First-line antiepileptic drug treatment in glioma patients with epilepsy: levetiracetam vs valproic acid

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Received: 7 November 2020 | Revised: 4 March 2021 | Accepted: 4 March 2021

DOI: 10.1111/epi.16880

Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

First-line antiepileptic drug treatment in glioma patients with epilepsy: Levetiracetam vs valproic acid

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Abstract

Objective: This study aimed at estimating the cumulative incidence of antiepileptic drug (AED) treatment failure of first-line monotherapy levetiracetam vs valproic acid in glioma patients with epilepsy.

Methods: In this retrospective observational study, a competing risks model was used to estimate the cumulative incidence of treatment failure, from AED treatment initiation, for the two AEDs with death as a competing event. Patients were matched on baseline covariates potentially related to treatment assignment and outcomes of interest according to the nearest neighbor propensity score matching technique. Maximum duration of follow-up was 36 months.

Results: In total, 776 patients using levetiracetam and 659 using valproic acid were identified. Matching resulted in two equal groups of 429 patients, with similar covariate distribution. The cumulative incidence of treatment failure for any reason was significantly lower for levetiracetam compared to valproic acid (12 months: 33% [95% confidence interval (CI) 29%–38%] vs 50% [95% CI 45%–55%]; $P < .001$). When looking at specific reasons of treatment failure, treatment failure due to uncontrolled seizures was significantly lower for levetiracetam compared to valproic acid (12 months: 16% [95% CI 12%–19%] vs 28% [95% CI 23%–32%]; $P < 0.001$), but no differences were found for treatment failure due to adverse effects (12 months: 14% [95% CI 11%–18%] vs 15% [95% CI 11%–18%]; $P = .636$).

Significance: Our results suggest that levetiracetam may have favorable efficacy compared to valproic acid, whereas level of toxicity seems similar. Therefore, levetiracetam seems to be the preferred choice for first-line AED treatment in patients with glioma.

KEYWORDS

antiepileptic drug, glioma, levetiracetam, seizures, valproic acid

Key Points

- Levetiracetam had better efficacy compared to valproic acid.
- Levetiracetam and valproic acid had a similar level of toxicity.
- Levetiracetam and valproic acid had a similar overall survival.
- Seizure control was similar in low-grade (grade 2) and high-grade (grade 3 or 4) glioma patients.

1 | INTRODUCTION

Gliomas are the most common malignant primary brain tumors and treatment options are multimodal.[1,2] Seizures are a well-recognized symptom in glioma patients and occur frequently, either as a presenting symptom or during the course of the disease.[3] The incidence of seizures is higher in slow-growing tumors.[4] Preoperative seizure incidence in diffuse gliomas ranges from ~25% in World Health Organization (WHO) grade 4 glioblastoma isocitrate dehydrogenase (IDH)-wildtype to ~75% in grade 2 diffuse astrocytoma IDH-mutant and oligodendroglioma IDH-mutant 1p/19q co-deleted patients.[4] Seizure control plays an important role in the clinical management of gliomas and standard-of-care involves treatment with an antiepileptic drug (AED) once a first seizure has occurred.[5] Seizure control can also be achieved with anti-tumor treatment, including surgical resection, radiotherapy, and chemotherapy.[6] Potential drug interactions between AEDs and chemotherapeutic drugs complicate seizure management in patients with glioma and therefore cytochrome P450 (CYP450) enzyme–inducing AEDs, such as phenytoin and carbamazepine, are generally not advised.[2] The choice of AED depends on physicians experience as the published literature lacks high-quality comparative effectiveness studies. Currently, levetiracetam and valproic acid are two of the most commonly prescribed first-line AEDs in patients with glioma.[6–9] Valproic acid is a first-generation AED and has been used in the treatment of epilepsy for more than 50 years.[10] It has a well-established reputation as a broad spectrum AED and has been associated with decreased psychiatric and behavioral adverse effects in patients with epilepsy.[10,11] As a CYP450 inhibitor, it has the potential to increase bioavailability of chemotherapeutic drugs and simultaneously increase toxicity of these drugs.[12] Valproic acid gained special attention approximately a decade ago, due to its supposed anti-tumoral properties as a histone deacetylase inhibitor, especially in combination with temozolomide chemotherapy and radiotherapy.[6] However, the results of a recent pooled analysis of prospective trials did not show improved survival outcomes in patients taking valproic acid.[13] Levetiracetam is a second-generation broad-spectrum AED and was licensed ~20 years ago.[14] It has several advantages, including a lack of hepatic metabolism and no known pharmacological interactions, and has a wider therapeutic index (the ratio between the median toxic dose and the median effective dose) than valproic acid.[12] Psychiatric and behavioral adverse effects are the most common adverse effects in patients using levetiracetam, frequently leading to discontinuation of the anticonvulsant.[15] Other commonly prescribed AEDs in the glioma population include lamotrigine, lacosamide, topiramate, and zonisamide, each with their own efficacy and adverse-effect profiles.[5,9,16]

