Optimizing antiseizure medication treatment in glioma patients with epilepsy

Meer, P.B. van der

PART I

Antiseizure medication efficacy

CHAPTER 2

Efficacy of antiepileptic drugs in glioma patients with epilepsy: a systematic review

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Pim B. van der Meer*, Marjolein E. de Bruin*
Linda Dirven
Martin J.B. Taphoorn
Johan A.F. Koekkoek

*Both authors contributed equally

Abstract

Background

Comprehensive data on the efficacy and tolerability of AED treatment in glioma patients with epilepsy is currently lacking. In this systematic review we specifically assessed the efficacy of AEDs in patients with a grade II-IV glioma.

Methods

Electronic databases PubMed/MEDLINE, EMBASE, Web of Science, and Cochrane library were searched up to June 2020. Three different outcomes for both mono- and polytherapy were extracted from all eligible articles: (I) seizure freedom; (II) ≥50% reduction in seizure frequency; and (III) treatment failure. Weighted averages (WA) were calculated for outcomes at 6 and 12 months.

Results

A total of 66 studies were included. Regarding the individual outcomes on the efficacy of monotherapy, the highest seizure freedom rate at 6 months was with phenytoin (WA=72%) while at 12 months pregabalin (WA=75%) and levetiracetam (WA=74%) showed highest efficacy. Concerning ≥50% seizure reduction rates, levetiracetam showed highest efficacy at 6 and 12 months (WAs of 82% and 97%, respectively). However, treatment failure rates at 12 months were highest for phenytoin (WA=34%) and pregabalin (41%). When comparing the described polytherapy combinations with follow-up of ≥6 months, levetiracetam combined with phenytoin was most effective followed by levetiracetam combined with valproic acid.

Conclusion

Given the heterogeneous patient populations and the low scientific quality across the different studies, seizure rates need to be interpreted with caution. Based on the current limited evidence, with the ranking of AEDs being confined to the AEDs studied, levetiracetam, phenytoin and pregabalin seem to be most effective as AED monotherapy in glioma patients with epilepsy, with levetiracetam showing the lowest treatment failure rate, compared to the other AEDs studied.

Keywords

Brain tumor, glioma, epilepsy, seizures, antiepileptic drugs

Introduction

Gliomas are the most common malignant primary brain tumors in adults, with glioblastoma accounting for the majority. Epileptic seizures occur frequently in glioma patients, either as a presenting symptom or during the course of the disease. The epileptogenicity of the tumor is inversely related with its growth rate.[1-3] The incidence of seizures ranges from 60 to 85% in patients with diffuse low-grade glioma and from 30 to 50% in patients with glioblastoma.[1] Epilepsy results in impaired social and economic participation, an increase in morbidity and mortality, and adversely affect health-related quality of life (HRQoL) in glioma patients. Both epilepsy and the use of antiepileptic drugs (AEDs) may worsen neurocognitive functioning, which subsequently has a negative impact on HRQoL.[4, 5] Since a reduction in seizure frequency is associated with less morbidity and improved HRQoL, achieving sustained seizure control is one of the main treatment goals in glioma patients who develop brain tumor-related epilepsy (BTRE).[4, 6]

Both anticonvulsant and antitumor treatment including surgical resection, radiotherapy and chemotherapy may contribute to seizure control.[6-10] The efficacy of primary prophylactic treatment with AEDs has not been demonstrated and according to several guidelines, patients should not receive primary anticonvulsant prophylaxis.[11-13] However, all brain tumor patients who experience a first seizure should be treated with AEDs because of the high risk of seizure recurrence.[11, 14-16] Treatment with AEDs can be challenging due to multidrug-resistance, adverse effects (AEs), and potential interactions between AEDs and chemotherapeutic agents.[1, 17] The epileptogenic mechanisms and drug targets in glioma patients are thought to be different from the general epilepsy population as possible explanation for drug-resistance.[17] Indeed, refractory epilepsy (i.e. failure to achieve seizure freedom even after AED polytherapy) is reported in ~20% of glioma patients following initial treatment and higher in patients with lowgrade gliomas (30-35%)..[18] Moreover, when compared to other epilepsy patients, AEs of AEDs occur more frequently in brain tumor patients.[17] When patients have become seizure free, seizure recurrence is often associated with tumor progression or recurrence.[19, 20]

The choice for a specific AED for glioma patients with epilepsy is determined by multiple factors, including availability, tolerability, efficacy, comorbidity, costs, ease of administration, titration schemes, pharmacokinetic characteristics, but also the physicians' preference.[21] General consensus exists that AEDs with less or no drug-to-drug interactions, like levetiracetam (LEV), lamotrigine (LTG), perampanel (PER), brivaracetam (BRV) , zonisamide (ZNS) and lacosamide (LCM), are preferable to enzyme-inducing AEDs, such as phenobarbital (PB), phenytoin (PHT) or carbamazepine (CBZ).[19, 21-23] However, comprehensive data on efficacy and tolerability of anticonvulsant treatment in glioma patients is currently lacking, while it may guide physicians in the selection of AEDs.[24] We performed a systematic review in which we specifically assessed the efficacy of AEDs in patients with a grade II-IV glioma.

Methods

Search strategy

We performed a literature review in the electronic databases PubMed/MEDLINE, EMBASE, Web of Science and Cochrane library up to June 1st 2020, for screening and selecting studies we followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The search included a combination of search terms related to "glioma", "epilepsy", "antiepileptic drugs" and "efficacy". The complete search strategy is described in Supplementary Table 1. Two authors (MB and PM) independently screened the articles by title and abstract, and served as reviewers of all potentially relevant full-text articles. Reference lists from the included full-text articles were searched manually for additional sources. Inclusion criteria were: (I) adult patients with BTRE, (II) ≥50% of patients with a histologically proven or suspected glioma, or outcomes categorized by histology, (III) ≥10 patients treated with the same AED, (IV) AED efficacy or effectiveness reported, and (V) written in English and published in a peer-reviewed journal. Exclusion criteria were: (I) ≥50% of patients treated with perioperative AED prophylaxis and no separate information of seizure outcome regarding this group and patients treated symptomatically, (II) no description of the different types of AEDs prescribed, and (III) no documentation of outcomes per AED in case <50% of patients received the same AED, (IV) articles focusing on treatment of a status epilepticus. Information was retrieved from interventional (randomized and non-randomized) and observational studies (cohort, case-control, and case-series).

Data extraction and selection criteria

For each selected study, we extracted the following characteristics: study design, number of patients recruited and number of patients using (prophylactic) AEDs, histology, type of AEDs, duration of follow-up, and AED efficacy. As a measure of AED efficacy, defined as the ability of an AED to achieve seizure freedom or reduction, three different outcomes were extracted: (I) seizure freedom; (II) ≥50% reduction in seizure frequency, including seizure freedom; and (III) treatment failure, defined as discontinuation of the initiated AED or the need to add-on a second AED due to inefficacy, AEs and/or other reasons.

For this review, we focused on seizure outcomes at 6 and 12 months, based on clinical relevance and availability in studies. We separately described studies with other time points for follow-up or in case no follow-up duration was mentioned (Supplementary Table 2, 3, and 4). Weighted average (WA) was calculated for outcomes with a similar follow-up duration to control for the varying number of patients included in the studies (Supplementary Table 5). The WA is the sum of outcomes in each study multiplied by a weighting factor, which is determined by dividing the amount of patients from that study by the total number of patients from all suitable studies.

To provide a clear overview, studies were categorized according to the AED(s) prescribed and discussed in the tables in more detail under the heading of the AED prescribed most frequently. Outcomes were discussed for mono- and polytherapy separately. In case it was unclear what combination of AEDs was prescribed, results were discussed in the paragraph of the AED which was most commonly part of the AED polytherapy.

Results

We retrieved 3582 unique records. After screening titles and abstracts, 193 full-text articles were assessed for further eligibility, after which 66 articles were considered eligible (Figure 1).

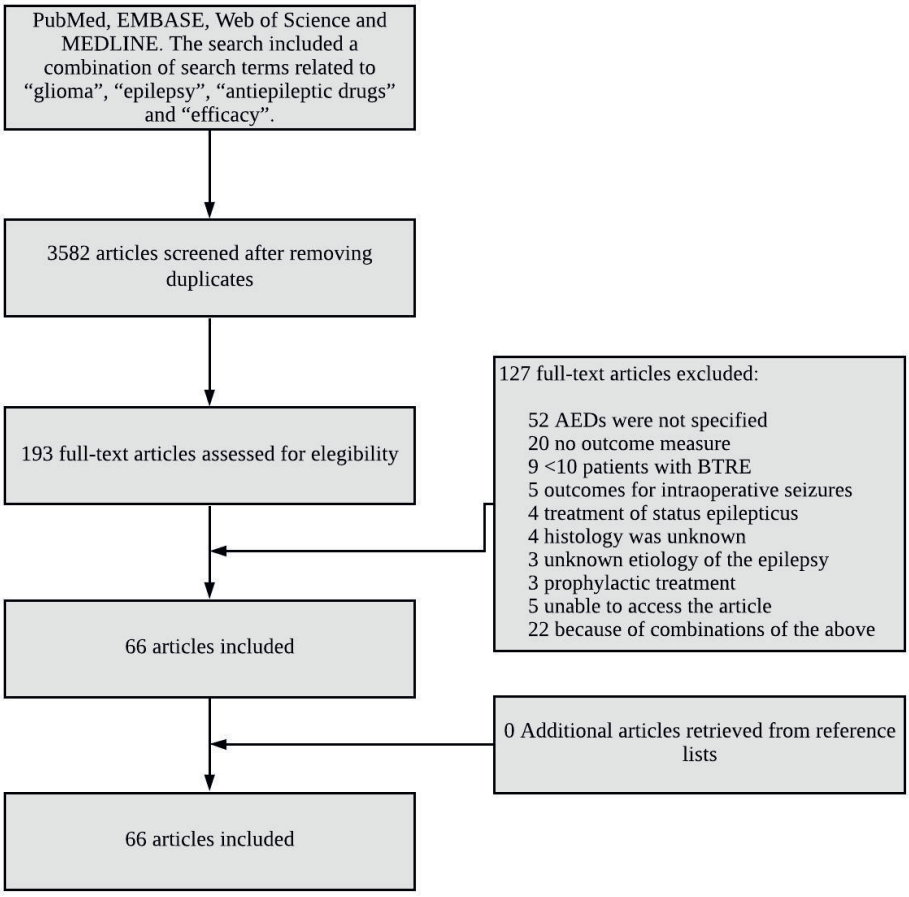

Figure 1. Literature selection procedure.

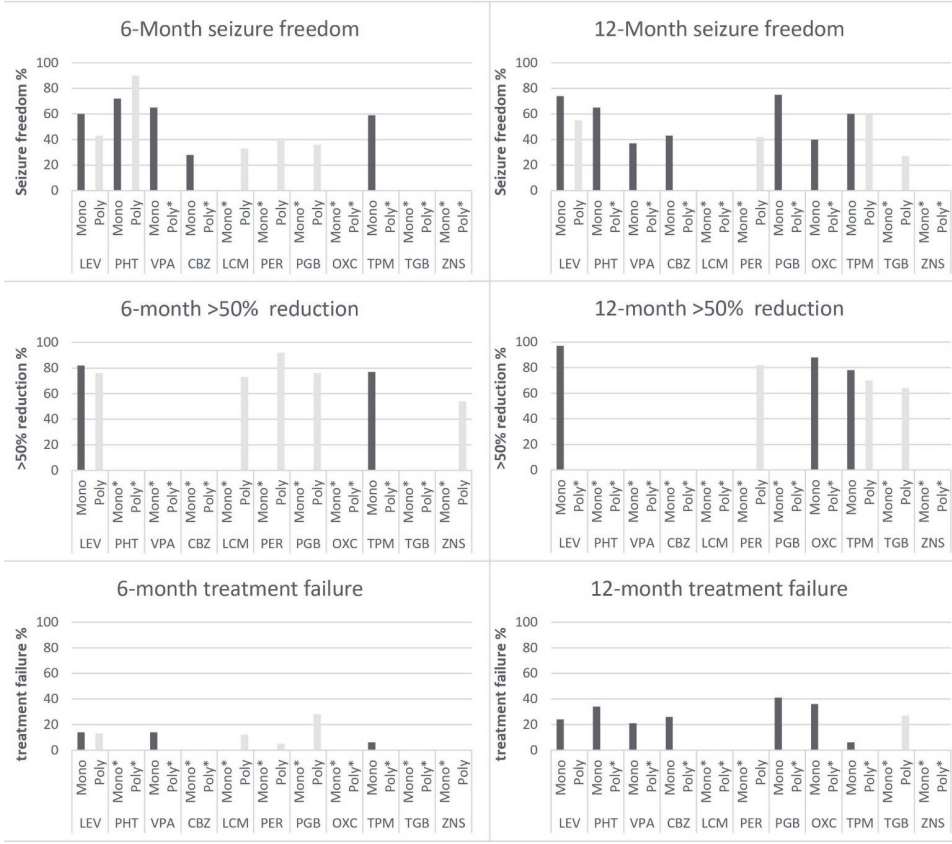

Figure 2. Weighted average (WA) calculated for outcomes at 6 and 12 months.
*No data available

Levetiracetam (LEV)

We found 1 case series, 2 randomized controlled trials, 8 non-randomized clinical trials, 9 prospective and 16 retrospective observational studies reporting on LEV (Table 1).[25-60]
In total, 25 studies documented efficacy of LEV monotherapy.[25-40, 48-50, 52, 54-58] The 6-month seizure freedom rate was presented in 9/25 studies and varied between 39-96% (WA=60%),[26, 27, 31, 33, 35, 38, 48, 55, 56] while the 12-month seizure freedom rate was presented in 4/25 studies, ranging between 68-96% (WA=74%).[32, 36, 54, 55] A seizure reduction rate ≥50% at 6 months was presented in 2/25 studies and varied between 71-100% (WA=82%).[26, 31] One study reported a seizure reduction rate of ≥50% at 12 months of 97%.[32] The WAs of 6- and 12-month treatment failure rates, documented in 4 and 2 studies respectively, were 14% and 24% due to any reason, 10% and 6% due to inefficacy, and 1% and 15% due to AEs.[26, 27, 31-33, 36]

Table 1. Efficacy of levetiracetam at 6 and 12 months follow-up.

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Levetiracetam (LEV)							
Bahr et al. (2012)[33]	Pros	N=30 (n=25)	GBM n=12; Grade III n=5; LGG n=5; MEN n=3; Unknown n=3 MET n=1; Other n=1;	LEV n=30		1 and 6 (after AED initiation)	1-Month seizure freedom LEV: 21/25=84% 1-Month treatment failure due to AEs (n=0), inefficacy (n=3), or unknown (n=0) LEV: 3/25=12% 6-Month seizure freedom LEV: 13/25=52% 6-Month treatment failure due to AEs (n=0), inefficacy (n=6), or unknown (n=1) LEV: 7/25=28%
Chonan et al. (2019)[51]	Discussed under perampanel						
De Groot et al. (2011)[31]	Pros clinical trial	N=35 (n=35)	GBM n=15; AODG n=6; AA n=4; A n=3; ODG n=3; AOA n=2 OA n=1	LEV n=35		6 (after AED initiation)	6-Month seizure freedom LEV: 21/35=59% 6-Month ≥50% Seizure reduction LEV: 26/35=74% 6-Month treatment failure due to AEs LEV: 1/35=3%
Dinapoli et al. (2009)[26]	Case series	N=18 (n=18)	GBM n=3; AA n=3; A n=3; OA n=3; ODG n=3; MEN n=2; Other n=1	LEV n=18		6 (after AED initiation)	6-Month seizure freedom LEV: 16/18=89% 6-Month ≥50% seizure reduction LEV: 18/18=100% 6-Month treatment failure due to AEs (n=0) or inefficacy (n=0) LEV=0/18=0%

Table 1. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Eseonu et al. (2018)[48]	Retro	N=81 (n=81),prophylactic n=36	Grade IV n=27; Grade II n=27; Grade III n=17; Other n=8; MET n= 2	LEV n=46	LEV+PHT n=30; LEV+Other n=5	6 (after surgery)	6-Month seizure freedom monotherapy (excl. prophylactic) LEV:15/25=60% 6-Month seizure freedom (excl. prophylactic) LEV+PHT(+/- Other): 18/20=90%
Ius et al. (2020)[54]	Retro	N=155 (n=155)	A; n=111; ODG n=44	LEV n=96; CBZ n=22; PHT n=10	Other n=27	12 (after surgery)	12-Month seizure freedom: 110/155=71%
Lim et al. (2009)[27]	RCT, unblinded	N=29 (n=29)	GBM n=9; AA n=4; A n=4; ODG n=2; AOA n=2; AODG n=1; Grade I n=1	LEV n=20; PHT n=9		6 (after AED initiation/ surgery)	6-Month seizure freedom LEV: 18/20=90% 6-Month treatment failure due to AEs (n=0), inefficacy (n=0), or unknown (n=5) LEV: 6/20=30%
Maialetti et al. (2020)[56]	Pros	N=33 (n=33)	HGG n=14; LGG n=12; Other n=7	LEV n=10; Other n=11	LEV+Other n=9; Other n=3	6 (after rehabilitation)	6-Month seizure freedom AEDs: 26/33=79% 6-Month ≥50% Seizure reduction AEDs: 28/33=85%
Maschio et al. (2011)[32]	Pros clinical trial	N=29 (n=29)	GBM n=9; AODG n=6; LGA n=5; AA n=4; MEN n=2; Other n=2; ODG n=1;	LEV n=29		12 (after AED initiation)	12-Month seizure freedom LEV: 21/29=72% 12-Month ≥50% Seizure reduction LEV: 28/29=97% 12-Month treatment failure due to AEs (n=1), inefficacy (n=2), or other (n=2) LEV: 5/29=17%
Maschio et al. (2017)[43]	Discussed under lacosamide						

