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

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Abstract

Background. Comprehensive data on the efficacy and tolerability of antiepileptic drugs (AED) treatment in glioma patients with epilepsy are 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-month 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

antiepileptic drugs | brain tumor | epilepsy | glioma | seizures

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 to 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 (ie, failure to achieve seizure freedom even after AED polytherapy) is reported in ~20% of glioma patients following initial treatment and higher in patients with low-grade 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 are currently lacking, while they 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 1, 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 (M.E.d.B. and P.B.v.d.M.) 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, (iii) no documentation of outcomes per AED in case <50% of patients received the same AED, and (iv) articles focusing on treatment of a status epilepticus. Information was retrieved from interventional (randomized and nonrandomized) 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, 3 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 Tables 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).

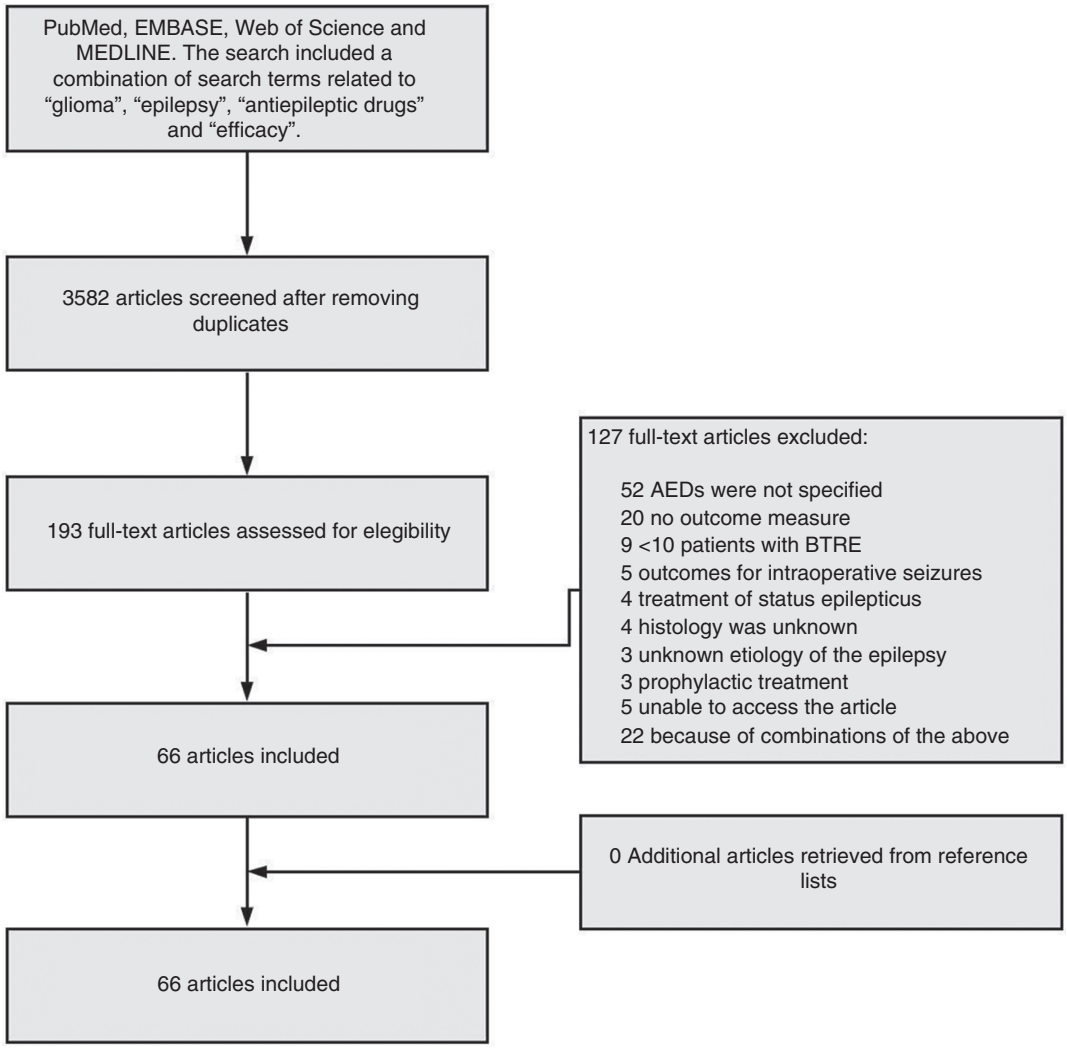

Figure 1. Literature selection procedure.