If more patients discontinue an AED due to inefficacy, intolerable adverse effects, or for alternative reasons, its usefulness decreases. The effectiveness of an AED is reflected in its treatment failure rates (or its inverse, retention rates), which encompasses both efficacy and tolerability of the treatment.[17] Apart from seizure freedom, the retention rate is one of the recommended primary outcomes by the International League Against Epilepsy (ILAE).[18] The effectiveness of levetiracetam compared with valproic acid has not been sufficiently investigated yet in patients with glioma. This retrospective observational study aimed to directly compare the effectiveness of first-line monotherapy levetiracetam vs valproic acid.

2 | METHODS

2.1 | Study population and procedures

The study population consisted of consecutive adult patients with a histological diagnosed World Health Organization (WHO) grade 2–4 glioma ([anaplastic] astrocytoma, [anaplastic] oligoastrocytoma, [anaplastic] oligodendroglioma, or glioblastoma) according to the WHO 2016 guidelines following biopsy or surgical (re)resection in Haaglanden Medical Center, Amsterdam University Medical Center, or Erasmus Medical Center, between January 1, 2004 and January 1, 2018, and first-line monotherapy treatment with levetiracetam or valproic acid after the occurrence of an epileptic seizure.[1] Patients diagnosed prior to the WHO 2016 guidelines were regraded according to the updated guidelines, but no new molecular diagnostics were performed. Patients were excluded from this study if: (1) they had a history of non–brain tumor-related epilepsy; (2) prophylactic or

first-line AED treatment other than levetiracetam or valproic acid was initiated; (3) the tumor was located infratentorially or in the spinal cord; and (4) the start date of first-line AED treatment was unknown. The medical ethics committee of each institution approved the protocol and consent of patients was obtained according to the institution's policy.

Patients' charts were examined to extract baseline sociodemographic data, tumor characteristics, information on anti-tumor treatment, radiological tumor progression data according to the Response Assessment in Neuro-Oncology (RANO) criteria,[19] and finally, the AED treatment information. More specifically, seizure type, start and end date of AED treatment, AED dosage at moment of treatment failure, and, if applicable, the reason for AED treatment failure (in case of adverse effects also the type and grade)[20] and date of first recurrent seizure after AED treatment initiation.

2.2 | Outcomes

The primary outcome was time to treatment failure for any reason, from initiation of first-line AED monotherapy to treatment failure, with a maximum follow-up duration of 36 months. AED treatment failure occurred when the initially prescribed AED was withdrawn, replaced with a new AED, or when an AED was added to the initial AED. A dose increase or dose reduction of the initially prescribed AED, addition of an AED taken only as needed, addition of an AED with a different indication than epileptic seizures, temporarily prophylactic addition of an AED during a perioperative period, poor adherence less than 1 week, or replacement with a non-oral AED in the end-of-life phase due to swallowing difficulties were not considered as treatment failure. In the event that patients were lost to follow-up due to progressive disease, post-drop-out information (ie, date of death) was used if available. If patients were lost to follow-up ≤3 months before death, patients were considered as showing continuation of AED treatment until date of death. Time to treatment failure was considered a measure for the effectiveness of AED treatment, encompassing both AED efficacy and tolerability.[21]