Table 1. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Michelucci et al. (2013)[35]	Pros	N=100 (n=97)	GBM n=52; AA n=15; ODG n=10; A n=9; AODG n=5; Other n=4; AOA n=3; Grade I n=2;	Mono- (n=64) and polytherapy (n=33): LEV n=63; OXC n=33; PHT n=16; CBZ n=10; Other n=8		6 (after surgery)	6-Month seizure freedom AEDs: 39/100=39%
Rahman et al. (2015)[38]	Pros	N=81 (n=55)	GBM n=27; ODG n=20; MEN n=13; A n=8; Grade I n=7; OA n=4; Other n=2	LEV n=21; Other n=11	LEV+Other n=9; Other n=14	6 (after AED initiation)	6-Month seizure freedom AEDs: 32/55=58%
Rossetti et al. (2014)[36]	Discussed under pregabaline						
Rudà et al. (2018)[44]	Discussed under lacosamide						
Rudà et al. (2020)[60]	Discussed under lacosamide						
Solomons et al. (2019)[59]	Retro	N=74 (n=66)	ODG n=32; A n=26; OA n=7; Other n=9		Mono- and polytherapy: LEV+/-Other n=44; Other n=22	12 (after AED initiation)	12-Month seizure freedom 38/66=57%

See supplementary table for the following articles. LEV: Bech et al. (2018), Berntsson et al. (2018), Breemen et al. (2009), Calatozzolo et al. (2012), Cardona et al. (2018), Casas Perera et al. (2019), Feyissa et al. (2019), Haggiagi & Avila (2018), Kerkhof et al. (2013), Kerkhof et al. (2019), Maschio et al. (2006), Merrel et al. (2010), Newton et al. (2006), Romoli et al. (2019), Rosati et al. (2010), Saria et al. (2013), Suzuki et al. (2020), Usery et al. (2010), Wagner et al. (2003), Wychowski et al. (2013)
Antiepileptic drugs (AEDS): CBZ=Carbamazepine; LEV=Levetiracetam; OXC=Oxcarbazepine; PHT=Phenytoin, **Histology:** A=(Pleiomorphic) astrocytoma grade II; AA=Anaplastic (pleiomorphic) astrocytoma; AOA=Anaplastic oligoastrocytoma; AODG=Anaplastic oligodendroglioma; GBM=Glioblastoma; HGG=High grade glioma; LGG=Low grade glioma; MEN=Meningioma; MET=Metastasis; OA=Oligoastrocytoma; ODG=Oligodendroglioma grade II, **General abbreviations:** AEs=Adverse effects; Excl.=excluding; N=number of patients; Pros=prospective; RCT=randomized controlled trial; Retro=retrospective

In total, 13 studies documented efficacy of polytherapy including LEV.[25, 41-48, 51, 53, 59, 60] The 6-month seizure freedom rate was presented in 5/13 studies and ranged between 28-90% (WA 43%),[43, 44, 48, 51, 60] while the 12-month seizure freedom rate was presented in 2/13 studies, ranging between 44-58% (WA 55%).[51, 59] A ≥50% seizure reduction rate at 6 months was presented in 4 studies and ranged between 74-77% (WA=76%).[42-44, 60] A total of 5 studies reported treatment failure rates of LEV polytherapy.[42, 46, 47, 51, 60] The 6-month treatment failure rate, documented in 2 studies, was 13% due to any reason, 2% due to inefficacy, and 5% due to AEs.[51, 60] One study reported a 0% treatment failure rate due to inefficacy at 12 months.[51]

Phenytoin (PHT)

We found 1 prospective and 11 retrospective observational studies reporting on PHT (Table 2).[4, 8, 28, 37, 48, 61-67]

In total, 9 studies documented efficacy of PHT monotherapy.[4, 8, 28, 37, 61-65] The 6-month seizure freedom rate was presented in 2/9 studies and varied between 67-87% (WA=72%).[8, 61] while the 12-month seizure freedom rate was presented in 5/9 studies and varied between 35-77% (WA=65%). [4, 8, 61, 62, 65] One study reported a 34% treatment failure rate due to AEs at 12 months of PHT treatment.[65]

In total, 3 studies documented efficacy of polytherapy including PHT.[48, 66, 67] The 6-month seizure freedom rate was 90% as reported in 1/3 studies.[48]

Valproic acid (VPA)

We found 1 prospective and 9 retrospective observational studies reporting on VPA (Table 2).[4, 25, 41, 65-71]

In total, 8 studies documented efficacy of VPA monotherapy.[4, 25, 41, 65, 68-70] Six-month seizure freedom rate was 65% as reported in one study,[69] while 12-month seizure freedom rate was presented in 4/8 studies and ranged between 30-62% (WA=37%). [4, 65, 69, 70] One study reported a 14% treatment failure rate due to inefficacy at 6 months and another study reported a 21% treatment failure rate due to AEs of VPA treatment at 12 months.[65, 71]

In total, 4 studies documented efficacy of polytherapy including VPA.[4, 25, 41, 66, 67] In these studies, no results were reported for 6 or 12 month follow-up duration.

Carbamazepine (CBZ)

We found 1 prospective and 6 retrospective observational studies reporting on CBZ (Table 2).[4, 8, 65-67, 72, 73]

Seizure freedom rate was described in all 5 studies on CBZ monotherapy. However, one study reported on the 6-month seizure freedom rate, i.e. 28%.[73] The 12-month seizure freedom rate was presented in 2/5 studies and varied between 30-55% (WA=43%).[4, 65] One study reported a 12-month treatment failure rate of 26% due to AEs.[65]

In total, 2 studies documented efficacy of polytherapy including CBZ. In these studies, no results were reported for 6 or 12 month follow-up duration.

Table 2. Efficacy of phenytoin, valproic acid, and carbamazepine at 6 and 12 months follow-up.

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Phenytoin (PHT)							
ChaiChana et al. (2009)[61]	Retro	N=648 (n=153)	GBM n=505; AA n=143	Preoperative AEDs: mono- (n=111) and polytherapy (n=42): PHT n=102; LEV n=13; DVX n=12; Other n=19; Unknown unclear		6 and 12 (after surgery)	6-Month seizure freedom AEDs: 79/91=87% 12-Month seizure freedom AEDs: 51/66=77%
Chang et al. (2008)[8]	Retro	N=332 (n=284)	A n=129; OA n=109; ODG n=95	PHT n=159; CBZ n=59; DVX n=29; PB n=26; Other n=15;	Unknown n=55	3 (before surgery), 6 and 12 (after surgery)	3-Month seizure freedom PHT: 84/159=53%; CBZ: 22/59=37%; PB: 11/26=42%; Divalproex sodium: 14/29=48% 6-Month seizure freedom AEDs: 169/253=67% 12-Month seizure freedom AEDs: 147/220=67%
Eseonu et al. (2018)[48]	Discussed under levetiracetam						
Hwang et al. (2004)[62]	Retro	N=101 (n=101), prophylactic n=87	GBM n=57; AA n=27; A n=17	PHT n=101		1, 3 and 12 (after surgery)	1-Month seizure freedom (excl. prophylactic) PHT: 12/14=86% 3-Month seizure freedom (excl. prophylactic) PHT: 11/14=79% 12-Month seizure freedom (excl. prophylactic) PHT: 9/14=64%

Table 2. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Klein et al. (2003)[4]	Discussed under carbamazepine						
Wick et al. (2005)[65]	Retro	N=107 (n=107), prophylactic n=32, unclear n=7	GBM n=45; AA n=17; ODG n=16; AODG n=14; A n=13; Grade I n=1; Other n=1	PHT n=35; VPA n=34; CBZ n=27; Unclear n=11		12 (after surgery)	12-Month seizure freedom (incl. prophylactic) PHT: 17/35=49%; VPA: 19/34=56%; CBZ: 8/27=30% 12-Month treatment failure due to AEs (incl. prophylactic) PHT: 12/35=34%; VPA: 7/34=21%; CBZ: 7/27=26%;
Valproic acid (VPA)							
Klein et al. (2003)[4]	Discussed under carbamazepine						
Wang et al. (2019)[71]	Retro	N=41 (n=41)	Grade II n=19; Grade III n=12; Grade IV n=10	VPA n=21; LEV n=11; Other n=4	VPA+LEV n=5	6 (after surgery)	6-Month treatment failure due to inefficacy AEDs: 5/37=14%
Wick et al. (2005)[65]	Discussed under phenytoin						
You et al. (2012)[69]	Retro	N=508 (n=502), prophylactic n=154	OA n=231; A n=229; ODG n=48	VPA n=444; Other n=8; Unknown n=2	Other n=50	6 and 12 (after surgery)	6-Month seizure freedom (excl. prophylactic) AEDs: 215/329=65%. 12-Month seizure freedom (exl. Prophylactic AEDs: 90/304=30%.
Yuan et al. (2013)[70]	Retro	N=93 (n=65)	ODG n=36; OA n=29; A n=28	VPA n>95%; Other n<5%		12 (after surgery)	12-Month seizure freedom AEDs: 37/65=57%

Table 2. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Carbamazepine (CBZ)							
Chang et al. (2008)[8]	Discussed under phenytoin						
Klein et al. (2003)[4]	Cross-sectional (seizure history retro)	N=156 (n=114)	A n=109; ODG n=38; OA n=9	CBZ n=29; VPA; n=13; PHT n=20; Other n=2	Other n=50	12 (after primary treatment)	12-Month seizure freedom CBZ: 16/29=55%; PHT 7/20=35%; VPA 8/13=62%
Warnke et al. (1997)[73]	Retro	N=80 (n=80), prophylactic n=8	A n=80	CBZ n=58; PHT n=12; PB n=10		6 (after radiosurgery)	6-Month seizure freedom (incl. prophylactic) CBZ: 16/58=28%
Wick et al. (2005)[65]	Discussed under phenytoin						

See supplementary table for the following articles. PHT: Merrel et al. (2010), Moots et al. (1995), Rosati et al. (2009), Wychowski et al. (2013), Zaatreh et al. (2002), Zaatreh et al. (2003); VPA: Breemen et al. (2009), Kerkhof et al. (2013), Simó et al. (2012), Zaatreh et al. (2002), Zaatreh et al. (2003); CBZ: Pace et al. (1998), Zaatreh et al. (2002), Zaatreh et al. (2003)

Antiepileptic drugs (AEDS): CBZ=Carbamazepine; DVX=Divalproex sodium; EIAEDs=Enzyme-inducing antiepileptic drugs; GBP=Gabapentin; LTG=Lamotrigine; LEV=Levetiracetam; PB=Phenobarbital; PRI=Primidone; PHT=Phenytoin; VPA=Valproic acid, **Histology:** A=(Pleiomorphic) astrocytoma grade II; AA=Anaplastic (pleiomorphic) astrocytoma; AOA=Anaplastic oligoastrocytoma; AODG=Anaplastic oligodendroglioma; GBM=Glioblastoma; HGG=High grade glioma; LGG=Low grade glioma; MEN=Meningioma; MET=Metastasis; OA=Oligoastrocytoma; ODG=Oligodendroglioma grade II, **General abbreviations:** AEs=Adverse effects; Excl.=excluding, Incl.=including; Pros=prospective; Retro=retrospective

Lacosamide (LCM)

No studies documented efficacy of LCM monotherapy. The efficacy of polytherapy including LCM was reported in 3 non-randomized clinical trials, 1 prospective and 3 retrospective observational studies (Table 3).[43-45, 60, 74-76] The 6-month seizure freedom rate with polytherapy including LCM was presented in 4/7 studies and varied between 26-43% (WA=33%).[43, 44, 60, 74] A seizure reduction rate ≥50% at 6 months was reported in 4 studies and varied between 66-77% (WA=73%).[43, 44, 60, 74] The WAs of 6-month treatment failure rates, documented in 4 studies, were 12% due to any reason, 2% due to inefficacy, and 5% due to AEs. [43, 60, 75, 76]

Perampanel (PER)

No studies documented efficacy of PER monotherapy. The efficacy of polytherapy including PER was reported in 1 non-randomized clinical trial, 1 prospective and 3 retrospective observational studies (Table 3).[51, 77-80]

The 6-month seizure freedom rate of polytherapy with PER was presented in 3/5 studies and ranged between 31-60% (WA=41%),[51, 77, 80] while the 12-month seizure freedom rate in 2/5 studies varied between 44-45% (WA=45%).[51, 79] Seizure reduction rates ≥50% at 6 and 12 months were 92% and 82%, respectively, as reported in 3 different studies.[77, 79, 80] Treatment failure rates with polytherapy including PER ranged between 0-17%. The WAs of 6-month treatment failure rates, documented in 3 studies, were 5% due to any reason, 0% due to inefficacy, and 5% due to AEs.[51, 77, 80] The WAs of 12-month treatment failure rates, documented in 2 studies, were 0% due to any reason, inefficacy and AEs.[51, 79]

Pregabalin (PGB)

We found 1 RCT reporting on PGB monotherapy and 1 non-randomized clinical trial reporting on PGB polytherapy (Table 3).[36, 81]

Seizure freedom rate at 12 months with PGB monotherapy was 75%, as reported in one RCT (n=52). Treatment failure rates at 12 months were 41% due to any reason, 15% due to inefficacy and 26% due to AEs.[36]

At 6 months, seizure freedom rate was reported in 36% and a ≥50% seizure reduction rate in 76% of patients on polytherapy including PGB, as reported in one non-randomized clinical trial (n= 25). Treatment failure rates with PGB polytherapy at 6 months was 28% due to any reason, 20% due to inefficacy and 8% due to AEs.[81]

Oxcarbazepine (OXC)

We found 1 non-randomized clinical trial and 1 retrospective observational study reporting on OXC monotherapy (Table 3).[82, 83]

As reported in 1 non-randomized clinical trial (n=25), the 12-month seizure freedom rate was 40% and a ≥50% seizure reduction was observed in 88% of patients.[82] Treatment

failure with OXC monotherapy ranged between 9-36%. The study provided reasons for the 12-month treatment failure rate: 12% due to inefficacy and 24% due to AEs.[82]

Topiramate (TPM)

We found 1 non-randomized clinical trial and 1 retrospective observational study reporting on TPM (Table 3).[84, 85]

Seizure freedom rate at 6 months with TPM monotherapy was 59%, as reported in one non-randomized clinical trial (n=47).[84] The 12-month seizure freedom rates were reported in both studies and varied between 57-71% (WA=60%). A ≥50% reduction in seizure frequency at 12 months was described in both studies and ranged between 75-86% (WA=78%).[84, 85] One study described the treatment failure rate at 6 and 12-months of 6% and was in all cases due to AEs.[84]

The efficacy of polytherapy including TPM was reported in one retrospective study, 40 patients used TPM in combination with another AED. The 12-month seizure freedom rate was 60% with a ≥50% seizure reduction of 70%.[85]

Other AEDs

The efficacy of polytherapy including tiagabine (TGB) was reported in 1 small prospective observational study (n=11 [Table 3]). The 12-month seizure freedom rate was 27%, and ≥50% seizure reduction was reported in 64% patients. Total treatment failure rate with TGB polytherapy at 12 months was 27%; 9% due to inefficacy and 18% due to AEs.[86]

The efficacy of polytherapy including zonisamide (ZNS) was reported in 1 small prospective observational study (n=13 [Table 3]). The 6-month seizure reduction rate ≥50% was 54%. No patients experienced treatment failure with ZNS polytherapy in the first 6 months.[87]

The efficacy of the other AEDs (PB, gabapentin (GBP), LTG, clonazepam, divalproex sodium, primidone and vigabatrin), with no outcomes reported at 6- or 12-month follow-up, was only discussed in 1 or 2 studies except for PB, which was discussed in 5 studies.

Table 3. Efficacy of lacosamide, perampanel, pregabalin, oxcarbazepine, topiramate, tiagabine, zonisamide at 6 and 12 months follow-up.