Levetiracetam (LEV)

We found 1 case series, 2 randomized controlled trials (RCTs), 8 nonrandomized clinical trials, and 9 prospective and 16 retrospective observational studies reporting on LEV (Table 1).[18,25–59]

In total, 25 studies documented efficacy of LEV monotherapy.[18,25–39,47–49,51,53–57] The 6-month seizure freedom rate was presented in 9/25 studies and varied between 39% and 96% (WA = 60%),[25,26,30,32,34,37,47,54,55] while the 12-month seizure freedom rate was presented in 4/25 studies, ranging between 68% and 96% (WA = 74%).[31,35,53,54] A seizure reduction rate ≥50% at 6 months was presented in 2/25 studies and varied between 71% and 100% (WA = 82%).[25,30] One study reported a seizure reduction rate of ≥50% at 12 months of 97%.[31] 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.[25,26,30–32,35]

In total, 13 studies documented efficacy of polytherapy including LEV.[18,40–47,50,52,58,59] The 6-month seizure freedom rate was presented in 5/13 studies and ranged between 28% and 90% (WA = 43%),[42,43,47,50,59] while the 12-month seizure freedom rate was presented in 2/13 studies, ranging between 44% and 58% (WA = 55%).[50,58] A ≥50% seizure reduction rate at 6 months was presented in 4 studies and ranged between 74% and 77% (WA = 76%).[41–43,59] A total of 5 studies reported treatment failure rates of LEV polytherapy.[41,45,46,50,59] 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.[50,59] One study reported a 0% treatment failure rate due to inefficacy at 12 months.[50]

Phenytoin (PHT)

We found 1 prospective and 11 retrospective observational studies reporting on PHT (Table 2).[4,8,27,36,47,60–66]

Table 1. Efficacy of Levetiracetam at 6- and 12-Month Follow-Up

Article	Study Design	Number of Patients in Study (Using AEDs)	Number of Patients Histology	Number of Patients Monotherapy AEDs	Number of Patients Polytherapy AEDs	Follow-Up (Months) AEDs	Outcomes
Levetiracetam (LEV)							
Bahr et al. (2012)[32]	Prospective clinical trial	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)	6-Month seizure freedom LEV: 13/25 = 52% 6-Month treatment failure due to AEs (n = 0), inefficacy (n = 6), and unknown (n = 1) LEV: 7/25 = 28%
Chonan et al. (2019)[50]	Discussed under perampanel						
de Groot et al. (2011)[30]	Prospective 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)[25]	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) and/or inefficacy (n = 0) LEV = 0/18 = 0%
Eseonu et al. (2018)[47]	Retrospective	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)[53]	Retrospective	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)[26]	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)[55]	Prospective	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)[31]	Prospective clinical trial	N = 29 (n = 29)	GBM, n = 9; AODG, n = 6; LGG, 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)[42]	Discussed under lacosamide						

Table 1. Continued

Article	Study Design	Number of Patients in Study (Using AEDs)	Number of Patients Histology	Number of Patients Monotherapy AEDs	Number of Patients Polytherapy AEDs	Follow-Up (Months) AEDs	Outcomes
Michelucci et al. (2013)[34]	Prospective	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)[37]	Prospective	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)[35]	Discussed under pregabalin						
Rudà et al. (2018)[43]	Discussed under lacosamide						
Rudà et al (2020)[59]	Discussed under lacosamide						
Solomons et al. (2019)[58]	Retrospective	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%

Abbreviations: AEDs, antiepileptic drugs; AEs, adverse effects; Excl., excluding; n, number of patients; RCT, randomized controlled trial.
See Supplementary Material 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 and 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).
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.
"Summary LEV: total number of patients using LEV included in retrospective (LEV: n = 239) and prospective studies (LEV: n = 369)."
"Summary PHT, VPA, and CBZ: total number of patients using PHT, VPA, and CBZ included in retrospective (PHT: n = 447; VPA: n = 610; CBZ: n = 173) and prospective studies (PHT: n = 0; VPA: n = 0; CBZ: n = 0)."
"Summary LCM, PER, PGB, OXC, TPM, TGB, and ZNS: total number of patients using LCM, PER, PGB, OXC, TPM, TGB, and ZNS included in retrospective (LCM: n = 105; PER: n = 41; PGB: n = 0; OXC: n = 0; TPM: n = 52; TGB: n = 0; ZNS: n = 0) and prospective studies (LCM: n = 203; PER: n = 26; PGB: n = 52; OXC: n = 25; TPM: n = 47; TGB: n = 11; ZNS: n = 13)."