Secondary outcomes were: (1) time to treatment failure with regard to specific reasons of treatment failure; (2) long-term time to treatment failure for any reason, in patients who reached the maximum of 36 months of follow-up; (3) second-line time to treatment failure for any reason of levetiracetam vs valproic acid, if first-line levetiracetam was replaced with monotherapy valproic acid after treatment failure due to adverse effects or vice versa; (4) time to first recurrent epileptic seizure after AED initiation, as a measure of efficacy; and (5) level of toxicity, defined as severity (grade 1–5) of intolerable adverse effects leading to AED discontinuation according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0,[20] as a measure of tolerability. Whether adverse effects improved or not, typically in a period of 1–2 months, was noted to determine to what extent the adverse effects were due to the AED.[22] If intolerable adverse effects were part of another (main) adverse effect (eg, abnormal laboratory results in case of hepatic failure), only the main adverse effect (hepatic failure) was reported. Maximum duration of follow-up was 36 months for all outcomes, except long-term time to treatment failure, which had no maximum duration of follow-up.

2.3 | Statistics

Competing risks models, with death as a competing event,[23,24] were employed to estimate the cumulative incidence function of time to treatment failure of AED treatment and time to occurrence of a recurrent seizure after AED treatment initiation. Different competing risks models were estimated: (1) a model with two competing events when analyzing treatment failure for any reason (treatment failure and death); (2) a model with five competing events when analyzing the specific reasons of treatment failure (uncontrolled seizures, adverse effects, withdrawal due to remission of seizures, other reasons of treatment failure, and death); and (3) a model with three competing events when analyzing recurrent seizure (recurrent seizure, death, and treatment failure). Patients who experienced treatment failure before experiencing their first recurrent seizure can no longer experience a recurrent seizure on their first-line monotherapy levetiracetam or valproic acid, and therefore, treatment failure was handled as a competing risk in the latter competing risk model. To assess the difference between the cumulative incidences, the Gray test was used.[25] Severity of intolerable adverse effects, whether adverse effects improved or not, presence of promotor methylated O6-methylguanine-DNA methyltransferase (MGMT) in patients experiencing treatment failure due to uncontrolled seizures, presence of radiological tumor progression at time of treatment failure due to uncontrolled seizures, use of chemotherapy at time of treatment failure due to adverse effects, and baseline characteristics between matched and non-matched patients were analyzed using the chi-square test. Dosage at the moment of treatment failure was compared using the Mann-Whitney *U* test. Overall survival (time since radiological diagnosis) was estimated with the Kaplan-Meier (KM) methodology; the log-rank test was used to assess differences between survival curves. Median time of follow-up was estimated with the reverse-KM. Patients using levetiracetam and valproic acid were matched according to the nearest neighbor propensity score matching technique, in order to obtain similar covariate distributions in the two AED groups. Caliper width was set at 0.01 on the logit scale, a 1:1 match ratio without replacement, and standardized mean difference <0.1 was regarded as acceptable balance.[26] The following baseline covariates, which

might be related to treatment assignment and outcomes of interest, were included in the matching procedure: age, sex, histopathological and molecular diagnosis, surgical resection, radiotherapy, systemic therapy, tumor location, Karnofsky Performance Status (KPS), history of psychiatric disorder (depression, anxiety, or psychotic disorder), and seizure type. Statistical analyses were performed using statistical packages SPSS version 25.0 and R version 3.6.3, an open software environment.[27,28] All analyses concerning the competing risks models were performed in R with the cmprsk library.[24] A *P*-value of <.05 was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Patient characteristics are depicted in Table 1. Of 1435 patients included, 776 were prescribed levetiracetam and 659 valproic acid. Eventually during the course of the disease, 30% (437/1435) received anticonvulsant polytherapy. A total of 21% (302/1435) received duotherapy (commonly levetiracetam combined with valproic acid), 9% (126/1435) received triple therapy (commonly levetiracetam combined with valproic acid and clobazam), and 1% (9/1435) received quadruple therapy due to uncontrolled seizures. AED treatment due to intolerable adverse effects was discontinued by 18% (253/1435) of the patients once, by 6% (87/1435) twice, and 1% (19/1435) three times.

A total of 858 patients could be matched, resulting in comparable groups of 429 patients each. The non-matched patients were at baseline significantly more often younger than 40 years; had received more often surgical resection, radiotherapy, systemic therapy; and had more often a history of psychiatric disease (Table S1). Most first seizures prior to AED initiation occurred before histological diagnosis (687/858 = 80%, which was before matching 1064/1435 = 74%). All results presented below refer to the 858 matched patients. Median overall survival did not differ significantly between patients on levetiracetam and valproic acid (26.7 months [95% confidence interval (CI) 21.4–32.0] vs 26.9 months [95% CI 21.6–32.2]; $P = .699$). Median follow-up was equal to 86.2 months (95% CI 76.2–96.2).