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Lacosamide (LCM)							
Maschio et al. (2011)[76]	Pros clinical trial	N=14 (n=14)	GBM n=5; AA n=2; AOA n=2; A n=2; AODG n=1; ODG n=1; GC n=1		LCM+Other n=14	3, 6 and 9 (after AED initiation)	3-Month treatment failure due to AEs (n=1) or inefficacy (n=0) LCM: 1/14=7% 6-Month treatment failure due to AEs (n=1) or inefficacy (n=0) LCM: 1/14=7% 9-Month seizure freedom LCM: 6/14=38% 9-Month ≥50% seizure reduction LCM: 11/14=79% 9-Month treatment failure due to AEs (n=1) or inefficacy (n=0) LCM: 1/14=7%
Maschio et al. (2017)[43]	Pros (compared to a historical control group) clinical trial	N=25 (n=25)	A n=8; AA n=6; GBM n=5; ODG n=3; AODG n=2; AOA n=1		LCM+LEV(+/- other) n=15; LCM+Other n=10	3 and 6 (after AED initiation)	3-Month seizure freedom LCM: 8/25=32% 3-Month ≥50% seizure reduction LCM: 19/25=76% 3-Month treatment failure due to AEs (n=0), poor compliance (n=4) or inefficacy (n=1) LCM: 5/25=20 6-Month seizure freedom LCM: 7/25=28% 6-Month ≥50% seizure reduction LCM: 19/25=76% 6-Month treatment failure due to AEs (n=0), poor compliance (n=4) or inefficacy (n=1) LCM: 5/25=20%

Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Rudà et al. (2018)[44]	Pros clinical trial	N=71 (n=71)	A n=44; ODG/ OA n=27		LCM+LEV(+/- Other) n=60; LCM+Other 11	3, 6 and 9 (after AED initiation)	3-Month seizure freedom LCM: 30/71=42% 3-Month ≥50% seizure reduction LCM: 53/71=75% 6-Month seizure freedom LCM: 28/65=43% 6-Month ≥50% seizure reduction LCM: 50/65=77% 9-Month seizure freedom LCM: 29/58=50% 9-Month ≥50% seizure reduction LCM: 50/58=86% 9-Month treatment failure due to AEs (n=2), inefficacy (n=1), or other reasons (n=1) LCM: 4/71=6%%
Rudà et al. (2020)[60]	Pros	N=93 (n=93)	ODG n=32; A n=29; OA n=13; Other n=16; MEN n=3		LCM+LEV(+/- Other) n=60; LCM+Other n=33	6 (after AED initiation)	6-Month seizure freedom LCM: 30/86=35% 6-Month ≥50% seizure reduction LCM: 66/86=77% 6-Month treatment failure due to AEs (n=5), inefficacy (n=2), or other reasons (n=7) LCM: 14/93=15%
Villanueva et al. (2016)[74]	Retro	N=105 (n=105)	A n=42; GBM n=13; MET n=12; MEN n=11; Grade I n=10; ODG n=7; OA n=5; Other n=2; Unknown n=2; GC n=1;	LCM n=3	LCM+Other n=102	3 and 6 (after AED initiation)	3-Month seizure freedom LCM: 32/105=30% 3-Month ≥50% seizure reduction LCM: 71/105=68% 3-Month treatment failure due to AEs (n=1), inefficacy (n=0), or other reasons (n=0) LCM: 1/105=1%

Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
							6-Month seizure freedom LCM: 25/97=26% 6-Month ≥50% seizure reduction LCM: 64/97=66% 6-Month treatment failure due to AEs (n=5), inefficacy (n=1), or other reasons (n=2) LCM: 8/105=8%
Perampanel (PER)							
Chonan et al. (2019)[51]	Retro	N=18 (n=18)	GBM n=7; AA n=5; ODG n=3; A n=2; AODG; n=1		PER+LEV n=18	1, 3, 6, 9, 12 (after AED initiation)	1-Month seizure freedom:10/18=56% 1-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 3-Month seizure freedom: 8/18=44% 3-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 6-Month seizure freedom: 8/18=44% 6-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 9-Month seizure freedom: 8/18=44% 9-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 12-Month seizure freedom: 8/18=44% 12-Month treatment failure due to AEs or inefficacy PER: 0/18=0%
Izumoto et al. (2018)[77]	Retro	N=12 (n=12)	AODG n=5; AA n=3; GBM n=2; A n=1; OA n=1		PER+Other n=12	6 (after AED initiation)	6-Month seizure freedom PER: 6/10=60% 6-Month ≥50% seizure reduction PER: 10/10=100% 6-Month treatment failure due to AEs PER: 1/12=8%

Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Maschio et al. (2018)[79]	Retro	N=11 (n=11)	A n=4; GBM n=3; AA n=2; AOA n=2		PER+Other n=11	12 (after AED initiation)	12-Month seizure freedom PER: 5/11=45% 12-Month ≥50% seizure reduction PER: 9/11=82% 12-Month treatment failure due to AEs PER: 0/11=0%
Maschio et al. (2020)[80]	Pros clinical trial	N=26 (n=26)	GBM n=7; AA n=7; A n=5; ODG n=3; MET n=2; MEN n=1; AOA n=1		PER+Other n=26	6 (after AED initiation)	6-Month seizure freedom PER: 8/26=31% 6-Month ≥50% seizure reduction PER: 23/26=88% 6-Month treatment failure due to AEs (n=2) or inefficacy (n=0) PER: 2/26=8%
Pregabaline (PGB)							
Maschio et al. (2012)[81]	Pros clinical trial	N=25 (n=25)	GBM n=6; AA n=4; AODG n=3; AOA n=3; A n=2; MET n=2; MEN n=2; GC n=2; OA n=1 MEN n=2		PGB+Other n=25	6 (after AED initiation)	6-Month seizure freedom PGB: 9/25=36% 6-Month ≥50% Seizure reduction PGB: 19/25=76% 6-Month treatment failure due to AEs (n=2) or inefficacy (n=5) PGB: 7/25=28%
Rossetti et al. (2014)[36]	RCT, unblinded phase II trial	N=52 (n=52)	HGG n=37; Recurrent tumor n=16	PGB n=27; LEV n=25		12 (after AED initiation)	12-Month seizure freedom PGB: 18/24=75%; LEV: 17/25=68% 12-Month treatment failure AEs (n=7) or inefficacy (n=4) PGB: 11/27=41%; AEs (n=7) or inefficacy (n=1) LEV: 8/25=32%
Oxcarbazepine (OXC)							
Maschio et al. (2012)[82]	Pros clinical trial	N=25 (n=25)	GBM n=12; AA n=4; GC n=3; A n=2; AODG n=1 AOA n=1; Grade I n=1; MEN n=1	OXC n=25		12 (after surgery)	12-Month seizure freedom OXC: 10/25=40% 12-Month ≥50% seizure reduction OXC: 22/25=88% 12-Month treatment failure due to AEs (n=6) or inefficacy (n=3) OXC: 9/25=36%

Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Topiramate (TPM)							
Lu et al. (2009)[85]	Retro	N=227 (n=227)	LGG n=54; Other n=173	TPM n=14	TPM+Other n=40	12 (after AED initiation)	12-Month seizure freedom mono-, polytherapy TPM: 10/14=71%; 24/40=60% 12-Month ≥50% seizure reduction mono- and polytherapy TPM: 12/14=86%; 28/40=70%
Maschio et al. (2008)[84]	Pros clinical trial	N=47 (n=47)	Grade III n=20; LGG n=13; GBM n=8; MEN n=4; MET n=2	TPM n=47		3, 6 and 12 (after AED initiation)	3-Month seizure freedom TPM: 27/45=60% 3-Month ≥50% seizure reduction TPM: 34/45=76% 3-Month treatment failure due to AEs (n=2) or inefficacy (n=0) TPM: 2/47=4% 6-Month seizure freedom TPM: 26/44=59% 6-Month ≥50% seizure reduction TPM: 34/44=77% 6-Month treatment failure due to AEs (n=3) or inefficacy (n=0) TPM: 3/47=6% 12-Month seizure freedom TPM: 25/44=57% 12-Month ≥50% seizure reduction TPM: 33/44=75% 12-Month treatment failure due to AEs (n=3) or inefficacy (n=0) TPM: 3/47=6%
Tiagabine (TGB)							
Striano et al. (2002)[86]	Pros	N=11 (n=11)	ODG n=6; A n=4; GBM n=1; A n=3; Grade I n=1		TGB+Other n=11	12 (after AED initiation)	12-Month seizure freedom TGB: 3/11=27% 12-Month ≥50% seizure reduction TGB: 7/11=64% 12-Month treatment failure due to AEs (n=2) or inefficacy (n=1) TGB: 3/11=27%

Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Zonisamide (ZNS)							
Maschio et al. (2017)[87]	Pros	N=13 (n=13)	GBM n=6; MEN n=3; OA n=2; ODG n=1; MET n=1		ZNS+Other n=13	6 (after AED initiation)	6-Month ≥50% seizure reduction ZNS: 7/13=54% 6-Month treatment failure due to AEs (n=0) or inefficacy (n=0) ZNS= 0/13=0%

See supplementary for the following articles. LCM: Saria et al. (2013), Toledo et al. (2018); PB: Chang et al. (2008), Maschio et al. (2009), Pace et al. (1998), Zaatreh et al. (2002), Zaatreh et al. (2003); PER: Vecht et al. (2017); OXC: Maschio et al. (2009); CZP: Koekkoek et al. (2016); GBP: Zaatreh et al. (2002), Zaatreh et al. (2003); LTG: Zaatreh et al. (2002), Zaatreh et al. (2003); DVX: Chang et al. (2008), PRI: Zaatreh et al. (2003) VGB: Pace et al. (1998)

Antiepileptic drugs (AEDs): CBZ=Carbamazepine; CZP=Clonazepam; DVX=Divalproex sodium; GBP=Gabapentin; LCM=Lacosamide; LEV=Levetiracetam; OXC=Oxcarbazepine; PB=Phenobarbital; PGB=Pregabaline; PRI=Primidone; PHT=Phenytoin; TGB=Tiagabine; TPM=Topiramate; VGB=Vigabatrin; ZNS=Zonisamide, **Histology:** A=(Pleiomorphic) astrocytoma grade II; AA=Anaplastic (pleiomorphic) astrocytoma; AOA=Anaplastic oligoastrocytoma; AODG=Anaplastic oligodendroglioma; GBM=Glioblastoma; GC=Gliomatosis cerebri; HGG=High grade glioma; LGG=Low grade glioma; MEN=Meningioma; MET=Metastasis; OA=Oligoastrocytoma; ODG=Oligodendroglioma grade II, **General abbreviations:** AEs=Adverse effects; Pros=prospective; Retro=retrospective

Discussion

In this review we summarized the current available literature on AED efficacy in patients with BTRE due to diffuse glioma. Overall, the interpretation of seizure outcome is hampered by the heterogeneous patient populations in terms of, for example, tumor histology, tumor location, seizure type, and use of concomitant medication. In addition, the effect of tumor status and concomitant antitumor treatment on the reduction in the number of seizures cannot be ruled out. Methodological limitations such as study design and inadequate statistical analysis make the results less interpretable as well. For example, methodological issues weren't always taken into account in the different studies, such as the presence of death as a competing risk.[88] Therefore, reported seizure rates need to be interpreted with caution. Moreover, efficacy of AEDs was not always the primary outcome in the studies, resulting in limited information available on the efficacy of specific (combinations of) AEDs, or different aspects of efficacy or time points were assessed, hampering comparability of studies.

To overcome variation with respect to the different sample sizes and reporting only a range, we calculated a WA to provide a more reliable estimate of AED efficacy. Furthermore, we purposefully chose to focus on the results for 6- and 12-month follow-up, as these time points were considered clinically relevant, most often described in the selected studies, and therefore making a comparison between AEDs possible. To better guide clinicians in their choice of AED treatment, we combined information on seizure freedom and seizure reduction with information about treatment failure.

Bearing in mind the limitations with regard to study heterogeneity, there was not one AED that clearly stood out in terms of efficacy. Indeed, based on the calculated WA's, 6-month seizure freedom rate with AED monotherapy was highest for PHT, whereas the 12-month seizure freedom rate was highest for PGB. However, the 12-months seizure freedom rate of PGB is based on only a small phase 2 study (n=52) in patients with mainly grade 3 and 4 glioma (treatment failure rate of 41%).[36] For achieving a ≥50% seizure reduction, LEV was found to be the most effective AED at 6 and 12 months. Nevertheless, a ≥50% seizure reduction with AED monotherapy was only mentioned for LEV/TPM and OXC. In line with the weighted data, one of the RCTs comparing LEV with PGB showed similar seizure freedom rates.[36] Thus, based on the currently available evidence, PHT, PGB, and LEV seem most effective as monotherapy in the treatment of epilepsy in glioma patients. It should be noted that the high seizure freedom rate of PHT at 6 months is based on only 2 retrospective studies[8, 61], compared to 9 studies on LEV including one RCT at 6 months.[27]

The results with respect to AED polytherapy were also ambiguous. Seizure freedom rates with polytherapy at 6 months and 12 months were highest for combinations with PHT and TPM, respectively. For achieving a ≥50% seizure reduction, PER was found to be the

most effective AED at both 6 and 12 months, based on studies with a small number of patients including mainly malignant brain tumours. Of note, in most studies it was unclear what combination of AEDs patients were taking when they were on AED polytherapy. The four known studied combinations with outcomes ≥6 months, were LEV+PHT,[89] LEV+LCM,[43, 44, 60] PER+LEV,[51] and LEV+VPA.[18, 41] Eseonu et al. (2018) reported a 6-month seizure freedom rate of 90% (18/20 patients) when combining LEV with PHT, although this rate was reported 6 months after tumor surgery, which is known to have an antiseizure effect in glioma patients.[89] Considering the known combinations, LEV+VPA was second-best and showed seizure freedom rates of 54% and 59% after a minimum follow-up of 6 months.[18, 41]

Nonetheless, it should be emphasized that PHT and PGB were associated with relatively high percentages of treatment failure. Specifically for monotherapy, treatment failure due to AEs for PHT was 34% (WA) at 12 months, followed by PGB and CBZ with 26% (WA), treatment failure due to any reason at 6 months was highest for PGB. Less information was available on the treatment failure rates of AED polytherapy, but again PGB showed the highest rate with 28% treatment failure due to any reason, while LEV, PER and ZNS showed most favorable tolerability. These findings provide substantiation of the general consensus that has emerged over the past two decades regarding the avoidance of cytochrome P450 enzyme-inducing AEDs, such as PHT, CBZ, and PB in glioma patients, due to its potential drug-to-drug interactions.[21, 22, 90] In the general epilepsy population, PHT has been known for its worse tolerability compared to newer agents, such as LEV.[91] In glioma patients, the P450 enzyme-inducing properties of PHT and its inherent interaction with other medications and antineoplastic drugs, such as corticosteroids, lomustine, and vincristine, are considered a risk factor for the occurrence of AEs.[11] Among other AEDs, LEV, PGB, and LTG are predominantly excreted by the renal system and do not have P450-inducing or inhibiting properties, leading to less drug-drug interactions.[92] Nonetheless, of these newer non-enzyme-inducing AEDs, we found LEV to show a better tolerability than PGB, which seems likely be attributed to a higher rate of side effects in patients on PGB compared to LEV.

LEV may nowadays be the most commonly prescribed AED in patients with BTRE, probably because of its good tolerability and the possibility to titrate rapidly.[93] However, it is associated with psychiatric AEs and it is therefore strongly advised not to be prescribed in patients with psychiatric comorbidities.[93] For those patients BRV may be a promising alternative with a comparable pharmacokinetic profile but higher tolerability regarding psychiatric AEs. Otherwise, PGB is prescribed less frequently for the treatment of epilepsy,[94] but effective in treating neuropathic pain and anxiety disorders which are both common symptoms in glioma patients (~20 and ~30%, respectively).[95, 96]

VPA has long been one of the first choice treatments in glioma patients with epilepsy partly due to its presumed antitumor effect, although a survival benefit in glioblastoma

could not be determined in a pooled analysis of prospective trials.[97] Due to its relatively lower seizure control rates compared to other AEDs, our data do no support VPA as first choice monotherapy. Supported by two studies, which showed reasonable seizure freedom rates, VPA can be a good option as second-line AED treatment combined with LEV in patients with uncontrolled seizures.[18, 41] Adverse effects of VPA include weight gain, encephalopathy, thrombocytopenia and platelet dysfunction. In addition VPA is a CYP450-inhibitor leading to drug-drug interactions and an increased toxicity of chemotherapeutic agents like procarbazine and irinotecan.[21] Because of its good tolerability and intravenous availability LCM is a suitable alternative as add-on AED, e.g. in combination with LEV.[21] Remarkably, we found very limited data on the efficacy of LTG and GBP in glioma patients. LTG is a first line treatment for focal seizures in non-tumour cases and has no enzyme-inducing properties.[93] LTG is considered the most effective AED (together with GBP) in treating elderly adults with focal-onset seizures,[98] and has been considered a suitable option for the treatment of BTRE.[21, 99, 100] Disadvantages of LTG are the need for slow titration, risk of dermatologic reactions, and the interaction with VPA.[93]

It needs to be emphasized that this review article does not provide a complete overview about AEs of AEDs. Initiating a second-line AED did not necessarily indicate failure of AED monotherapy but might have been caused by initiating early polytherapy instead of adequately dose escalation,[25] making it difficult to compare AED treatment failure rates. For example, in the unblinded RCT by Rossetti et al. (2014), patients with primary brain tumors and epilepsy were titrated to monotherapy LEV or PGB, and efficacy and tolerability were assessed. If necessary, LEV was increased to 3000 mg/day leading to relatively less AED discontinuation due to inefficacy, but more because of AEs.[36] In general, a retrospective study design is not the most suitable design to report the AED tolerability accurately. Nonetheless, even in retrospective study designs, treatment failure due to adverse effects rates can reliably be estimated as a change in AED regimen and the reason for this is well reported in medical charts. Therefore, with regard to AEs we focused solely on treatment failure rates. However, most studies reporting treatment failure rates included only a limited number of patients, meaning the reported effect size can vary widely from the true (population) effect size.

