy and single seizures, Neurology 68 (2007) 1188–1196.

[8] S. Li, J. Chen, X. Tong, A.T.A. Abdulaziz, X. Liu, M. Su, C. Wang, Z. Li, D. Zhou, Factors associated with seizure-related motor vehicle accidents among patients with epilepsy in West China, Seizure 66 (2019) 42–46.

[9] X. Zou, Z. Hong, J. Chen, D. Zhou, Is antiepileptic drug withdrawal status related to quality of life in seizure-free adult patients with epilepsy? Epilepsy Behav. 31 (2014) 129–135.

[10] M.J. Glantz, B.F. Cole, P.A. Forsyth, L.D. Recht, P.Y. Wen, M.C. Chamberlain, S.A. Grossman, J.G. Cairncross, Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology, Neurology 54 (2000) 1886–1893.

[11] M.C. Dewan, R.C. Thompson, S.N. Kalkanis, F.G. Barker 2nd, C.G. Hadjipanayis, Prophylactic antiepileptic drug administration following brain tumor resection: results of a recent AANS/CNS Section on Tumors survey, J. Neurosurg. 126 (2017) 1772–1778.

[12] E.F. Joiner, B.E. Youngerman, T.S. Hudson, J. Yang, M.R. Welch, G.M. McKhann 2nd, A.I. Neugut, J.N. Bruce, Effectiveness of perioperative antiepileptic drug prophylaxis for early and late seizures following oncologic neurosurgery: a meta-analysis, J. Neurosurg. (2018) 1–9.

[13] J.A. de Oliveira, I.A. Santana, I.Q. Caires, R. Caires-Lima, V.C. Miranda, B.M. Protasio, L.S. Rocha, H.F. Braga, A.M. Mencarini, M.J. Teixeira, L.H. Castro, O. Feher, Antiepileptic drug prophylaxis in primary brain tumor patients: is current practice in agreement to the consensus? J. Neurooncol. 120 (2014) 399–403.

[14] M.C. Dewan, G.A. White-Dzuro, P.R. Brinson, S.L. Zuckerman, P.J. Morone, R.C. Thompson, J.C. Wellons 3rd, L.B. Chambless, The Influence of Perioperative Seizure Prophylaxis on Seizure Rate and Hospital Quality Metrics Following Glioma Resection, Neurosurgery 80 (2017) 563–570.

[15] D.J. Boarini, D.W. Beck, J.C. VanGilder, Postoperative prophylactic anticonvulsant therapy in cerebral gliomas, Neurosurgery 16 (1985) 290–292.

[16] D. Garbossa, P.P. Panciani, R. Angeleri, L. Battaglia, F. Tartara, M. Ajello, A. Agnoletti, P. Versari, A. Ducati, M. Fontanella, G. Spena, A retrospective two-center study of antiepileptic prophylaxis in patients with surgically treated high-grade gliomas, Neurol. India 61 (2013) 131–137.

[17] S. Lapointe, M. Florescu, D.K. Nguyen, C. Djeffal, K. Belanger, Prophylactic anticonvulsants for gliomas: a seven-year retrospective analysis, Neurooncol. Pract. 2 (2015) 192–198.

[18] S. Liang, J. Zhang, S. Zhang, X. Fu, Epilepsy in Adults with Supratentorial Glioblastoma: Incidence and Influence Factors and Prophylaxis in 184 Patients, PLoS One 11 (2016) e0158206.

[19] S. Lwu, M.G. Hamilton, P.A. Forsyth, J.G. Cairncross, I.F. Parney, Use of peri-operative anti-epileptic drugs in patients with newly diagnosed high grade malignant glioma: a single center experience, J. Neurooncol. 96 (2010) 403–408.

[20] A.S. Wu, V.T. Trinh, D. Suki, S. Graham, A. Forman, J.S. Weinberg, I.E. McCutcheon, S.S. Prabhu, A.B. Heimberger, R. Sawaya, X. Wang, W. Qiao, K. Hess, F.F. Lang, A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors, J. Neurosurg. 118 (2013) 873–883.

[21] T. Wychowski, H. Wang, L. Buniak, J.C. Henry, N. Mohile, Considerations in prophylaxis for tumor-associated epilepsy: prevention of status epilepticus and tolerability of newer generation AEDs, Clin. Neurol. Neurosurg. 115 (2013) 2365–2369.

[22] M.S. Mahaley Jr., L. Dudka, The role of anticonvulsant medications in the management of patients with anaplastic gliomas, Surg. Neurol. 16 (1981) 399–401.

[23] J. Greenhalgh, J. Weston, Y. Dundar, S.J. Nevitt, A.G. Marson, Antiepileptic drugs as prophylaxis for postcraniotomy seizures, Cochrane Database Syst. Rev. 5 (2018) CD007286.

[24] S.T. Herman, Epilepsy after brain insult: targeting epileptogenesis, Neurology 59 (2002) S21–26.

[25] D.J. Englot, S.J. Han, M.S. Berger, N.M. Barbaro, E.F. Chang, Extent of surgical resection predicts seizure freedom in low-grade temporal lobe brain tumors, Neurosurgery 70 (2012) 921–928 discussion 928.

[26] E. Trinka, F. Brigo, Antiepileptogenesis in humans: disappointing clinical evidence and ways to move forward, Curr. Opin. Neurol. 27 (2014) 227–235.

[27] M. Kerkhof, C.J. Vecht, Seizure characteristics and prognostic factors of gliomas, Epilepsia 54 (Suppl. 9) (2013) 12–17.

[28] I. Zachenhofer, M. Donat, S. Oberndorfer, K. Roessler, Perioperative levetiracetam for prevention of seizures in supratentorial brain tumor surgery, J. Neurooncol. 101 (2011) 101–106.

[29] E. Fonkem, P. Bricker, D. Mungall, E. Aceves, E. Ebwe, W. Tang, B. Kirmani, The role of levetiracetam in treatment of seizures in brain tumor patients, Front. Neurol. 4 (2013) 153.

[30] Y. Yuan, W. Xiang, M. Qing, L. Yanhui, L. Jiewen, M. Yunhe, Survival analysis for valproic acid use in adult glioblastoma multiforme: a meta-analysis of individual patient data and a systematic review, Seizure 23 (2014) 830–835.