3.2 | Time to treatment failure

A total of 40% (173/429) of patients who used levetiracetam showed treatment failure within 36 months follow-up, vs 59% (253/429) of patients who used valproic acid. The main reason for treatment failure for both levetiracetam and valproic acid was uncontrolled seizures (19% [81/429] vs 32% [136/429]), followed by adverse effects (16% [69/429] vs 17% [75/429]).

The cumulative incidence of treatment failure for any reason of levetiracetam was significantly lower compared to valproic acid (12 months: 33% [95% CI 29%–38%] vs 50% [95% CI 45%–55%]; $P < .001$ [Figure 1]). When looking at the specific reasons of treatment failure, the cumulative incidence for treatment failure due to uncontrolled seizures for levetiracetam and valproic acid (12 months: 16% [95% CI 12%–19%] vs 28% [95% CI 23%–32%]; $P < .001$) and treatment failure due to other reasons (12 months: 3% [95% CI 1%–5%] vs 7% [95% CI 5%–10%]; ($P = .004$) was significantly lower for levetiracetam, but no significant differences were found for treatment failure due to adverse effects (12 months: 14% [95% CI 11%–18%] vs 15% [95% CI 11%–18%]; $P = .636$) and withdrawal due to remission of seizures (36 months: 3% [95% CI 1%–5%] vs 2% [95% CI 1%–4%]; $P = .746$ [Figure S1]). The cumulative incidence of treatment failure due to adverse effects was significantly lower for males compared to females (12 months: 12% [95% CI 10%–15%] vs 19% [95% CI 15%–24%]; $P = .043$).

Comparison of daily dosages in patients who showed treatment failure due to uncontrolled seizures revealed that the median dosage was significantly lower for valproic acid than levetiracetam (1500 mg [IQR = 1500–2000] vs 2000 mg [IQR = 1500–2500]; $P = .005$) at the moment of treatment failure, whereas this was not true for treatment failure due to adverse effects (1000 mg [IQR = 1000–1500] vs 1000 mg [IQR = 1000–1000]; $P = .059$). Treatment failure due to uncontrolled seizures did not occur significantly more often in promotor methylated MGMT compared to non-methylated MGMT levetiracetam patients (18% [9/49] vs 21% [24/106]; $P = .546$) or in promotor methylated MGMT compared to non-methylated MGMT valproic acid patients (32% [9/28] vs 38% [23/60]; $P = .574$). Neither did levetiracetam differ significantly from valproic acid with regard to radiological tumor progression at the time of treatment failure due to uncontrolled seizures (36% [29/81] vs 26% [36/136]; $P = .147$) or use of chemotherapy at time of treatment failure due to adverse effects (30% [21/69] vs 36% [27/75]; $P = .479$).

The cumulative incidence of treatment failure for any reason in patients who showed retention of at least 36 months on their first-line AED (61 levetiracetam and 49 valproic acid patients) did not differ significantly between levetiracetam and valproic acid (72 months: 27% [95% CI 15%–42%] vs 40% [95% CI 26%–55%], 108 months: 41% [95% CI 23%–59%] vs 54% [95% CI 38%–68%]; $P = .243$).

Of the 429 valproic acid patients, 14% (59/429) switched to second-line monotherapy levetiracetam after treatment failure due to adverse effects, whereas this was true for 10% (45/429) of levetiracetam patients who switched to second-line monotherapy valproic acid. The cumulative incidence of treatment failure for any reason in these patients was significantly lower for second-line monotherapy levetiracetam compared to second-line monotherapy valproic acid (12 months: 26% [95%

TABLE 1 Demographic characteristics of the patients at baseline before and after matching