To conclude, based on the current limited evidence, monotherapy with LEV, PHT and PGB seem to be most effective in glioma patients, compared to the other AEDs studied (VPA, CBZ, TPM, OXC), of which LEV shows a favorable tolerability as well. TPM and PER appear relatively good choices for add-on treatment, and LEV with PHT as well as LEV with VPA are relatively effective dual therapy combinations. However, due to heterogeneous patient populations and low scientific quality of the studies, results should be interpreted with caution. Although well-powered comparative efficacy RCTs are still lacking, in clinical practice newer AEDs with limited to no interactions, such as LEV and LCM, have become increasingly preferred in glioma patients. As long as clear evidence for

AED treatment in BTRE is absent, recommendations by the International League Against Epilepsy (ILAE) for treating focal seizures in non-tumour cases can be used, considering side effects and drug interactions.[98] Currently, an RCT is being conducted in which LEV and VPA are compared (NCT03048084). Other prospective studies, particularly focusing on AED polytherapy are also warranted. Since improving HRQoL, partly by means of controlling seizures, is one of the main treatment goals in glioma patients with epilepsy, future studies should incorporate appropriate outcome measures that reflect efficacy as much as tolerability of AED treatment. RCT's and well-designed observational studies are desirable for the frequently used and well tolerated AED LTG in addition to the newer AEDs LCM, PER and BRV. Outcomes such as seizure freedom and 50% seizure reduction along with AED treatment failure should be used, adjusting for potential confounders such as tumor status and concomitant tumor treatment. The results of this review may serve as historical control data for future trials. More clinically relevant are probably HRQoL questionaries.

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Conflict of interest
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Supplementary material

Supplementary Table 1. Search strategy

Date	Database	Strategy
01-06-2020	PubMed	((("Glioma"[Mesh] OR glioma*[tw] OR neuroglioma*[tw] OR xanthoastrocytoma*[tw] OR xantoastrocytoma*[tw] OR astrocytoma*[tw] OR astro-cytoma*[tw] OR astroglioma*[tw] OR astro-glioma*[tw] OR oligoastrocytoma*[tw] OR oligoastro-cytoma*[tw] OR glioblastom*[tw] OR glio-blastom*[tw] OR oligodendroglioma*[tw] OR oligo-dendroglioma*[tw] OR oligoden-droglioma*[tw] OR oligodendroblastoma*[tw] OR oligo-dendro-blastoma*[tw] OR oligo-dendroblastoma*[tw] OR oligoden-droblastoma*[tw] OR oligodendro-blastoma*[tw] OR brain malign*[tw] OR malignant primary brain*[tw] OR primary malignant brain*[tw] OR malignant brain*[tw] OR glial tumour*[tw] OR glial tumor*[tw] OR glial neoplasm*[tw] OR glial cancer*[tw] OR "glial carcinoma"[tw] OR "glial carcinomas"[tw] OR glial malignan*[tw] OR glial cell tumour*[tw] OR glial cell tumor*[tw] OR glial cell neoplasm*[tw] OR "glial cell cancer"[tw] OR "glial cell cancers"[tw] OR "glial cell carcinoma"[tw] OR "glial cell carcinomas"[tw] OR "glial cell malignancy"[tw] OR "glial cell malignancies"[tw] OR neuroglial tumour*[tw] OR neuroglial tumor*[tw] OR neuroglial neoplasm*[tw] OR "neuroglial cancer"[tw] OR "neuroglial cancers"[tw] OR "neuroglial carcinoma"[tw] OR "neuroglial carcinomas"[tw] OR "neuroglial malignancy"[tw] OR "neuroglial malignancies"[tw] OR "neuroglial cell tumour"[tw] OR "neuroglial cell tumours"[tw] OR "neuroglial cell tumor"[tw] OR "neuroglial cell tumors"[tw] OR "neuroglial cell neoplasm"[tw] OR "neuroglial cell neoplasms"[tw] OR "neuroglial cell cancer"[tw] OR "neuroglial cell cancers"[tw] OR "neuroglial cell carcinoma"[tw] OR "neuroglial cell carcinomas"[tw] OR "neuroglial cell malignancy"[tw] OR "neuroglial cell malignancies"[tw]) OR ("Brain Neoplasms"[Mesh] OR ((tumour*[ti] OR tumor*[ti]) AND ("brain"[ti] OR "brains"[ti] OR "cns"[ti] OR central nervous system*[ti] OR intracranial*[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR tumour of brain*[tw] OR tumor of brain*[tw] OR "tumours of brain"[tw] OR "tumors of brain"[tw] OR tumour of the brain*[tw] OR tumor of the brain*[tw] OR "tumours of the brain"[tw] OR "tumors of the brain"[tw] OR brain tumour*[tw] OR brain tumor*[tw] OR "tumour of cns"[tw] OR tumor of cns*[tw] OR "tumours of cns"[tw] OR "tumors of cns"[tw] OR tumour of the cns*[tw] OR tumor of the cns*[tw] OR "tumours of the cns"[tw] OR "tumors of the cns"[tw] OR cns tumour*[tw] OR cns tumor*[tw] OR "tumour of central nervous system"[tw] OR tumor of central nervous system*[tw] OR "tumours of central nervous system"[tw] OR "tumors of central nervous system"[tw] OR tumour of the central nervous system*[tw] OR tumor of the central nervous system*[tw] OR "tumours of the central nervous system"[tw] OR "tumors of the central nervous system"[tw] OR central nervous system tumour*[tw] OR central nervous system tumor*[tw] OR intracranial tumour*[tw] OR intracranial tumor*[tw] OR cerebral tumour*[tw] OR cerebral tumor*[tw] OR intracerebral tumour*[tw] OR intracerebral tumor*[tw] OR ((neoplasm*[ti]) AND ("brain"[ti] OR "brains"[ti] OR "cns"[ti] OR central nervous system*[ti] OR intracranial*[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR neoplasm of brain*[tw] OR "neoplasms of brain"[tw] OR neoplasm of the brain*[tw] OR "neoplasms of the brain"[tw] OR brain neoplasm*[tw] OR neoplasm of cns*[tw] OR "neoplasms of cns"[tw] OR neoplasm of the cns*[tw] OR "neoplasms of the cns"[tw] OR cns neoplasm*[tw] OR "neoplasm of central nervous system"[tw] OR "neoplasms of central nervous system"[tw] OR neoplasm of the central nervous system*[tw] OR "neoplasms of the central nervous system"[tw] OR central nervous system neoplasm*[tw] OR intracranial neoplasm*[tw] OR cerebral neoplasm*[tw] OR intracerebral neoplasm*[tw] OR ((cancer*[ti]) AND ("brain"[ti] OR "brains"[ti] OR "cns"[ti] OR central nervous system*[ti] OR intracranial*[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR cancer of brain*[tw] OR "cancers of brain"[tw] OR cancer of the brain*[tw] OR "cancers of the brain"[tw] OR brain cancer*[tw] OR "cancer of cns"[tw] OR "cancers of cns"[tw] OR "cancer of the cns"[tw] OR "cancers of the cns"[tw] OR cns cancer*[tw] OR "cancer of central nervous system"[tw] OR "cancers of central nervous system"[tw] OR cancer of the central nervous system*[tw] OR "cancers of the central nervous system"[tw] OR central nervous system cancer*[tw] OR intracranial cancer*[tw] OR cerebral cancer*[tw] OR "intracerebral cancer"[tw] OR "intracerebral cancers"[tw] OR ((carcinoma*[ti]) AND ("brain"[ti] OR "brains"[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR "carcinoma of brain"[tw] OR "carcinomas of brain"[tw] OR "carcinoma of the brain"[tw] OR "carcinomas of the brain"[tw] OR brain carcinoma*[tw] OR cerebral carcinoma*[tw] OR "intracerebral carcinoma"[tw] OR "intracerebral carcinomas"[tw] OR ((malignan*[ti]) AND (intracranial*[ti] OR cerebral*[ti] OR intracerebral*[ti] OR glial*[ti] OR neuroglia*[ti])) OR cns malignan*[tw] OR central nervous system malignan*[tw] OR intracranial malignan*[tw] OR cerebral malignan*[tw] OR intracerebral malignan*[tw])) AND ("Epilepsy"[Mesh] OR epilep*[tiab] OR seizure*[tiab] OR seisure*[tiab] OR epilep*[ta] OR seizure*[ta] OR convulsi*[tiab] OR "aura"[tiab] OR aura'*[tiab] OR auras*[tiab] OR "Anticonvulsants"[Mesh] OR anticonvul*[tiab] OR anti-convul*[tiab] OR antiepilep*[tiab] OR anti-epilep*[tiab] OR "aed"[ti] OR aed'*[ti] OR aeds*[ti] OR "Carbamazepine"[Mesh] OR carbamazepin*[tiab] OR carba-mazepin*[tiab] OR tegretol*[tiab] OR "Clonazepam"[Mesh] OR clonazepam*[tiab] OR "gabapentin" [Supplementary Concept] OR gabapentin*[tiab] OR gaba-pentin*[tiab] OR "lacosamide" [Supplementary Concept] OR lacosamid*[tiab] OR "lamotrigine" [Supplementary Concept] OR lamotrigin*[tiab] OR lamo-trigin*[tiab] OR "oxcarbazepine" [Supplementary Concept] OR oxcarbazepin*[tiab] OR "Phenytoin"[Mesh] OR phenytoin*[tiab] OR fenytoin*[tiab] OR "Pregabalin"[Mesh] OR pregabalin*[tiab] OR "topiramate" [Supplementary Concept] OR topiramat*[tiab] OR "Valproic Acid"[Mesh] OR (valproic*[ti] AND acid*[ti]) OR valproic acid*[tiab] OR depakin*[tiab] OR "zonisamide" [Supplementary Concept] OR zonisamid*[tiab] OR "etiracetam" [Supplementary Concept] OR etiracetam*[tiab] OR levetiracetam*[tiab] OR keppra*[tiab] OR "perampanel" [Supplementary Concept] OR perampanel*[tiab] OR "clobazam" [Supplementary Concept] OR clobazam*[tiab] OR "Phenobarbital"[Mesh] OR phenobarbital*[tiab] OR pheno-barbital*[tiab] OR fenobarbital*[tiab] OR feno-barbital*[tiab] OR phenylbarbital*[tiab] OR phenyl-barbital*[tiab] OR fenylbarbital*[tiab] OR fenyl-barbital*[tiab] OR phenylethylbarbitur*[tiab] OR phenyl-ethylbarbitur*[tiab] OR phenyl-ethyl-barbitur*[tiab] OR phenylethyl-barbitur*[tiab] OR fenylethylbarbitur*[tiab] OR fenyl-ethylbarbitur*[tiab] OR fenyl-ethyl-barbitur*[tiab] OR fenylethyl-barbitur*[tiab] OR phenemal*[tiab] OR phene-mal*[tiab] OR fenemal*[tiab] OR fene-mal*[tiab] OR phenobarbiton*[tiab] OR pheno-barbiton*[tiab] OR fenobarbiton*[tiab] OR feno-barbiton*[tiab] OR hystep*[tiab] OR gardenal*[tiab]) AND ("Treatment Outcome"[Mesh] OR outcome*[tiab] OR effective*[tiab] OR efficac*[tiab] OR treatment fail*[tiab] OR freedom*[tiab] OR seizure free*[tiab] OR seizure reduc*[tiab] OR seizure decreas*[tiab] OR "seizure decline"[tiab] OR seizure control*[tiab] OR seizure duration*[tiab] OR seizure type*[tiab] OR seizure frequen*[tiab] OR seizure respon*[tiab] OR retention rat*[tiab] OR engel scale*[tiab] OR international league against epilep*[tiab] OR (international*[ti] AND league*[ti] AND against*[ti] AND epilep*[ti]) OR "ilae"[tiab] OR ilae'*[tiab]) AND english[lang]) NOT ((("Adolescent"[Mesh] OR "Child"[Mesh] OR "Infant"[Mesh]) NOT "Adult"[Mesh]) OR ("Animals"[Mesh] NOT "Humans"[Mesh]) OR "Review" [Publication Type] OR "Case Reports" [Publication Type] OR "Comment" [Publication Type] OR "Editorial" [Publication Type])