Table 2. Efficacy of Phenytoin, Valproic Acid, and Carbamazepine at 6- and 12-Month Follow-Up

Article	Study Design	No. of Study (No. of AEDs)	Histology(No. of Study)	Monotherapy (No. of AEDs)	Polytherapy (No. of AEDs)	Follow-Up (Months) AEDs	Outcomes
Phenytoin (PHT)							
ChaiChana et al. (2009)[60]	Retrospective	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]	Retrospective	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)	6-Month seizure freedom AEDs: 169/253 = 67% 12-Month seizure freedom AEDs: 147/220 = 67%
Eseonu et al. (2018)[47]	Discussed under levetiracetam						
Hwang et al. (2004)[61]	Retrospective	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)	12-Month seizure freedom (excl. prophylactic) PHT: 9/14 = 64%
Klein et al. (2003)[4]	Discussed under carbamazepine						
Wick et al. (2005)[64]	Retrospective	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)[67]	Retrospective	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)[64]	Discussed under phenytoin						
You et al. (2012)[68]	Retrospective	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)[69]	Retrospective	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%
Carbamazepine (CBZ)							

Table 2. Continued

Article	Study Design	No. of Study (No. of AEDs)	Histology(No. of Study)	Monotherapy (No. of AEDs)	Polytherapy (No. of AEDs)	Follow-Up (Months) AEDs	Outcomes
Chang et al. (2008)[8]	Discussed under phenytoin						
Klein et al. (2003)[4]	Retrospective	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)[70]	Retrospective	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)[64]	Discussed under phenytoin						

Abbreviations: AEDs, antiepileptic drugs; AEs, adverse effects; Excl., excluding, Incl., including.
See Supplementary Material 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).
AEDs: CBZ, carbamazepine; DVX, divalproex sodium; 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.
"Summary LEV: total number of patients using LEV included in retrospective (LEV: n = 239) and prospective studies (LEV: n = 369)."
"Summary PHT, VPA, and CBZ: total number of patients using PHT, VPA, and CBZ included in retrospective (PHT: n = 447; VPA: n = 610; CBZ: n = 173) and prospective studies (PHT: n = 0; VPA: n = 0; CBZ: n = 0)."
"Summary LCM, PER, PGB, OXC, TPM, TGB, and ZNS: total number of patients using LCM, PER, PGB, OXC, TPM, TGB, and ZNS included in retrospective (LCM: n = 105; PER: n = 41; PGB: n = 0; OXC: n = 0; TPM: n = 52; TGB: n = 0; ZNS: n = 0) and prospective studies (LCM: n = 203; PER: n = 26; PGB: n = 52; OXC: n = 25; TPM: n = 47; TGB: n = 11; ZNS: n = 13)."

total, 9 studies documented efficacy of PHT monotherapy.[4,8,27,36,60–64] The 6-month seizure freedom rate was presented in 2/9 studies and varied between 67% and 87% (WA = 72%).[8,60] while the 12-month seizure freedom rate was presented in 5/9 studies and varied between 35% and 77% (WA = 65%).[4,8,60,61,64] One study reported a 34% treatment failure rate due to AEs at 12 months of PHT treatment.[64]

In total, 3 studies documented efficacy of polytherapy including PHT.[47,65,66] The 6-month seizure freedom rate was 90% as reported in 1/3 studies.[47]

Valproic Acid (VPA)

We found 1 prospective and 9 retrospective observational studies reporting on VPA (Table 2).[4,18,40,64–69,71]

In total, 8 studies documented efficacy of VPA monotherapy.[18,40,64,68,69,71] Six-month seizure freedom rate was 65% as reported in one study,[68] while 12-month seizure freedom rate was presented in 4/8 studies and ranged between 30% and 62% (WA = 37%).[4,64,68,69] 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.[64,67] In total, 4 studies documented efficacy of polytherapy including VPA.[4,18,40,65,66] 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).[4,8,64–66,70,72]

Seizure freedom rate was described in all 5 studies on CBZ monotherapy. However, one study reported on the 6-month seizure freedom rate, that is, 28%.[70] The 12-month seizure freedom rate was presented in 2/5 studies and varied between 30% and 55% (WA = 43%).[4,64] One study reported a 12-month treatment failure rate of 26% due to AEs.[64]

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.