Characteristics	Before matching			After matching		
	LEV	VPA	SMD	LEV	VPA	SMD
Patients included, no. (%)	776	659		429	429	
Age, no. (%)						
≤40 years	136 (18)	180 (27)	0.219	83 (19)	82 (19)	0
>40 years	640 (82)	479 (73)		346 (81)	347 (81)	
Sex, no. (%)						
Male	506 (65)	426 (65)	0	280 (65)	262 (61)	0.083
Female	270 (35)	233 (35)		149 (35)	167 (39)	
Tumor grade and pathology, no. (%)						
Grade 2	155 (20)	216 (33)		108 (25)	105 (24)	
Diffuse astrocytoma NOS	32 (4)	85 (13)	0.333	30 (7)	29 (7)	0
Diffuse astrocytoma IDH-mutant	54 (7)	29 (4)	0.129	25 (6)	29 (7)	0.041
Oligodendroglioma NOS	15 (2)	43 (7)	0.255	13 (3)	9 (2)	0.063
Oligodendroglioma IDH-mutant 1p/19q co-deletion	48 (6)	47 (7)	0.040	35 (8)	33 (8)	0
Oligoastrocytoma NOS	5 (1)	10 (2)	0.099	4 (1)	4 (1)	0
Pleiomorphic xanthroastrocytoma	1 (0)	2 (0)	0	1 (0)	1 (0)	0
Grade 3	61 (8)	105 (16)		44 (10)	44 (10)	
Anaplastic astrocytoma NOS	17 (2)	50 (8)	0.289	15 (3)	17 (4)	0.053
Anaplastic astrocytoma IDH-mutant	16 (2)	8 (1)	0.078	5 (1)	6 (1)	0
Anaplastic oligodendroglioma NOS	16 (2)	25 (4)	0.120	14 (3)	12 (3)	0
Anaplastic oligodendroglioma IDH-mutant 1p/19q co-deletion	12 (2)	17 (3)	0.071	10 (2)	9 (2)	0
Anaplastic oligoastrocytoma NOS	0 (0)	5 (1)	0.170	0 (0)	0 (0)	-
Grade 4	560 (72)	338 (51)		277 (65)	280 (65)	
Diffuse astrocytoma IDH-wildtype	17 (2)	11 (2)	0	5 (1)	7 (2)	0.085
Anaplastic astrocytoma IDH-wildtype	12 (2)	6 (1)	0.090	5 (1)	4 (1)	0
Glioblastoma NOS	339 (44)	283 (43)	0.020	229 (53)	234 (55)	0.040
Glioblastoma IDH-wildtype	178 (23)	30 (5)	0.529	29 (7)	30 (7)	0
Glioblastoma IDH-mutant	14 (2)	8 (1)	0.081	9 (2)	5 (1)	0.079
Surgical resection, no. (%)						
Yes	237 (31)	82 (12)	0.468	75 (17)	68 (16)	0.027
No (including biopsy)	539 (69)	577 (88)		354 (83)	361 (84)	

(Continues)

TABLE 1 (Continued)

Characteristics	Before matching			After matching		
	LEV	VPA	SMD	LEV	VPA	SMD
Radiotherapy, no. (%)						
Yes	190 (24)	77 (12)	0.313	64 (15)	56 (13)	0.058
No	586 (76)	582 (88)		365 (85)	373 (87)	
Systemic therapy,[a] no. (%)						
Yes	181 (23)	56 (8)	0.412	54 (13)	47 (11)	0.062
Temozolomide (+ additional agents)	173 (22)	52 (8)		51 (12)	44 (10)	
Temozolomide rechallenge (+ additional agents)	5 (1)	2 (0)		1 (0)	2 (0)	
PCV (+ additional agents)	7 (1)	4 (1)		2 (0)	2 (0)	
Lomustine (+ additional agents)	28 (4)	5 (1)		8 (2)	4 (1)	
Other	11 (1)	5 (1)		3 (1)	2 (0)	
No	595 (77)	603 (92)		375 (87)	382 (89)	
Tumor involvement of the temporal lobe						
Yes	367 (47)	298 (45)	0.040	187 (44)	205 (48)	0.080
No	409 (53)	361 (55)		242 (56)	224 (52)	
Tumor involvement of the frontal lobe						
Yes	474 (61)	406 (62)	0.021	267 (62)	250 (58)	0.082
No	302 (39)	253 (38)		162 (38)	179 (42)	
Karnofsky Performance Status, no. (%)						
≥70	717 (92)	626 (95)	0.123	406 (95)	405 (94)	0.044
<70	59 (8)	33 (5)		23 (5)	24 (6)	
History of a psychiatric disease,[b] no. (%)						
Yes	43 (6)	53 (8)	0.080	20 (5)	24 (6)	0.045
No	733 (94)	606 (92)		409 (95)	405 (94)	
Seizure type,[c] no. (%)						
Focal	358 (46)	249 (38)	0.161	193 (45)	168 (39)	0.080
Focal to bilateral tonic-clonic[d]	378 (49)	356 (54)		214 (50)	226 (53)	
Unknown	40 (5)	54 (8)		22 (5)	35 (8)	