Date	Database	Strategy
01-06-2020	MEDLINE (OVID-version)	(((exp GLIOMA/ OR glioma*.ti,ab,kf. OR neuroglioma*.ti,ab,kf. OR xanthoastrocytoma*.ti,ab,kf. OR xantoastrocytoma*.ti,ab,kf. OR astrocytoma*.ti,ab,kf. OR astro-cytoma*.ti,ab,kf. OR astroglioma*.ti,ab,kf. OR astro-glioma*.ti,ab,kf. OR oligoastrocytoma*.ti,ab,kf. OR oligoastro-cytoma*.ti,ab,kf. OR glioblastom*.ti,ab,kf. OR glio-blastom*.ti,ab,kf. OR oligodendroglioma*.ti,ab,kf. OR oligo-dendroglioma*.ti,ab,kf. OR oligoden-droglioma*.ti,ab,kf. OR oligodendroblastoma*.ti,ab,kf. OR oligo-dendro-blastoma*.ti,ab,kf. OR oligo-dendroblastoma*.ti,ab,kf. OR oligoden-droblastoma*.ti,ab,kf. OR oligodendro-blastoma*.ti,ab,kf. OR brain malign*.ti,ab,kf. OR malignant primary brain*.ti,ab,kf. OR primary malignant brain*.ti,ab,kf. OR malignant brain*.ti,ab,kf. OR glial tumour*.ti,ab,kf. OR glial tumor*.ti,ab,kf. OR glial neoplasm*.ti,ab,kf. OR glial cancer*.ti,ab,kf. OR glial carcinoma*.ti,ab,kf. OR glial carcinoma*.ti,ab,kf. OR glial malignan*.ti,ab,kf. OR glial cell tumour*.ti,ab,kf. OR glial cell tumor*.ti,ab,kf. OR glial cell neoplasm*.ti,ab,kf. OR glial cell cancer*.ti,ab,kf. OR glial cell carcinoma*.ti,ab,kf. OR glial cell malignan*.ti,ab,kf. OR neuroglial tumour*.ti,ab,kf. OR neuroglial tumor*.ti,ab,kf. OR neuroglial neoplasm*.ti,ab,kf. OR neuroglial cancer*.ti,ab,kf. OR neuroglial carcinoma*.ti,ab,kf. OR neuroglial malignan*.ti,ab,kf. OR neuroglial cell tumour*.ti,ab,kf. OR neuroglial cell tumor*.ti,ab,kf. OR neuroglial cell neoplasm*.ti,ab,kf. OR neuroglial cell cancer*.ti,ab,kf. OR neuroglial cell carcinoma*.ti,ab,kf. OR neuroglial cell malignan*.ti,ab,kf.) OR (exp Brain Neoplasms/ OR ((tumour*.ti. OR tumor*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR tumour o? brain*.ti,ab,kf. OR tumor o? brain*.ti,ab,kf. OR tumours o? brain*.ti,ab,kf. OR tumors o? brain*.ti,ab,kf. OR tumour o? the brain*.ti,ab,kf. OR tumor o? the brain*.ti,ab,kf. OR tumours o? the brain*.ti,ab,kf. OR tumors o? the brain*.ti,ab,kf. OR brain tumour*.ti,ab,kf. OR brain tumor*.ti,ab,kf. OR tumour o? cns*.ti,ab,kf. OR tumor o? cns*.ti,ab,kf. OR tumours o? cns.ti,ab,kf. OR tumors o? cns*.ti,ab,kf. OR tumour o? the cns*.ti,ab,kf. OR tumor o? the cns*.ti,ab,kf. OR tumours o? the cns*.ti,ab,kf. OR tumors o? the cns*.ti,ab,kf. OR cns tumour*.ti,ab,kf. OR cns tumor*.ti,ab,kf. OR tumour o? central nervous system*.ti,ab,kf. OR tumor o? central nervous system*.ti,ab,kf. OR tumours o? central nervous system*.ti,ab,kf. OR tumors o? central nervous system*.ti,ab,kf. OR tumour o? the central nervous system*.ti,ab,kf. OR tumor o? the central nervous system*.ti,ab,kf. OR tumours o? the central nervous system*.ti,ab,kf. OR tumors o? the central nervous system*.ti,ab,kf. OR central nervous system tumour*.ti,ab,kf. OR central nervous system tumor*.ti,ab,kf. OR intracranial tumour*.ti,ab,kf. OR intracranial tumor*.ti,ab,kf. OR cerebral tumour*.ti,ab,kf. OR cerebral tumor*.ti,ab,kf. OR intracerebral tumour*.ti,ab,kf. OR intracerebral tumor*.ti,ab,kf. OR ((neoplasm*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR neoplasm o? brain*.ti,ab,kf. OR neoplasms o? brain*.ti,ab,kf. OR neoplasm o? the brain*.ti,ab,kf. OR neoplasms o? the brain*.ti,ab,kf. OR brain neoplasm*.ti,ab,kf. OR neoplasm o? cns*.ti,ab,kf. OR neoplasms o? cns*.ti,ab,kf. OR neoplasm o? the cns*.ti,ab,kf. OR neoplasms o? the cns*.ti,ab,kf. OR cns neoplasm*.ti,ab,kf. OR neoplasm o? central nervous system*.ti,ab,kf. OR neoplasms o? central nervous system*.ti,ab,kf. OR neoplasm o? the central nervous system*.ti,ab,kf. OR neoplasms o? the central nervous system*.ti,ab,kf. OR central nervous system neoplasm*.ti,ab,kf. OR intracranial neoplasm*.ti,ab,kf. OR cerebral neoplasm*.ti,ab,kf. OR intracerebral neoplasm*.ti,ab,kf. OR ((cancer*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR cancer o? brain*.ti,ab,kf. OR cancers o? brain*.ti,ab,kf. OR cancer o? the brain*.ti,ab,kf. OR cancers o? the brain*.ti,ab,kf. OR brain cancer*.ti,ab,kf. OR cancer o? cns*.ti,ab,kf. OR cancers o? cns*.ti,ab,kf. OR cancer o? the cns*.ti,ab,kf. OR cancers o? the cns*.ti,ab,kf. OR cns cancer*.ti,ab,kf. OR cancer o? central nervous system*.ti,ab,kf. OR cancers o? central nervous system*.ti,ab,kf. OR cancer o? the central nervous system*.ti,ab,kf. OR cancers o? the central nervous system*.ti,ab,kf. OR central nervous system cancer*.ti,ab,kf. OR intracranial cancer*.ti,ab,kf. OR cerebral cancer*.ti,ab,kf. OR intracerebral cancer*.ti,ab,kf. OR ((carcinoma*.ti.) AND ("brain".ti. OR "brains".ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR carcinoma o? brain*.ti,ab,kf. OR carcinomas o? brain*.ti,ab,kf. OR carcinoma o? the brain*.ti,ab,kf. OR carcinomas o? the brain*.ti,ab,kf. OR brain carcinoma*.ti,ab,kf. OR cerebral carcinoma*.ti,ab,kf. OR intracerebral carcinoma*.ti,ab,kf. OR ((malignan*.ti.) AND (intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR cns malignan*.ti,ab,kf. OR central nervous system malignan*.ti,ab,kf. OR intracranial malignan*.ti,ab,kf. OR cerebral malignan*.ti,ab,kf. OR intracerebral malignan*.ti,ab,kf.)) AND (exp EPILEPSY/ OR epilep*.ab,ti. OR seizure*.ab,ti. OR seisure*.ab,ti. OR epilep*.jn. OR seizure*.jn. OR convulsi*.ab,ti. OR "aura".ab,ti. OR aura'*.ab,ti. OR auras*.ab,ti. OR exp Anticonvulsants/ OR anticonvul*.ab,ti. OR anti-convul*.ab,ti. OR antiepilep*.ab,ti. OR anti-epilep*.ab,ti. OR "aed".ti. OR aed'*.ti. OR aeds*.ti. OR exp CARBAMAZEPINE/ OR carbamazepin*.ab,ti. OR carba-mazepin*.ab,ti. OR tegretol*.ab,ti. OR exp CLONAZEPAM/ OR clonazepam*.ab,ti. OR gabapentin.nm. OR gabapentin*.ab,ti. OR gaba-pentin*.ab,ti. OR lacosamide.nm. OR lacosamid*.ab,ti. OR lamotrigine.nm. OR lamotrigin*.ab,ti. OR lamo-trigin*.ab,ti. OR oxcarbazepine.nm. OR oxcarbazepin*.ab,ti. OR exp PHENYTOIN/ OR phenytoin*.ab,ti. OR fenytoin*.ab,ti. OR exp PREGABALIN/ OR pregabalin*.ab,ti. OR topiramate.nm. OR topiramat*.ab,ti. OR exp Valproic Acid/ OR (valproic*.ti. AND acid*.ti.) OR (valproic*.ab,ti. adj3 acid*.ab,ti.) OR depakin*.ab,ti. OR zonisamide.nm. OR zonisamid*.ab,ti. OR etiracetam.nm. OR etiracetam*.ab,ti. OR levetiracetam*.ab,ti. OR keppra*.ab,ti. OR perampanel.nm. OR perampanel*.ab,ti. OR clobazam.nm. OR clobazam*.ab,ti. OR exp PHENOBARBITAL/ OR phenobarbital*.ab,ti. OR pheno-barbital*.ab,ti. OR fenobarbital*.ab,ti. OR feno-barbital*.ab,ti. OR phenylbarbital*.ab,ti. OR phenyl-barbital*.ab,ti. OR fenylbarbital*.ab,ti. OR fenyl-barbital*.ab,ti. OR phenylethylbarbitur*.ab,ti. OR phenyl-ethylbarbitur*.ab,ti. OR phenyl-ethyl-barbitur*.ab,ti. OR phenylethyl-barbitur*.ab,ti. OR fenylethylbarbitur*.ab,ti. OR fenyl-ethylbarbitur*.ab,ti. OR fenyl-ethyl-barbitur*.ab,ti. OR fenylethyl-barbitur*.ab,ti. OR phenemal*.ab,ti. OR phene-mal*.ab,ti. OR fenemal*.ab,ti. OR fene-mal*.ab,ti. OR phenobarbiton*.ab,ti. OR pheno-barbiton*.ab,ti. OR fenobarbiton*.ab,ti. OR feno-barbiton*.ab,ti. OR hystep*.ab,ti. OR gardenal*.ab,ti.) AND (exp Treatment Outcome/ OR outcome*.ab,ti. OR effective*.ab,ti. OR efficac*.ab,ti. OR treatment fail*.ab,ti. OR freedom*.ab,ti. OR seizure free*.ab,ti. OR seizure reduc*.ab,ti. OR seizure decreas*.ab,ti. OR seizure declin*.ab,ti. OR seizure control*.ab,ti. OR seizure duration*.ab,ti. OR seizure type*.ab,ti. OR seizure frequen*.ab,ti. OR seizure respon*.ab,ti. OR retention rat*.ab,ti. OR engel scale*.ab,ti. OR international league against epilep*.ab,ti. OR (international*.ti. AND league*.ti. AND against*.ti. AND epilep*.ti.) OR (international*.ab,ti. ADJ3 league*.ab,ti. ADJ3 against*.ab,ti. ADJ3 epilep*.ab,ti.) OR "ilae".ab,ti. OR ilae'*.ab,ti.) AND english.lg.) NOT (((exp ADOLESCENT/ OR exp CHILD/ OR exp INFANT/) NOT exp ADULT/) OR (exp Animals/ NOT exp Humans/) OR review.pt. OR case reports.pt. OR comment.pt. OR editorial.pt.)

Date	Database	Strategy
01-06-2020	EMBASE (OVID-version)	(((exp glioma/ OR glioma*.ti,ab,kw. OR neuroglioma*.ti,ab,kw. OR xanthoastrocytoma*.ti,ab,kw. OR xantoastrocytoma*.ti,ab,kw. OR astrocytoma*.ti,ab,kw. OR astro-cytoma*.ti,ab,kw. OR astroglioma*.ti,ab,kw. OR astro-glioma*.ti,ab,kw. OR oligoastrocytoma*.ti,ab,kw. OR oligoastro-cytoma*.ti,ab,kw. OR glioblastom*.ti,ab,kw. OR glio-blastom*.ti,ab,kw. OR oligodendroglioma*.ti,ab,kw. OR oligo-dendroglioma*.ti,ab,kw. OR oligoden-droglioma*.ti,ab,kw. OR oligodendroblastoma*.ti,ab,kw. OR oligo-dendro-blastoma*.ti,ab,kw. OR oligo-dendroblastoma*.ti,ab,kw. OR oligoden-droblastoma*.ti,ab,kw. OR oligodendro-blastoma*.ti,ab,kw. OR brain malign*.ti,ab,kw. OR malignant primary brain*.ti,ab,kw. OR primary malignant brain*.ti,ab,kw. OR malignant brain*.ti,ab,kw. OR glial tumour*.ti,ab,kw. OR glial tumor*.ti,ab,kw. OR glial neoplasm*.ti,ab,kw. OR glial cancer*.ti,ab,kw. OR "glial carcinoma".ti,ab,kw. OR "glial carcinomas".ti,ab,kw. OR glial malignan*.ti,ab,kw. OR glial cell tumour*.ti,ab,kw. OR glial cell tumor*.ti,ab,kw. OR glial cell neoplasm*.ti,ab,kw. OR "glial cell cancer".ti,ab,kw. OR "glial cell cancers".ti,ab,kw. OR "glial cell carcinoma".ti,ab,kw. OR "glial cell carcinomas".ti,ab,kw. OR "glial cell malignancy".ti,ab,kw. OR "glial cell malignancies".ti,ab,kw. OR neuroglial tumour*.ti,ab,kw. OR neuroglial tumor*.ti,ab,kw. OR neuroglial neoplasm*.ti,ab,kw. OR "neuroglial cancer".ti,ab,kw. OR "neuroglial cancers".ti,ab,kw. OR "neuroglial carcinoma".ti,ab,kw. OR "neuroglial carcinomas".ti,ab,kw. OR "neuroglial malignancy".ti,ab,kw. OR "neuroglial malignancies".ti,ab,kw. OR "neuroglial cell tumour".ti,ab,kw. OR "neuroglial cell tumours".ti,ab,kw. OR "neuroglial cell tumor".ti,ab,kw. OR "neuroglial cell tumors".ti,ab,kw. OR "neuroglial cell neoplasm".ti,ab,kw. OR "neuroglial cell neoplasms".ti,ab,kw. OR "neuroglial cell cancer".ti,ab,kw. OR "neuroglial cell cancers".ti,ab,kw. OR "neuroglial cell carcinoma".ti,ab,kw. OR "neuroglial cell carcinomas".ti,ab,kw. OR "neuroglial cell malignancy".ti,ab,kw. OR "neuroglial cell malignancies".ti,ab,kw.) OR (exp brain tumor/ OR ((tumour*.ti. OR tumor*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR tumour of brain*.ti,ab,kw. OR tumor of brain*.ti,ab,kw. OR "tumours of brain".ti,ab,kw. OR "tumors of brain".ti,ab,kw. OR tumour of the brain*.ti,ab,kw. OR tumor of the brain*.ti,ab,kw. OR "tumours of the brain".ti,ab,kw. OR "tumors of the brain".ti,ab,kw. OR brain tumour*.ti,ab,kw. OR brain tumor*.ti,ab,kw. OR "tumour of cns".ti,ab,kw. OR tumor of cns*.ti,ab,kw. OR "tumours of cns".ti,ab,kw. OR "tumors of cns".ti,ab,kw. OR tumour of the cns*.ti,ab,kw. OR tumor of the cns*.ti,ab,kw. OR "tumours of the cns".ti,ab,kw. OR "tumors of the cns".ti,ab,kw. OR cns tumour*.ti,ab,kw. OR cns tumor*.ti,ab,kw. OR "tumour of central nervous system".ti,ab,kw. OR tumor of central nervous system*.ti,ab,kw. OR "tumours of central nervous system".ti,ab,kw. OR "tumors of central nervous system".ti,ab,kw. OR tumour of the central nervous system*.ti,ab,kw. OR tumor of the central nervous system*.ti,ab,kw. OR "tumours of the central nervous system".ti,ab,kw. OR "tumors of the central nervous system".ti,ab,kw. OR central nervous system tumour*.ti,ab,kw. OR central nervous system tumor*.ti,ab,kw. OR intracranial tumour*.ti,ab,kw. OR intracranial tumor*.ti,ab,kw. OR cerebral tumour*.ti,ab,kw. OR cerebral tumor*.ti,ab,kw. OR intracerebral tumour*.ti,ab,kw. OR intracerebral tumor*.ti,ab,kw. OR ((neoplasm*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR neoplasm of brain*.ti,ab,kw. OR "neoplasms of brain".ti,ab,kw. OR neoplasm of the brain*.ti,ab,kw. OR "neoplasms of the brain".ti,ab,kw. OR brain neoplasm*.ti,ab,kw. OR neoplasm of cns*.ti,ab,kw. OR "neoplasms of cns".ti,ab,kw. OR neoplasm of the cns*.ti,ab,kw. OR "neoplasms of the cns".ti,ab,kw. OR cns neoplasm*.ti,ab,kw. OR "neoplasm of central nervous system".ti,ab,kw. OR "neoplasms of central nervous system".ti,ab,kw. OR neoplasm of the central nervous system*.ti,ab,kw. OR "neoplasms of the central nervous system".ti,ab,kw. OR central nervous system neoplasm*.ti,ab,kw. OR intracranial neoplasm*.ti,ab,kw. OR cerebral neoplasm*.ti,ab,kw. OR intracerebral neoplasm*.ti,ab,kw. OR ((cancer*.ti.) AND ("brain".ti. OR "brains".ti. OR "cns".ti. OR central nervous system*.ti. OR intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR cancer of brain*.ti,ab,kw. OR "cancers of brain".ti,ab,kw. OR cancer of the brain*.ti,ab,kw. OR "cancers of the brain".ti,ab,kw. OR brain cancer*.ti,ab,kw. OR "cancer of cns".ti,ab,kw. OR "cancers of cns".ti,ab,kw. OR "cancer of the cns".ti,ab,kw. OR "cancers of the cns".ti,ab,kw. OR cns cancer*.ti,ab,kw. OR "cancer of central nervous system".ti,ab,kw. OR "cancers of central nervous system".ti,ab,kw. OR cancer of the central nervous system*.ti,ab,kw. OR "cancers of the central nervous system".ti,ab,kw. OR central nervous system cancer*.ti,ab,kw. OR intracranial cancer*.ti,ab,kw. OR cerebral cancer*.ti,ab,kw. OR "intracerebral cancer".ti,ab,kw. OR "intracerebral cancers".ti,ab,kw. OR ((carcinoma*.ti.) AND ("brain".ti. OR "brains".ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR "carcinoma of brain".ti,ab,kw. OR "carcinomas of brain".ti,ab,kw. OR "carcinoma of the brain".ti,ab,kw. OR "carcinomas of the brain".ti,ab,kw. OR brain carcinoma*.ti,ab,kw. OR cerebral carcinoma*.ti,ab,kw. OR "intracerebral carcinoma".ti,ab,kw. OR "intracerebral carcinomas".ti,ab,kw. OR ((malignan*.ti.) AND (intracranial*.ti. OR cerebral*.ti. OR intracerebral*.ti. OR glial*.ti. OR neuroglia*.ti.)) OR cns malignan*.ti,ab,kw. OR central nervous system malignan*.ti,ab,kw. OR intracranial malignan*.ti,ab,kw. OR cerebral malignan*.ti,ab,kw. OR intracerebral malignan*.ti,ab,kw.)) AND (exp epilepsy/ OR epilep*.ab,ti. OR seizure*.ab,ti. OR seisure*.ab,ti. OR epilep*.jn. OR seizure*.jn. OR convulsi*.ab,ti. OR "aura".ab,ti. OR aura'*.ab,ti. OR auras*.ab,ti. OR exp anticonvulsive agent/ OR anticonvul*.ab,ti. OR anti-convul*.ab,ti. OR antiepilep*.ab,ti. OR anti-epilep*.ab,ti. OR "aed".ti. OR aed'*.ti. OR aeds*.ti. OR exp carbamazepine/ OR carbamazepin*.ab,ti. OR carba-mazepin*.ab,ti. OR tegretol*.ab,ti. OR exp clonazepam/ OR clonazepam*.ab,ti. OR exp gabapentin/ OR gabapentin*.ab,ti. OR gaba-pentin*.ab,ti. OR exp lacosamide/ OR lacosamid*.ab,ti. OR exp lamotrigine/ OR lamotrigin*.ab,ti. OR lamo-trigin*.ab,ti. OR exp oxcarbazepine/ OR oxcarbazepin*.ab,ti. OR exp phenytoin/ OR phenytoin*.ab,ti. OR fenytoin*.ab,ti. OR exp pregabalin/ OR pregabalin*.ab,ti. OR exp topiramate/ OR topiramat*.ab,ti. OR exp valproic acid/ OR (valproic*.ti. AND acid*.ti.) OR (valproic*.ab,ti. adj3 acid*.ab,ti.) OR depakin*.ab,ti. OR exp zonisamide/ OR zonisamid*.ab,ti. OR exp etiracetam/ OR etiracetam*.ab,ti. OR levetiracetam*.ab,ti. OR keppra*.ab,ti. OR exp perampanel/ OR perampanel*.ab,ti. OR exp clobazam/ OR clobazam*.ab,ti. OR exp phenobarbital/ OR phenobarbital*.ab,ti. OR pheno-barbital*.ab,ti. OR fenobarbital*.ab,ti. OR feno-barbital*.ab,ti. OR phenylbarbital*.ab,ti. OR phenyl-barbital*.ab,ti. OR fenylbarbital*.ab,ti. OR fenyl-barbital*.ab,ti. OR phenylethylbarbitur*.ab,ti. OR phenyl-ethylbarbitur*.ab,ti. OR phenyl-ethyl-barbitur*.ab,ti. OR phenylethyl-barbitur*.ab,ti. OR fenylethylbarbitur*.ab,ti. OR fenyl-ethylbarbitur*.ab,ti. OR fenyl-ethyl-barbitur*.ab,ti. OR fenylethyl-barbitur*.ab,ti. OR phenemal*.ab,ti. OR phene-mal*.ab,ti. OR fenemal*.ab,ti. OR fene-mal*.ab,ti. OR phenobarbiton*.ab,ti. OR pheno-barbiton*.ab,ti. OR fenobarbiton*.ab,ti. OR feno-barbiton*.ab,ti. OR hystep*.ab,ti. OR gardenal*.ab,ti.) AND (exp treatment outcome/ OR outcome*.ab,ti. OR effective*.ab,ti. OR efficac*.ab,ti. OR treatment fail*.ab,ti. OR freedom*.ab,ti. OR seizure free*.ab,ti. OR seizure reduc*.ab,ti. OR seizure decreas*.ab,ti. OR seizure declin*.ab,ti. OR seizure control*.ab,ti. OR seizure duration*.ab,ti. OR seizure type*.ab,ti. OR seizure frequen*.ab,ti. OR seizure respon*.ab,ti. OR retention rat*.ab,ti. OR engel scale*.ab,ti. OR international league against epilep*.ab,ti. OR (international*.ti. AND league*.ti. AND against*.ti. AND epilep*.ti.) OR (international*.ab,ti. ADJ3 league*.ab,ti. ADJ3 against*.ab,ti. ADJ3 epilep*.ab,ti.) OR "ilae".ab,ti. OR ilae'*.ab,ti.) AND english.lg.) NOT (((exp embryo/ OR exp fetus/ OR exp juvenile/) NOT exp adult/) OR ((exp animal/ OR exp animal experiment/ OR exp nonhuman/) NOT exp human/) OR "review".pt. OR exp case report/ OR editorial.pt. OR conference abstract.pt.)