Lacosamide (LCM)

No studies documented efficacy of LCM monotherapy. The efficacy of polytherapy including LCM was reported in 3 nonrandomized clinical trials, 1 prospective, and 3 retrospective observational studies (Table 3).[42–44,59,73–75] The 6-month seizure freedom rate with polytherapy including LCM was presented in 4/7 studies and varied between 26% and 43% (WA = 33%).[42,43,59,73] A seizure reduction rate ≥50% at 6 months was reported in 4 studies and varied between 66% and 77% (WA = 73%).[42,43,59,73] 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.[42,59,74,75]

Perampanel (PER)

No studies documented efficacy of PER monotherapy. The efficacy of polytherapy including PER was reported in 1 nonrandomized clinical trial, 1 prospective, and 3 retrospective observational studies (Table 3).[50,76–78,85]

The 6-month seizure freedom rate of polytherapy with PER was presented in 3/5 studies and ranged between 31% and 60% (WA = 41%),[50,76,78] while the 12-month seizure freedom rate in 2/5 studies varied between 44% and 45% (WA = 45%).[50,77] Seizure reduction rates ≥50% at 6 and 12 months were 92% and 82%, respectively, as reported in 3 different studies.[76–78]

Treatment failure rates with polytherapy including PER ranged between 0% and 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.[50,76,78] The WAs of 12-month treatment failure rates, documented in 2 studies, were 0% due to any reason, inefficacy, and AEs.[50,77]

Pregabalin (PGB)

We found 1 RCT reporting on PGB monotherapy and 1 nonrandomized clinical trial reporting on PGB polytherapy (Table 3).[35,79]

Seizure freedom rate at 12 months with PGB monotherapy was 75%, as reported in 1 RCT (n = 52). Treatment failure rates at 12 months were 41% due to any reason, 15% due to inefficacy, and 26% due to AEs.[35]

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 1 nonrandomized 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.[79]

Oxcarbazepine (OXC)

We found 1 nonrandomized clinical trial and 1 retrospective observational study reporting on OXC monotherapy (Table 3).[80,86]

As reported in 1 nonrandomized clinical trial (n = 25), the 12-month seizure freedom rate was 40% and a ≥50% seizure reduction was observed in 88% of patients.[80] Treatment failure with OXC monotherapy ranged between 9% and 36%. The study provided reasons for the 12-month treatment failure rate: 12% due to inefficacy and 24% due to AEs.[80]

Topiramate (TPM)

We found 1 nonrandomized clinical trial and 1 retrospective observational study reporting on TPM (Table 3).[81,82]

Seizure freedom rate at 6 months with TPM monotherapy was 59%, as reported in 1 nonrandomized clinical trial (n = 47).[82] The 12-month seizure freedom rates were reported in both studies and varied between 57% and 71% (WA = 60%). A ≥50% reduction in seizure frequency at 12 months was described in both studies and ranged between 75% and 86% (WA = 78%).[81,82] One study described the treatment failure rate at 6 and 12 months of 6% and was in all cases due to AEs.[82]

Table 3. Efficacy of Lacosamide, Perampanel, Pregabalin, Oxcarbazepine, Topiramate, Tiagabine, Zonisamide at 6- and 12-Month' Follow-Up

Article	Study design	No. of Study (No. of AEDs)	Histology (No. of Study)	Monotherapy (No. of AEDs)	Polytherapy (No. of AEDs)	Follow-Up AEDs, Months	Outcomes
Lacosamide (LCM)							
Maschio et al. (2011)[75]	Prospective 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)	6-Month treatment failure due to AEs (n = 1) and/or inefficacy (n = 0) LCM: 1/14 = 7%
Maschio et al. (2017)[42]	Prospective (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)	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) and inefficacy (n = 1) LCM: 5/25 = 20%
Rudà et al. (2018)[43]	Prospective clinical trial	N = 71 (n = 71)	A, n = 44; ODG/OA, n = 27		LCM + LEV (+/–Other), n = 60; LCM + Other, n = 11	3, 6 and 9 (after AED initiation)	6-Month seizure freedom LCM: 28/65 = 43% 6-Month ≥50% seizure reduction LCM: 50/65 = 77%
Rudà et al. (2020)[59]	Prospective	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)[73]	Retrospective	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)	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)[50]	Retrospective	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, and 12 (after AED initiation)	6-Month seizure freedom: 8/18 = 44% 6-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)[76]	Retrospective	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%
Maschio et al. (2018)[77]	Retrospective	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%