Date	Database	Strategy
01-06-2020	Web of Science	(TS=(glioma* OR neuroglioma* OR xanthoastrocytoma* OR xantoastrocytoma* OR astrocytoma* OR astro-cytoma* OR astroglioma* OR astro-glioma* OR oligoastrocytoma* OR oligoastro-cytoma* OR glioblastom* OR glio-blastom* OR oligodendroglioma* OR oligo-dendroglioma* OR oligoden-droglioma* OR oligodendroblastoma* OR oligo-dendro-blastoma* OR oligo-dendroblastoma* OR oligoden-droblastoma* OR oligodendro-blastoma* OR brain-malign* OR malignant-primary-brain* OR primary-malignant-brain* OR malignant-brain* OR glial-tumour* OR glial-tumor* OR glial-neoplasm* OR glial-cancer* OR glial-carcinoma* OR glial-malignan* OR glial-cell-tumour* OR glial-cell-tumor* OR glial-cell-neoplasm* OR glial-cell-cancer* OR glial-cell-carcinoma* OR glial-cell-malignan* OR neuroglial-tumour* OR neuroglial-tumor* OR neuroglial-neoplasm* OR neuroglial-cancer* OR neuroglial-carcinoma* OR neuroglial-malignan* OR neuroglial-cell-tumour* OR neuroglial-cell-tumor* OR neuroglial-cell-neoplasm* OR neuroglial-cell-cancer* OR neuroglial-cell-carcinoma* OR neuroglial-cell-malignan*) OR TS=(tumo$r*-of-brain* OR tumo$r*-of-the-brain* OR brain-tumo$r* OR tumo$r*-of-cns* OR tumo$r*-of-the-cns* OR cns-tumo$r* OR tumo$r*-of-central-nervous-system* OR tumo$r*-of-the-central-nervous-system* OR central-nervous-system-tumo$r* OR intracranial-tumo$r* OR cerebral-tumo$r* OR intracerebral-tumo$r* OR neoplasm*-of-brain* OR neoplasm*-of-the-brain* OR brain-neoplasm* OR neoplasm*-of-cns* OR neoplasm*-of-the-cns* OR cns-neoplasm* OR neoplasm*-of-central-nervous-system* OR neoplasm*-of-the-central-nervous-system* OR central-nervous-system-neoplasm* OR intracranial-neoplasm* OR cerebral-neoplasm* OR intracerebral-neoplasm* OR cancer*-of-brain* OR cancer*-of-the-brain* OR brain-cancer* OR cancer*-of-cns OR cancer*-of-the-cns OR cns-cancer* OR cancer*-of-central-nervous-system* OR cancer*-of-the-central-nervous-system* OR central-nervous-system-cancer* OR intracranial-cancer* OR cerebral-cancer* OR intracerebral-cancer* OR carcinoma*-of-brain* OR carcinoma*-of-the-brain* OR brain-carcinoma* OR cerebral-carcinoma* OR intracerebral-carcinoma* OR cns-malignan* OR central-nervous-system-malignan* OR intracranial-malignan* OR cerebral-malignan* OR intracerebral-malignan*) OR TI=((tumo$r*) AND ("brain" OR "brains" OR "cns" OR central-nervous-system* OR intracranial* OR cerebral* OR intracerebral* OR glial* OR neuroglia*)) OR TI=((neoplasm*) AND ("brain" OR "brains" OR "cns" OR central-nervous-system* OR intracranial* OR cerebral* OR intracerebral* OR glial* OR neuroglia*)) OR TI=((cancer*) AND ("brain" OR "brains" OR "cns" OR central-nervous-system* OR intracranial* OR cerebral* OR intracerebral* OR glial* OR neuroglia*)) OR TI=((carcinoma*) AND ("brain" OR "brains" OR cerebral* OR intracerebral* OR glial* OR neuroglia*)) OR TI=((malignan*) AND (intracranial* OR cerebral* OR intracerebral* OR glial* OR neuroglia*))) AND (TS=(epilep* OR seizure* OR seisure* OR convulsi* OR "aura" OR aura'* OR auras*) OR SO=(epilep* OR seizure*) OR TS=(anticonvul* OR anti-convul* OR antiepilep* OR anti-epilep* OR carbamazepin* OR carba-mazepin* OR tegretol* OR clonazepam* OR gabapentin* OR gaba-pentin* OR lacosamid* OR lamotrigin* OR lamo-trigin* OR oxcarbazepin* OR phenytoin* OR fenytoin* OR pregabalin* OR topiramat* OR (valproic* NEAR/3 acid*) OR depakin* OR zonisamid* OR etiracetam* OR levetiracetam* OR keppra* OR perampanel* OR clobazam* OR phenobarbital* OR pheno-barbital* OR fenobarbital* OR feno-barbital* OR phenylbarbital* OR phenyl-barbital* OR fenylbarbital* OR fenyl-barbital* OR phenylethylbarbitur* OR phenyl-ethylbarbitur* OR phenyl-ethyl-barbitur* OR phenylethyl-barbitur* OR fenylethylbarbitur* OR fenyl-ethylbarbitur* OR fenyl-ethyl-barbitur* OR fenylethyl-barbitur* OR phenemal* OR phene-mal* OR fenemal* OR fene-mal* OR phenobarbiton* OR pheno-barbiton* OR fenobarbiton* OR feno-barbiton* OR hystep* OR gardenal*) OR TI=("aed" OR aed'* OR aeds* OR (valproic* AND acid*))) AND (TS=(outcome* OR effective* OR efficac* OR treatment-fail* OR freedom* OR seizure-free* OR seizure-reduc* OR seizure-decreas* OR seizure-decline* OR seizure-control* OR seizure-duration* OR seizure-type* OR seizure-frequen* OR seizure-respon* OR retention-rat* OR engel-scale* OR (international* NEAR/3 league* NEAR/3 against* NEAR/3 epilep*)) OR TI=((international* AND league* AND against* AND epilep*) OR "ilae" OR ilae'*)) AND LA=english

Date	Database	Strategy
01-06-2020	Cochrane Library	((glioma* OR neuroglioma* OR xanthoastrocytoma* OR xantoastrocytoma* OR astrocytoma* OR astro NEXT cytoma* OR astroglioma* OR astro NEXT glioma* OR oligoastrocytoma* OR oligoastro NEXT cytoma* OR glioblastom* OR glio NEXT blastom* OR oligodendroglioma* OR oligo NEXT dendroglioma* OR oligoden NEXT drogliomа* OR oligodendroblastoma* OR oligo NEXT dendro NEXT blastoma* OR oligo NEXT dendroblastoma* OR oligoden NEXT droblastoma* OR oligodendro NEXT blastoma* OR brain NEXT malign* OR malignant NEXT primary NEXT brain* OR primary NEXT malignant NEXT brain* OR malignant NEXT brain* OR glial NEXT tumour* OR glial NEXT tumor* OR glial NEXT neoplasm* OR glial NEXT cancer* OR glial NEXT carcinoma* OR glial NEXT malignan* OR glial NEXT cell NEXT tumour* OR glial NEXT cell NEXT tumor* OR glial NEXT cell NEXT neoplasm* OR glial NEXT cell NEXT cancer* OR glial NEXT cell NEXT carcinoma* OR glial NEXT cell NEXT malignan* OR neuroglial NEXT tumour* OR neuroglial NEXT tumor* 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glial* OR neuroglia*)):ti OR ((carcinoma*) AND ("brain" OR "brains" OR cerebral* OR intracerebral* OR glial* OR neuroglia*)):ti OR ((malignan*) AND (intracranial* OR cerebral* OR intracerebral* OR glial* OR neuroglia*)):ti) AND ((epilep* OR seizure* OR seisure* OR convulsi* OR "aura" OR aura'* OR auras*):ti,ab,kw OR (epilep* OR seizure*):so OR (anticonvul* OR anti NEXT convul* OR antiepilep* OR anti NEXT epilep* OR carbamazepin* OR carba NEXT mazepin* OR tegretol* OR clonazepam* OR gabapentin* OR gaba NEXT pentin* OR lacosamid* OR lamotrigin* OR lamo NEXT trigin* OR oxcarbazepin* OR phenytoin* OR fenytoin* OR pregabalin* OR topiramat* OR (valproic* NEAR/3 acid*) OR depakin* OR zonisamid* OR etiracetam* OR levetiracetam* OR keppra* OR perampanel* OR clobazam* OR phenobarbital* OR pheno NEXT barbital* OR fenobarbital* OR feno NEXT barbital* OR phenylbarbital* OR phenyl NEXT barbital* OR fenylbarbital* OR fenyl NEXT barbital* OR phenylethylbarbitur* OR phenyl NEXT ethylbarbitur* OR phenyl 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Supplementary Table 2. Efficacy of levetiracetam including all studies

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Levetiracetam (LEV)							
Bahr et al. (2012)[1]	Pros	N=30 (n=25)	GBM n=12; Grade III n=5; LGG n=5; MEN n=3; Unknown n=3 MET n=1; Other n=1;	LEV n=30		1 and 6 (after AED initiation)	1-Month seizure freedom LEV: 21/25=84% 1-Month treatment failure due to AEs (n=0), inefficacy (n=3), or unknown (n=0) LEV: 3/25=12% 6-Month seizure freedom LEV: 13/25=52% 6-Month treatment failure due to AEs (n=0), inefficacy (n=6), or unknown (n=1) LEV: 7/25=28%
Bech et al. (2018)[2]	Retro	N=282 (n=105)	GBM n=205; AA n=25; Other n=19; A=17; AODG n=9; ODG n=7	Vast majority LEV n=97		3 (after surgery)	1-Month seizure freedom AEDs: 80/97=82% 3-Month Seizure freedom AEDs: 66/97=68%
Berntsson et al. (2018)[3]	Retro case-control	N=4533 (n=1087)	GBM n=2772; AA n=529; OA/ ODG n=451; A n=373; AOA/ AODG n=275; Other n=133	LEV n=668; Other n=112; Unknown AED n=173	Other n=161	2 (before the interview)	Seizure freedom AEDs: 731/1087=67%
Breemen et al. (2009)[4]	Discussed under valproic acid						
Calatozzolo et al. (2012)[5]	Pros	N=35 (n=35)	GBM n=15; AA n=7; A n=6; OA n=4; ODG n=3	LEV n=12; Other: n=19	LEV+Other n=1; Other n=3	Median 12 (unspecified)	Seizure freedom LEV: 7/13=54%
Cardona et al. (2018)[6]	Pros	N=213 (n=136)	GBM n=213	LEV n=82; Other n=54		-	Treatment failure due to inefficacy LEV: 16/82=20%

Supplementary Table 2. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Casas Parera et al. (2019)[7]	Pros	N=82 (n=75), prophylactic n=20	GBM n=28; A n=22; ODG n=14; AA n=8; AODG n=7; Other n=3	LEV n=43; Other n=32		-	Seizure freedom (excl. prophylactic) LEV: 41/43=95% Treatment failure due to inefficacy (excl. prophylactic) LEV: 2/43=5%
Chonan et al. (2019)[8]	Discussed under perampanel						
De Groot et al. (2011)[9]	Pros clinical trial	N=35 (n=35)	GBM n=15; AODG n=6; AA n=4; A n=3; ODG n=3; AOA n=2 OA n=1	LEV n=35		6 (after AED initiation)	6-Month seizure freedom LEV: 21/35=59% 6-Month ≥50% Seizure reduction LEV: 26/35=74% 6-Month treatment failure due to AEs LEV: 1/35=3%
Dinapoli et al. (2009)[10]	Case series	N=18 (n=18)	GBM n=3; AA n=3; A n=3; OA n=3; ODG n=3; MEN n=2; Other n=1	LEV n=18		6 (after AED initiation)	6-Month seizure freedom LEV: 16/18=89% 6-Month ≥50% seizure reduction LEV: 18/18=100% 6-Month treatment failure due to AEs (n=0) or inefficacy (n=0) LEV=0/18=0%
Eseonu et al. (2018)[11]	Retro	N=81 (n=81), prophylactic n=36	Grade IV n=27; Grade II n=27; Grade III n=17; Other n=8; MET n= 2	LEV n=46	LEV+PHT n=30; LEV+Other n=5	6 (after surgery)	6-Month seizure freedom monotherapy (excl. prophylactic) LEV:15/25=60% 6-Month seizure freedom (excl. prophylactic) LEV+PHT(+/-Other): 18/20=90%
Feyissa et al. (2019)[12]	Retro	N=68 (n=59), prophylactic n=13	GBM n=31; AA n=16; ODG n=14; A n=6; AODG n=1	LEV n=48; Other n=11		Median 15 (after surgery)	Seizure freedom (excl. prophylactic) AEDs: 31/46=67%

Supplementary Table 2. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Haggiagi & Avila (2018)[13]	Retro	N=39 (n=39)	ODG n=39		Mono- (n=18) and polytherapy (n=21) LEV+/-Other n=26; Other n=13	Median n=12 temozolomide cycles (after temozolomide initiation)	≥50% Seizure reduction AEDs: 35/39=90%
Ius et al. (2020)[14]	Retro	N=155 (n=155)	A; n=111; ODG n=44	LEV n=96; CBZ n=22; PHT n=10	Other n=27	12 (after surgery)	12-Month seizure freedom: 110/155=71%
Kerkhof et al. (2013)[15]	Discussed under valproic acid						
Kerkhof et al. (2019)[16]	Pros	N=71 (n=71), AED withdrawal n=46	A/ODG/OA n=41; AA/ AODG/AOA n=30	LEV n=41; VPA n=16; Other n= 14		Median 20 (after AED initiation)	1-Month seizure freedom (excl. AED withdrawal) AEDs: 25/25=100% 3-Month seizure freedom (excl. AED withdrawal) AEDs: 25/25=100% 6-Month seizure freedom (excl. AED withdrawal) AEDs: 24/25=96% 9-Month seizure freedom (excl. AED withdrawal) AEDs: 24/25=96% 12-Month seizure freedom (excl. AED withdrawal) AEDs: 24/25=96%
Lim et al. (2009)[17]	RCT, unblinded	N=29 (n=29)	GBM n=9; AA n=4; A n=4; ODG n=2; AOA n=2; AODG n=1; Grade I n=1	LEV n=20; PHT n=9		6 (after AED initiation/ surgery)	6-Month seizure freedom LEV: 18/20=90% 6-Month treatment failure due to AEs (n=0), inefficacy (n=0), or unknown (n=5) LEV: 6/20=30%

Supplementary Table 2. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Maialetti et al. (2020)[18]	Pros	N=33 (n=33)	HGG n=14; LGG n=12; Other n=7	LEV n=10; Other n=11	LEV+Other n=9; Other n=3	6 (after rehabilitation)	6-Month seizure freedom AEDs: 26/33=79% 6-Month ≥50% Seizure reduction AEDs: 28/33=85%
Maschio et al. (2006)[19]	Pros clinical trial	N=19 (n=19)	GBM n=7; A n=6; AA n=5; MEN n=1		LEV+Other n=19	Median 20 (after AED initiation)	Seizure freedom last follow-up LEV: 9/19=47% 6-Month ≥50% seizure reduction LEV: 14/19=74% (ref. Maschio et al. 2017) Treatment failure due to AEs LEV: 0/19=0%
Maschio et al. (2011)[20]	Pros clinical trial	N=29 (n=29)	GBM n=9; AODG n=6; LGA n=5; AA n=4; MEN n=2; Other n=2; ODG n=1;	LEV n=29		12 (after AED initiation)	12-Month seizure freedom LEV: 21/29=72% 12-Month ≥50% Seizure reduction LEV: 28/29=97% 12-Month treatment failure due to AEs (n=1), inefficacy (n=2), or other (n=2) LEV: 5/29=17%
Maschio et al. (2017)[21]	Discussed under lacosamide						
Merrel et al. (2010)[22]	Pros	N=76 (n=76)	GBM n=49; LGG n=27	LEV n=51; PHT n=25		1 and minimum of 6 (after surgery)	Seizure freedom LEV: 24/51=47%; PHT: 10/25=40% 1-Month treatment failure due to AEs (n=1) and clinicians preference (n=0) LEV: 1/36=3%; due to AEs (n=5), or clinicians preference (n=11) PHT: 16/40=40%

Supplementary Table 2. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Michelucci et al. (2013)[23]	Pros	N=100 (n=97)	GBM n=52; AA n=15; ODG n=10; A n=9; AODG n=5; Other n=4; AOA n=3; Grade I n=2;	Mono- (n=64) and polytherapy (n=33): LEV n=63; OXC n=33; PHT n=16; CBZ n=10; Other n=8		6 (after surgery)	6-Month seizure freedom AEDs: 39/100=39%
Newton et al. (2006)[24]	Retro	N=41 (n=41)	AA n=13; GBM n=12; MET n=7; ODG n=5; LGG n=2; Other n=2	LEV n=8	LEV+Other n=33	1 (after AED initiation)	1-Month seizure freedom in gliomas LEV: 17/32=53% 1-Month ≥50% seizure reduction in gliomas LEV: 28/32=88% 1-Month treatment failure due to AEs LEV: 1/41=2%
Rahman et al. (2015)[25]	Pros	N=81 (n=55)	GBM n=27; ODG n=20; MEN n=13; A n=8; Grade I n=7; OA n=4; Other n=2	LEV n=21; Other n=11	LEV+Other n=9; Other n=14	6 (after AED initiation)	6-Month seizure freedom AEDs: 32/55=58%
Romoli et al. (2019)[26]	Pros	N=18 (n=18)	GBM n=8; ODG n=6; A n=3; OA n=1	LEV n=18		-	≥50% Seizure reduction LEV: 18/18=100%
Rosati et al. (2010)[27]	Pros clinical trial	N=176 (n=82)	GBM n=118; AA n=23; ODG n=13; A n=8; AODG n=7; AOA n=6; Grade I n=1	LEV n=82		Mean 13 (after AED initiation)	Seizure freedom LEV: 75/82=91% Treatment failure due to AEs (n=2) or inefficacy (n=7) LEV: 9/82=11%
Rossetti et al. (2014)[28]	Discussed under pregabaline						
Rudà et al. (2018)[29]	Discussed under lacosamide						

Supplementary Table 2. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Rudà et al. (2020)[30]	Discussed under lacosamide						
Saria et al. (2013)[31]	Discussed under lacosamide						
Solomons et al. (2019)[32]	Retro	N=74 (n=66)	ODG n=32; A n=26; OA n=7; Other n=9		Mono- and polytherapy: LEV+/-Other n=44; Other n=22	12 (after AED initiation)	12-Month seizure freedom 38/66=57%
Suzuki et al. (2020)[33]	Retro	N=36 (n=33), prophylactic n=6	A n=22; ODG n=14	LEV n=22; Other n=11		Median 32 (after surgery)	Treatment failure due to AEs (n=0) or inefficacy (n=13) (excl. prophylactic) AEDs: 13/27=48%
Usery et al. (2010)[34]	Pros	N=17 (n=17)	GBM n=7; Other n=5; ODG n=2; MEN n=2; AA n=1;	LEV n=17		1 (after AED initiation/ surgery)	1-Month seizure freedom LEV: 15/17=88% 1-Month ≥50% Seizure reduction LEV: 16/17=94% 1-Month treatment failure due to AEs (n=0) or inefficacy (n=0) LEV: 0/17=0%
Wagner et al. (2003)[35]	Pros clinical trial	N=26 (n=26)	HGG n=18; LGG n=8	LEV n=1	LEV+Other n=25	Median 9 (after AED initiation)	Seizure freedom LEV: 10/26=38% >50% Seizure reduction LEV: 19/26=73% Treatment failure due to AEs (n=1) or unknown (n=1) LEV: 2/26=8%
Wychowski et al. (2013)[36]	Retro	N=172 (n=124), prophylactic n=70	GBM n=172	LEV 28; PHT 13; Other n=4	Other n=9	-	Seizure freedom (excl. prophylactic) AEDs: 26/54=48% Treatment failure due to AEs (excl. prophylactic) LEV: 5/28=18%; PHT 5/13=38%

Antiepileptic drugs (AEDS): CBZ=Carbamazepine; LEV=Levetiracetam; OXC=Oxcarbazepine; PHT=Phenytoin, **Histology:** A=(Pleiomorphic) astrocytoma grade II; AA=Anaplastic (pleiomorphic) astrocytoma; AOA=Anaplastic oligoastrocytoma; AODG=Anaplastic oligodendroglioma; GBM=Glioblastoma; HGG=High grade glioma; LGG=Low grade glioma; MEN=Meningioma; MET=Metastasis; OA=Oligoastrocytoma; ODG=Oligodendroglioma grade II, **General abbreviations:** AEs=Adverse effects; Excl.=excluding; N=number of patients; Pros=prospective; RCT=randomized controlled trial; Retro=retrospective

Supplementary Table 3. Efficacy of phenytoin, valproic acid, and carbamazepine including all studies.

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Phenytoin (PHT)							
ChaiChana et al. (2009)[37]	Retro	N=648 (n=153)	GBM n=505; AA n=143	Preoperative AEDs: mono- (n=111) and polytherapy (n=42): PHT n=102; LEV n=13; DVX n=12; Other n=19; Unknown unclear		6 and 12 (after surgery)	6-Month seizure freedom AEDs: 79/91=87% 12-Month seizure freedom AEDs: 51/66=77%
Chang et al. (2008)[38]	Retro	N=332 (n=284)	A n=129; OA n=109; ODG n=95	PHT n=159; CBZ n=59; DVX n=29; PB n=26; Other n=15;	Unknown n=55	3 (before surgery), 6 and 12 (after surgery)	3-Month seizure freedom PHT: 84/159=53%; CBZ: 22/59=37%; PB: 11/26=42%; Divalproex sodium: 14/29=48% 6-Month seizure freedom AEDs: 169/253=67% 12-Month seizure freedom AEDs: 147/220=67%
Eseonu et al. (2018)[11]	Discussed under levetiracetam						
Hwang et al. (2004)[39]	Retro	N=101 (n=101), prophylactic n=87	GBM n=57; AA n=27; A n=17	PHT n=101		1, 3 and 12 (after surgery)	1-Month seizure freedom (excl. prophylactic) PHT: 12/14=86% 3-Month seizure freedom (excl. prophylactic) PHT: 11/14=79% 12-Month seizure freedom (excl. prophylactic) PHT: 9/14=64%

Supplementary Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Klein et al. (2003)[40]	Discussed under carbamazepine						
Merrel et al. (2010)[22]	Discussed under levetiracetam						
Moots et al. (1995)[41]	Retro	N=65 (n=63), prophylactic n=34	GBM n=47; AA n=18	Mono- and polytherapy: PHT n=62; PB n=18; CBZ n=12; Other n=4		Median 14 (after surgery)	Seizure freedom (excl. prophylactic) PHT: 8/29=28% Treatment failure due to inefficacy (excl. prophylactic) PHT: 8/29=28%
Rosati et al. (2009)[42]	Pros	N=64 (n=27)	GBM n=43; AODG n=7; AA 5; AOA n=3; ODG n=3; A n=3	PHT n=10; Other n=15	Other n=2	Median 19 (after surgery)	Seizure freedom PHT: 5/10=50%
Wick et al. (2005)[43]	Retro	N=107 (n=107), prophylactic n=32, unclear n=7	GBM n=45; AA n=17; ODG n=16; AODG n=14; A n=13; Grade I n=1; Other n=1	PHT n=35; VPA n=34; CBZ n=27; Unclear n=11		12 (after surgery)	12-Month seizure freedom (incl. prophylactic) PHT: 17/35=49%; VPA: 19/34=56%; CBZ: 8/27=30% 12-Month treatment failure due to AEs (incl. prophylactic) PHT: 12/35=34%; VPA: 7/34=21%; CBZ: 7/27=26%;
Wychowski et al. (2013)[36]	Discussed under levetiracetam						
Zaatreh et al. (2002)[44]	Discussed under carbamazepine						

Supplementary Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Zaatreh et al. (2003)[45]	Retro	N=68 (68)	A n=31; Grade I n=19; ODG n=12; AA n=4; MEN n=2	Mono- and polytherapy: PHT n=62; CBZ n=59; PB n=32; VPA n=28; PRI n=17; LTG n=12; GBP n=10; Other n=21		-	≥50% Seizure reduction: PHT: 26/62=42%; CBZ 24/59=41%; PB 10/32=31%; VPA 9/28-32%; PRI 4/17=23%; LTG 3/12=25%; GBP 2/10=20% Treatment failure due to AEs PHT: 10/62=16%; CBZ 10/59=17%; PB 3/32=9%; VPA 5/28=18%; PRI 2/17=12%; LTG 2/12=17%; GBP 2/10=20%
Valproic acid (VPA)							
Breemen et al. (2009)[4]	Retro	N=140 (n=99)	GBM n=56; A n=22; MET n=19; AODG n=10; AA n=8; ODG n=8; MEN n=6; Grade I n=4; OA n=3; Other n=3; AOA n=1	VPA n=80; CBZ n=12; Other n=7	LEV+Other n=41; Other n=22	Minimum of 6 (after AED initiation)	Seizure freedom: VPA (without LEV +/- other AEDs): 15/29=52%; VPA+LEV (+/- other AEDs): 16/27=59%; LEV (without VPA +/- other AEDs): 5/16=31% Treatment failure (any reason) in gliomas mono- (first-line) AED: 56/85=66%
Kerkhof et al. (2013)[15]	Retro	N=145 (n=145)	GBM n=145	VPA n=100; LEV n=37; Other n=8	VPA+LEV n=59; Other n=4	Minimum of 6 (after AED initiation)	Seizure freedom VPA: 41/100=41%; LEV: 16/37=43% Seizure freedom VPA+LEV: 32/59=54% Treatment failure (any reason) VPA: 66/100=66%; LEV: 15/37=41%
Klein et al. (2003)[40]	Discussed under carbamazepine						
Simó et al. (2012)[46]	Pros	N=101 (n=60), prophylactic n=7	GBM n=101	VPA n=38; LEV n=12; EIAEDs n=10		-	Treatment failure (incl. prophylactic, any reason) AEDs: 13/60=22%

Supplementary Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Wang et al. (2019)[47]	Retro	N=41 (n=41)	Grade II n=19; Grade III n=12; Grade IV n=10	VPA n=21; LEV n=11; Other n=4	VPA+LEV n=5	6 (after surgery)	6-Month treatment failure due to inefficacy AEDs: 5/37=14%
Wick et al. (2005)[43]	Discussed under phenytoin						
You et al. (2012)[48]	Retro	N=508 (n=502), prophylactic n=154	OA n=231; A n=229; ODG n=48	VPA n=444; Other n=8; Unknown n=2	Other n=50	6 and 12 (after surgery)	6-Month seizure freedom (excl. prophylactic) AEDs: 215/329=65%. 12-Month seizure freedom (exl. Prophylactic AEDs: 90/304=30%.
Yuan et al. (2013)[49]	Retro	N=93 (n=65)	ODG n=36; OA n=29; A n=28	VPA n>95%; Other n<5%		12 (after surgery)	12-Month seizure freedom AEDs: 37/65=57%
Zaatreh et al. (2002)[44]	Discussed under carbamazepine						
Zaatreh et al. (2003)[45]	Discussed under phenytoin						
Carbamazepine (CBZ)							
Chang et al. (2008)[38]	Discussed under phenytoin						
Klein et al. (2003)[40]	Cross-sectional (seizure history retro)	N=156 (n=114)	A n=109; ODG n=38; OA n=9	CBZ n=29; VPA; n=13; PHT n=20; Other n=2	Other n=50	12 (after primary treatment)	12-Month seizure freedom CBZ: 16/29=55%; PHT 7/20=35%; VPA 8/13=62%
Pace et al. (1998)[50]	Discussed under phenobarbital						

Supplementary Table 3. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Warnke et al. (1997)[51]	Retro	N=80 (n=80), prophylactic n=8	A n=80	CBZ n=58; PHT n=12; PB n=10		6 (after radiosurgery)	6-Month seizure freedom (incl. prophylactic) CBZ: 16/58=28%
Wick et al. (2005)[43]	Discussed under phenytoin						
Zaatreh et al. (2002)[44]	Retro	N=37 (n=37)	ODG n=12; LGG n=10; MEN n=8; Grade I n=4; AA n=1; OA n=1 Other n=1	Mono- and polytherapy: CBZ n=33; PHT n=32; Other n=24; PB n=23; VPA n=18; GBP n=14; LTG n=10		-	≥50% Seizure reduction CBZ: 12/33=36%; PHT: 11/32=34%; PB 11/23=48%; VPA 3/18=17%; GBP 3/14=21%; LTG 2/10=20% Treatment failure due to AEs CBZ: 8/33=24%; PHT: 7/32=22%; PB: 4/23=17%; VPA: 5/18=28%; GBP 2/14=14%; LTG: 2/10=20%
Zaatreh et al. (2003)[45]	Discussed under phenytoin						

Antiepileptic drugs (AEDS): CBZ=Carbamazepine; DVX=Divalproex sodium; EIAEDs=Enzyme-inducing antiepileptic drugs; GBP=Gabapentin; LTG=Lamotrigine; LEV=Levetiracetam; PB=Phenobarbital; PRI=Primidone; PHT=Phenytoin; VPA=Valproic acid, **Histology:** A=(Pleiomorphic) astrocytoma grade II; AA=Anaplastic (pleiomorphic) astrocytoma; AOA=Anaplastic oligoastrocytoma; AODG=Anaplastic oligodendroglioma; GBM=Glioblastoma; HGG=High grade glioma; LGG=Low grade glioma; MEN=Meningioma; MET=Metastasis; OA=Oligoastrocytoma; ODG=Oligodendroglioma grade II, **General abbreviations:** AEs=Adverse effects; Excl.=excluding, Incl.=including; Pros=prospective; Retro=retrospective

Supplementary Table 4. Efficacy of lacosamide, phenobarbital, perampanel, pregabaline, oxcarbazepine, topiramate, tiagabine, zonisamide, gabapentin, lamotrigine, divalproex sodium, primidone, vigabatrin including all studies.