Table 3. Continued

Article	Study design	No. of Study (No. of AEDs)	Histology (No. of Study)	Mono-therapy (No. of AEDs)	Polytherapy (No. of AEDs)	Fol-low-Up AEDs, Months	Outcomes
Maschio et al. (2020)[78]	Prospective 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%
Pregabalin (PGB)							
Maschio et al. (2012)[79]	Prospective 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		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) and inefficacy (n = 5) PGB: 7/25 = 28%
Rossetti et al. (2013)[35]	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) and inefficacy (n = 4) PGB: 11/27 = 41%; AEs (n = 7) and inefficacy (n = 1) LEV: 8/25 = 32%
Oxcarbazepine (OXC)							
Maschio et al. (2012)[80]	Prospective 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) and inefficacy (n = 3) OXC: 9/25 = 36%
Topiramate (TPM)							
Lu et al. (2009)[81]	Retrospective	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)[82]	Prospective 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)	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) and/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) and/or inefficacy (n = 0) TPM: 3/47 = 6%
Tiagabine (TGB)							
Striano et al. (2002)[83]	Prospective	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) and inefficacy (n = 1) TGB: 3/11 = 27%

Table 3. Continued

Article	Study design	No. of Study (No. of AEDs)	Histology (No. of Study)	Mono-therapy (No. of AEDs)	Polytherapy (No. of AEDs)	Fol-low-Up AEDs, Months	Outcomes
Zonisamide (ZNS)							
Maschio et al. (2017)[84]	Prospective	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%

Abbreviations: AEDs, antiepileptic drugs; AEs, adverse effects; RCT, randomized controlled trial.
See Supplementary Material 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).
AEDs: CBZ, carbamazepine; CZP, clonazepam; DVX, divalproex sodium; GBP, gabapentin; LCM, lacosamide; LEV, levetiracetam; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; 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.
"Summary LEV: total number of patients using LEV included in retrospective (LEV: n = 239) and prospective studies (LEV: n = 369)."
"Summary PHT, VPA, and CBZ: total number of patients using PHT, VPA, and CBZ included in retrospective (PHT: n = 447; VPA: n = 610; CBZ: n = 173) and prospective studies (PHT: n = 0; VPA: n = 0; CBZ: n = 0)."
"Summary LCM, PER, PGB, OXC, TPM, TGB, and ZNS: total number of patients using LCM, PER, PGB, OXC, TPM, TGB, and ZNS included in retrospective (LCM: n = 105; PER: n = 41; PGB: n = 0; OXC: n = 0; TPM: n = 52; TGB: n = 0; ZNS: n = 0) and prospective studies (LCM: n = 203; PER: n = 26; PGB: n = 52; OXC: n = 25; TPM: n = 47; TGB: n = 11; ZNS: n = 13)."

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%.[81]

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.[83]

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.[84]

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.

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.[87] 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 (Figure 2). 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 1 AED that clearly stood out in terms of efficacy. Indeed, based on the calculated WAs, 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-month 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%).[35] 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.[35] 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,[8,60] compared to 9 studies on LEV including 1 RCT at 6 months.[26]

The results with respect to AED polytherapy were also ambiguous. Seizure freedom rates with polytherapy at 6 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 tumors. Of note, in most studies, it was unclear what combination of AEDs patients were taking when they were on AED polytherapy. The 4 known studied combinations with outcomes ≥6 months, were LEV + PHT,[88] LEV + LCM,[42,43,59] PER + LEV,[50] and LEV + VPA.[18,40] 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.[88] 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.[18,40]

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 the most favorable tolerability. These findings provide substantiation of the general consensus that has emerged over the past 2 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.[21,22,89] In the general epilepsy population, PHT has been known for its worse tolerability compared to newer agents, such as LEV.[90] 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.[91] Nonetheless, of these newer nonenzyme-inducing AEDs, we found LEV to show