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Lacosamide (LCM)							
Maschio et al. (2011)[52]	Pros clinical trial	N=14 (n=14)	GBM n=5; AA n=2; AOA n=2; A n=2; AODG n=1; ODG n=1; GC n=1		LCM+Other n=14	3, 6 and 9 (after AED initiation)	3-Month treatment failure due to AEs (n=1) or inefficacy (n=0) LCM: 1/14=7% 6-Month treatment failure due to AEs (n=1) or inefficacy (n=0) LCM: 1/14=7% 9-Month seizure freedom LCM: 6/14=38% 9-Month ≥50% seizure reduction LCM: 11/14=79% 9-Month treatment failure due to AEs (n=1) or inefficacy (n=0) LCM: 1/14=7%
Maschio et al. (2017)[21]	Pros (compared to a historical control group) clinical trial	N=25 (n=25)	A n=8; AA n=6; GBM n=5; ODG n=3; AODG n=2; AOA n=1		LCM+LEV(+/- other) n=15; LCM+Other n=10	3 and 6 (after AED initiation)	3-Month seizure freedom LCM: 8/25=32% 3-Month ≥50% seizure reduction LCM: 19/25=76% 3-Month treatment failure due to AEs (n=0), poor compliance (n=4) or inefficacy (n=1) LCM: 5/25=20 6-Month seizure freedom LCM: 7/25=28% 6-Month ≥50% seizure reduction LCM: 19/25=76% 6-Month treatment failure due to AEs (n=0), poor compliance (n=4) or inefficacy (n=1) LCM: 5/25=20%

Supplementary Table 4. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Rudà et al. (2018)[29]	Pros clinical trial	N=71 (n=71)	A n=44; ODG/ OA n=27		LCM+LEV(+/- Other) n=60; LCM+Other 11	3, 6 and 9 (after AED initiation)	3-Month seizure freedom LCM: 30/71=42% 3-Month ≥50% seizure reduction LCM: 53/71=75% 6-Month seizure freedom LCM: 28/65=43% 6-Month ≥50% seizure reduction LCM: 50/65=77% 9-Month seizure freedom LCM: 29/58=50% 9-Month ≥50% seizure reduction LCM: 50/58=86% 9-Month treatment failure due to AEs (n=2), inefficacy (n=1), or other reasons (n=1) LCM: 4/71=6%%
Rudà et al. (2020)[30]	Pros	N=93 (n=93)	ODG n=32; A n=29; OA n=13; Other n=16; MEN n=3		LCM+LEV(+/- Other) n=60; LCM+Other n=33	6 (after AED initiation)	6-Month seizure freedom LCM: 30/86=35% 6-Month ≥50% seizure reduction LCM: 66/86=77% 6-Month treatment failure due to AEs (n=5), inefficacy (n=2), or other reasons (n=7) LCM: 14/93=15%
Saria et al. (2013)[31]	Retro	N=70 (n=70)	GBM n=28; A/ OA/ODG n=26; AA/AODG n=12; MEN n=3; Other n=1	LCM n=12	LCM+LEV n=35; LCM+Other n=23	Median 6 (after AED initiation)	≥50% Seizure reduction LCM: 38/70=66% Treatment failure due to inefficacy LCM: 16/70=23%

Supplementary Table 4. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Toledo et al. (2018)[53]	Retro	N=48 (n=48)	GBM n=14; A/OA n=8; MET n=7; AA n=4; Grade 1 n=4; MEN n=3; Other n=8		LCM+Other n=48	Minimum of 6 (after AED initiation)	Seizure freedom LCM: 8/48=17% ≥50% Seizure reduction LCM: 32/48=67% Treatment failure due to AEs (n=0) or inefficacy (n=1) LCM: 1/48=2%
Villanueva et al. (2016)[54]	Retro	N=105 (n=105)	A n=42; GBM n=13; MET n=12; MEN n=11; Grade I n=10; ODG n=7; OA n=5; Other n=2; Unknown n=2; GC n=1;	LCM n=3	LCM+Other n=102	3 and 6 (after AED initiation)	3-Month seizure freedom LCM: 32/105=30% 3-Month ≥50% seizure reduction LCM: 71/105=68% 3-Month treatment failure due to AEs (n=1), inefficacy (n=0), or other reasons (n=0) LCM: 1/105=1% 6-Month seizure freedom LCM: 25/97=26% 6-Month ≥50% seizure reduction LCM: 64/97=66% 6-Month treatment failure due to AEs (n=5), inefficacy (n=1), or other reasons (n=2) LCM: 8/105=8%
Phenobarbital (PB)							
Chang et al. (2008)[38]	Discussed under phenytoin						
Maschio et al. (2009)[55]	Discussed under oxcarbazepine						
Pace et al. (1998)[50]	Pros	N=119 (n=119), prophylactic n=57	GBM n=50; AA n=38; A n=31	PB n=59; CBZ n=35; VGB n=25		Mean 27 (after surgery)	Seizure freedom (excl. prophylactic) PB: 12/28=43%; CBZ: 9/22=41%; VGB: 6/12=50% Treatment failure due to AEs or inefficacy (incl. prophylactic) PB: 38/59=64%; CBZ: 14/35=40%; VGB: 8/25=32%

Supplementary Table 4. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Zaatreh et al. (2002)[44]	Discussed under carbamazepine						
Zaatreh et al. (2003)[45]	Discussed under phenytoin						
Perampanel (PER)							
Chonan et al. (2019)[8]	Retro	N=18 (n=18)	GBM n=7; AA n=5; ODG n=3; A n=2; AODG; n=1		PER+LEV n=18	1, 3, 6, 9, 12 (after AED initiation)	1-Month seizure freedom:10/18=56% 1-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 3-Month seizure freedom: 8/18=44% 3-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 6-Month seizure freedom: 8/18=44% 6-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 9-Month seizure freedom: 8/18=44% 9-Month treatment failure due to AEs or inefficacy PER: 0/18=0% 12-Month seizure freedom: 8/18=44% 12-Month treatment failure due to AEs or inefficacy PER: 0/18=0%
Izumoto et al. (2018)[56]	Retro	N=12 (n=12)	AODG n=5; AA n=3; GBM n=2; A n=1; OA n=1		PER+Other n=12	6 (after AED initiation)	6-Month seizure freedom PER: 6/10=60% 6-Month ≥50% seizure reduction PER: 10/10=100% 6-Month treatment failure due to AEs PER: 1/12=8%

Supplementary Table 4. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Maschio et al. (2018)[57]	Retro	N=11 (n=11)	A n=4; GBM n=3; AA n=2; AOA n=2		PER+Other n=11	12 (after AED initiation)	12-Month seizure freedom PER: 5/11=45% 12-Month ≥50% seizure reduction PER: 9/11=82% 12-Month treatment failure due to AEs PER: 0/11=0%
Maschio et al. (2020)[58]	Pros clinical trial	N=26 (n=26)	GBM n=7; AA n=7; A n=5; ODG n=3; MET n=2; MEN n=1; AOA n=1		PER+Other n=26	6 (after AED initiation)	6-Month seizure freedom PER: 8/26=31% 6-Month ≥50% seizure reduction PER: 23/26=88% 6-Month treatment failure due to AEs (n=2) or inefficacy (n=0) PER: 2/26=8%
Vecht et al. (2017)[59]	Pros	N=12 (n=12)	A/OA/ODG n=6; AA/AO/ AODG n=3; GBM n=2; Grade I n=1		PER+Other n=12	Median 6 (after AED initiation)	Seizure freedom PER: 6/12=50% ≥50% Seizure reduction PER: 9/12=75% Treatment failure due to AEs (n=1) or inefficacy (n=1) PER: 2/12=17%
Pregabaline (PGB)							
Maschio et al. (2012)[60]	Pros clinical trial	N=25 (n=25)	GBM n=6; AA n=4; AODG n=3; AOA n=3; A n=2; MET n=2; MEN n=2; GC n=2; OA n=1 MEN n=2		PGB+Other n=25	6 (after AED initiation)	6-Month seizure freedom PGB: 9/25=36% 6-Month ≥50% Seizure reduction PGB: 19/25=76% 6-Month treatment failure due to AEs (n=2) or inefficacy (n=5) PGB: 7/25=28%
Rossetti et al. (2014)[28]	RCT, unblinded phase II trial	N=52 (n=52)	HGG n=37; Recurrent tumor n=16	PGB n=27; LEV n=25		12 (after AED initiation)	12-Month seizure freedom PGB: 18/24=75%; LEV: 17/25=68% 12-Month treatment failure AEs (n=7) or inefficacy (n=4) PGB: 11/27=41%; AEs (n=7) or inefficacy (n=1) LEV: 8/25=32%

Supplementary Table 4. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Oxcarbazepine (OXC)							
Maschio et al. (2009)[55]	Retro	N=70 (n=70)	OXC group: MET n=12; AA n=10; A n=6; GBM n=4; MEN=2; OA n=1 Traditional AED group: GBM n=16; A n=8; AA n=5; AODG n=4; ODG n=2	OXC n=35; Traditional AED group (PB n=24; Other n=11) n=35		Mean OXC 16; traditional AED group 14	Seizure freedom OXC: 22/35=63%; Traditional AED group: 16/35=46% Treatment failure due to AEs OXC: 3/35=9%; PB 11/24=46%; Traditional AED group: 15/35=43%
Maschio et al. (2012)[61]	Pros clinical trial	N=25 (n=25)	GBM n=12; AA n=4; GC n=3; A n=2; AODG n=1 AOA n=1; Grade I n=1; MEN n=1	OXC n=25		12 (after surgery)	12-Month seizure freedom OXC: 10/25=40% 12-Month ≥50% seizure reduction OXC: 22/25=88% 12-Month treatment failure due to AEs (n=6) or inefficacy (n=3) OXC: 9/25=36%
Topiramate (TPM)							
Lu et al. (2009)[62]	Retro	N=227 (n=227)	LGG n=54; Other n=173	TPM n=14	TPM+Other n=40	12 (after AED initiation)	12-Month seizure freedom mono-, polytherapy TPM: 10/14=71%; 24/40=60% 12-Month ≥50% seizure reduction mono- and polytherapy TPM: 12/14=86%; 28/40=70%
Maschio et al. (2008)[63]	Pros clinical trial	N=47 (n=47)	Grade III n=20; LGG n=13; GBM n=8; MEN n=4; MET n=2	TPM n=47		3, 6 and 12 (after AED initiation)	3-Month seizure freedom TPM: 27/45=60% 3-Month ≥50% seizure reduction TPM: 34/45=76% 3-Month treatment failure due to AEs (n=2) or inefficacy (n=0) TPM: 2/47=4%

Supplementary Table 4. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
							6-Month seizure freedom TPM: 26/44=59% 6-Month ≥50% seizure reduction TPM: 34/44=77% 6-Month treatment failure due to AEs (n=3) or inefficacy (n=0) TPM: 3/47=6% 12-Month seizure freedom TPM: 25/44=57% 12-Month ≥50% seizure reduction TPM: 33/44=75% 12-Month treatment failure due to AEs (n=3) or inefficacy (n=0) TPM: 3/47=6%
Clonazepam (CZP)							
Koekkoek et al. (2016)[64]	Pros	N=25 (n=13)	GBM n=13; AA n=3; A n=3; AODG=2; Unknown n=2; AOA=1; OA=1;	CZP n=13		Median 3 (after AED initiation)	Seizure freedom CZP: 8/13=62%
Tiagabine (TGB)							
Striano et al. (2002)[65]	Pros	N=11 (n=11)	ODG n=6; A n=4; GBM n=1; A n=3; Grade I n=1		TGB+Other n=11	12 (after AED initiation)	12-Month seizure freedom TGB: 3/11=27% 12-Month ≥50% seizure reduction TGB: 7/11=64% 12-Month treatment failure due to AEs (n=2) or inefficacy (n=1) TGB: 3/11=27%
Zonisamide (ZNS)							
Maschio et al. (2017)[66]	Pros	N=13 (n=13)	GBM n=6; MEN n=3; OA n=2; ODG n=1; MET n=1		ZNS+Other n=13	6 (after AED initiation)	6-Month ≥50% seizure reduction ZNS: 7/13=54% 6-Month treatment failure due to AEs (n=0) or inefficacy (n=0) ZNS= 0/13=0%

Supplementary Table 4. Continued

Article	Study design	N study (N AEDs)	Histology, N study	Monotherapy, N AEDs	Polytherapy, N AEDs	Follow-up (months) AEDs	Outcomes
Gabapentin (GBP)							
Zaatreh et al. (2002)[44]	Discussed under carbamazepine						
Zaatreh et al. (2003)[45]	Discussed under phenytoin						
Lamotrigine (LTG)							
Zaatreh et al. (2002)[44]	Discussed under carbamazepine						
Zaatreh et al. (2003)[45]	Discussed under phenytoin						
Divalproex sodium (DVX)							
Chang et al. (2008)[38]	Discussed under phenytoin						
Primidone (PRI)							
Zaatreh et al. (2003)[45]	Discussed under phenytoin						
Vigabatrin (VGB)							
Pace et al. (1998)[50]	Discussed under phenobarbital						

Antiepileptic drugs (AEDs): CBZ=Carbamazepine; CZP=Clonazepam; DVX=Divalproex sodium; GBP=Gabapentin; LCM=Lacosamide; LEV=Levetiracetam; OXC=Oxcarbazepine; PB=Phenobarbital; PGB=Pregabaline; PRI=Primidone; PHT=Phenytoin; TGB=Tiagabine; TPM=Topiramate; VGB=Vigabatrin; ZNS=Zonisamide, **Histology:** A=(Pleiomorphic) astrocytoma grade II; AA=Anaplastic (pleiomorphic) astrocytoma; AOA=Anaplastic oligoastrocytoma; AODG=Anaplastic oligodendroglioma; GBM=Glioblastoma; GC=Gliomatosis cerebri; HGG=High grade glioma; LGG=Low grade glioma; MEN=Meningioma; MET=Metastasis; OA=Oligoastrocytoma; ODG=Oligodendroglioma grade II, **General abbreviations:** AEs=Adverse effects; Pros=prospective; Retro=retrospective

Supplementary Table 5. Weighted averages of all included studies.

	Seizure freedom, %		>50% reduction, %		Treatment failure (any reason), %		Treatment failure (inefficacy), %		Treatment failure (adverse effects), %	
Follow-up	**Mono-**	**Poly-**	**Mono-**	**Poly-**	**Mono-**	**Poly-**	**Mono-**	**Poly-**	**Mono-**	**Poly-**
Levetiracetam (LEV)										
1-month	86	54	94	88	5	2	7	0	1	2
3-month	75	40	-	75	-	0	-	0	-	-
6-month	60	43	82	76	14	13	10	2	1	5
9-month	96	49	-	86	-	0	-	0	-	-
12-month	74	55	97	-	24	0	6	0	15	-
unknown	66	51	100	68	20	4	16	-	5	2
Phenytoin (PHT)										
1-month	86	-	-	-	40	-	-	-	13	-
3-month	55	-	-	-	-	-	-	-	-	-
6-month	72	90	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	65	-	-	-	34	-	-	-	34	-
unknown	36	-	-	39	31	18	28	-	38	18
Valproic acid (VPA)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	65	-	-	-	14	-	14	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	37	-	-	-	21	-	-	-	21	-
unknown	43	56	-	26	55	22	-	-	-	22
Carbamazepine (CBZ)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	37	-	-	-	-	-	-	-	-	-
6-month	28	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	43	-	-	-	26	-	-	-	26	-
unknown	43	-	-	39	64	20	-	-	-	20
Lacosamide (LCM)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month		37	-	71	-	5	-	1	-	1
6-month	-	33	-	73	-	12	-	2	-	5
9-month	-	49	-	85	-	6	-	2	-	4
12-month	-	-	-	-	-	-	-	-	-	-
unknown	-	17	-	59	-	14	-	13	-	2
Phenobarbital (PB)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	42	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-
unknown	44	-	-	38	59	13	-	-	46	13
Perampanel (PER)										
1-month	-	56	-	-	-	0	-	0	-	0
3-month	-	44	-	-	-	0	-	0	-	0
6-month	-	41	-	92	-	5	-	0	-	5
9-month	-	44	-	-	-	0	-	0	-	0
12-month	-	45	-	82	-	0	-	0	-	0
unknown	-	50	-	75	-	17	-	8	-	8

Supplementary Table 5. Continued

	Seizure freedom, %		>50% reduction, %		Treatment failure (any reason), %		Treatment failure (inefficacy), %		Treatment failure (adverse effects), %	
Follow-up	**Mono-**	**Poly-**	**Mono-**	**Poly-**	**Mono-**	**Poly-**	**Mono-**	**Poly-**	**Mono-**	**Poly-**
Pregabaline (PGB)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	36	-	76	-	28	-	20	-	8
9-month	-	-	-	-	-	-	-	-	-	-
12-month	75	-	-	-	41	-	15	-	26	-
unknown	-	-	-	-	-	-	-	-	-	-
Oxcarbazepine (OXC)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	40	-	88	-	36	-	12	-	24	-
unknown	63	-	-	-	9	-	-	-	9	-
Topiramate (TPM)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	60	-	76	-	4	-	0	-	4	-
6-month	59	-	77	-	6	-	0	-	6	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	60	60	78	70	6	-	0	-	6	-
unknown	-	-	-	-	-	-	-	-	-	-
Clonazepam (CZP)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-
unknown	62	-	-	-	-	-	-	-	-	-
Tiagabine (TGB)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	27	-	64	-	27	-	9	-	18
unknown	-	-	-	-	-	-	-	-	-	-
Zonisamide (ZNS)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	54	-	0	-	0	-	0
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-
unknown	-	-	-	-	-	-	-	-	-	-
Gabapentin (GBP)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-

Supplementary Table 5. Continued

Follow-up	Seizure freedom, %		>50% reduction, %		Treatment failure (any reason), %		Treatment failure (inefficacy), %		Treatment failure (adverse effects), %	
	Mono-	Poly-	Mono-	Poly-	Mono-	Poly-	Mono-	Poly-	Mono-	Poly-
unknown	-	-	-	21	-	17	-	-	-	17
Lamotrigine (LTG)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-
unknown	-	-	-	23	-	18	-	-	-	18
Divalproex sodium (DVX)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	48	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-
unknown	-	-	-	-	-	-	-	-	-	-
Primidone (PRI)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-
unknown	-	-	-	24	-	12	-	-	-	12
Vigabatrin (VGB)										
1-month	-	-	-	-	-	-	-	-	-	-
3-month	-	-	-	-	-	-	-	-	-	-
6-month	-	-	-	-	-	-	-	-	-	-
9-month	-	-	-	-	-	-	-	-	-	-
12-month	-	-	-	-	-	-	-	-	-	-
unknown	43	-	-	-	64	-	-	-	-	-

Mono-=monotherapy; Poly-=polytherapy

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