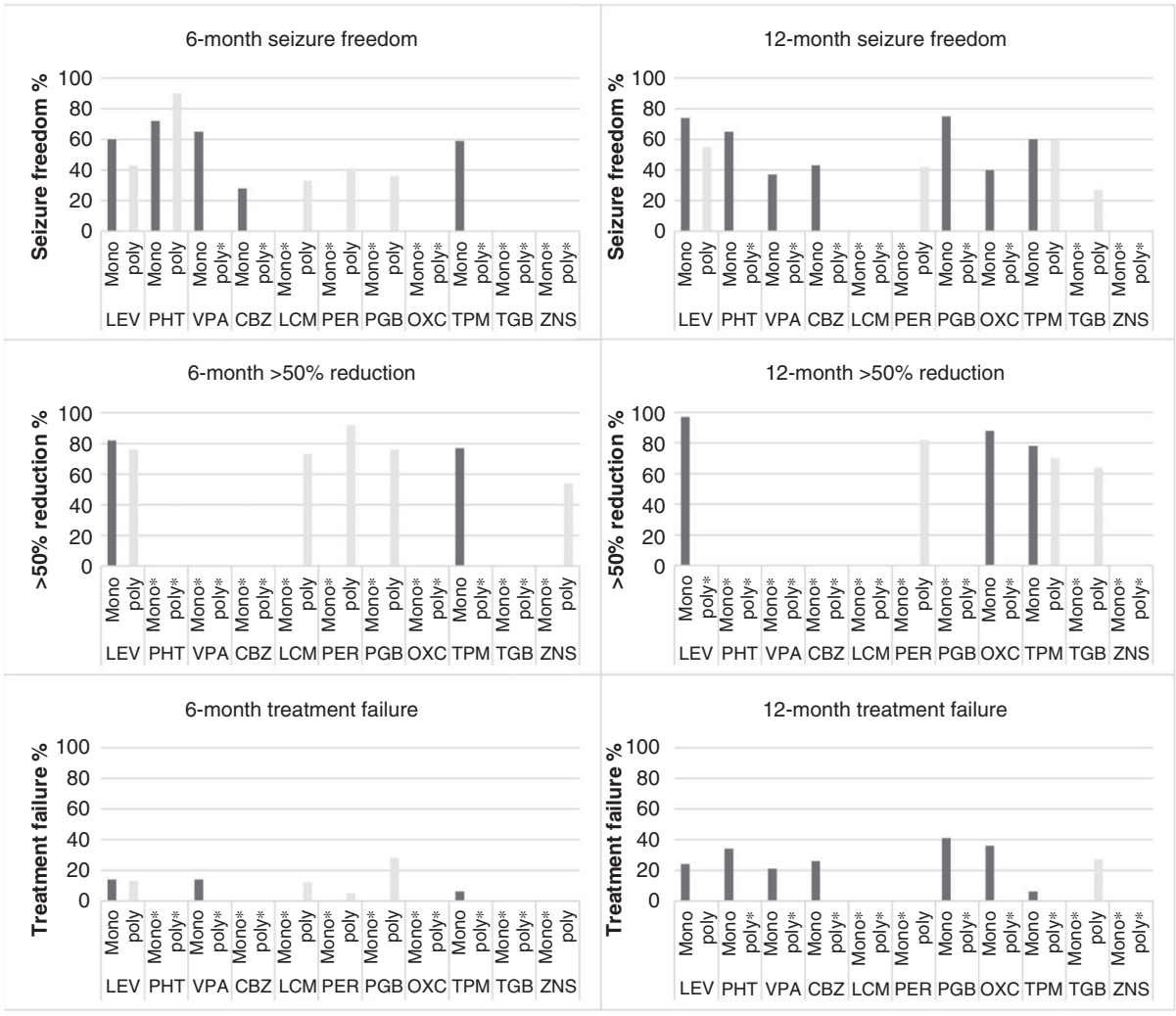

Figure 2. Weighted average (WA) calculated for outcomes at 6 and 12 months.

a better tolerability than PGB, which seems likely to 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.[92] However, it is associated with psychiatric AEs and it is therefore strongly advised not to be prescribed in patients with psychiatric comorbidities.[92] 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,[93] but effective in treating neuropathic pain and anxiety disorders which are both common symptoms in glioma patients (~20% and ~30%, respectively).[94,95]

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.[96] Due to its relatively lower seizure control rates compared to other AEDs, our data do no support VPA as first choice monotherapy. Supported by 2 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.[18,40] AEs 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, for example, 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-tumor cases and has no enzyme-inducing properties.[92] LTG is considered the most

effective AED (together with GBP) in treating elderly adults with focal-onset seizures[97] and has been considered a suitable option for the treatment of BTRE.[19,21,22] Disadvantages of LTG are the need for slow titration, risk of dermatologic reactions, and the interaction with VPA.[92]

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,[18] 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.[35] 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 AE 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, and 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-tumor cases can be used, considering side effects and drug interactions.[97] 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. RCTs 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 questionnaires.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Practice* online.

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