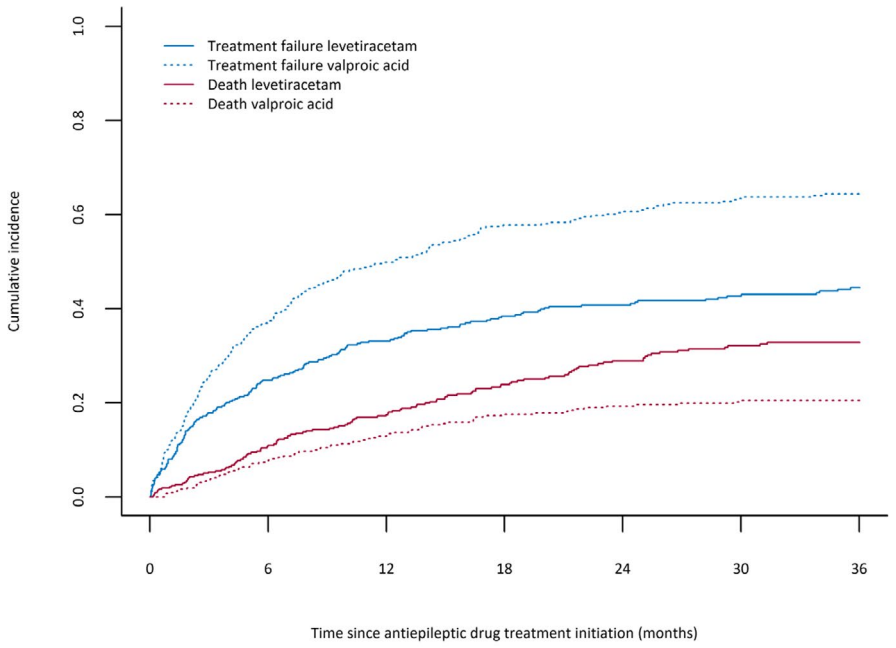
IDH, Isocitrate dehydrogenase; LEV, levetiracetam; no., number of patients; NOS, Not otherwise specified; PCV, procarbazine, lomustine, and vincristine; SMD, standardized mean difference, <0.1 indicates acceptable balance; VPA, valproic acid

[a]Yes vs no.

[b]History of a psychiatric disease included depression, anxiety, or psychotic disorders.

[c]Was not included in propensity score matching due to the high number of patients with an unknown seizure type.

[d]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures.



Time in months	0	3	6	12	24	36	
No. at risk							
LEV, no.	429	316	253	183	100	0	
VPA, no.	429	291	214	138	68	0	
No. censored							
LEV, no.	0	16	28	41	58	134	
VPA, no.	0	15	31	37	46	98	
Event treatment failure for any reason							p<0.001
CIF (95%CI), LEV	0	18 (14-22)	25 (21-29)	33 (29-38)	41 (36-46)	44 (39-49)	
CIF (95%CI), VPA	0	26 (21-30)	37 (32-42)	50 (45-55)	61 (56-65)	64 (59-69)	
Event death							p<0.001
CIF (95%CI), LEV	0	5 (3-8)	11 (8-14)	17 (14-21)	29 (24-34)	33 (28-38)	
CIF (95%CI), VPA	0	4 (2-6)	8 (5-10)	13 (10-17)	19 (16-23)	21 (17-25)	

FIGURE 1 Time to treatment failure for any reason, from antiepileptic drug treatment initiation, in 858 matched patients: levetiracetam vs valproic acid. CI, confidence interval; CIF, cumulative incidence function; LEV, levetiracetam; no., number of patients; VPA, valproic acid

CI 15%–37%] vs 44% [95% CI 28%–59%], 36 months: 36% [95% CI 23%–48%] vs 66% [95% CI 48%–79%]; $P = .007$).

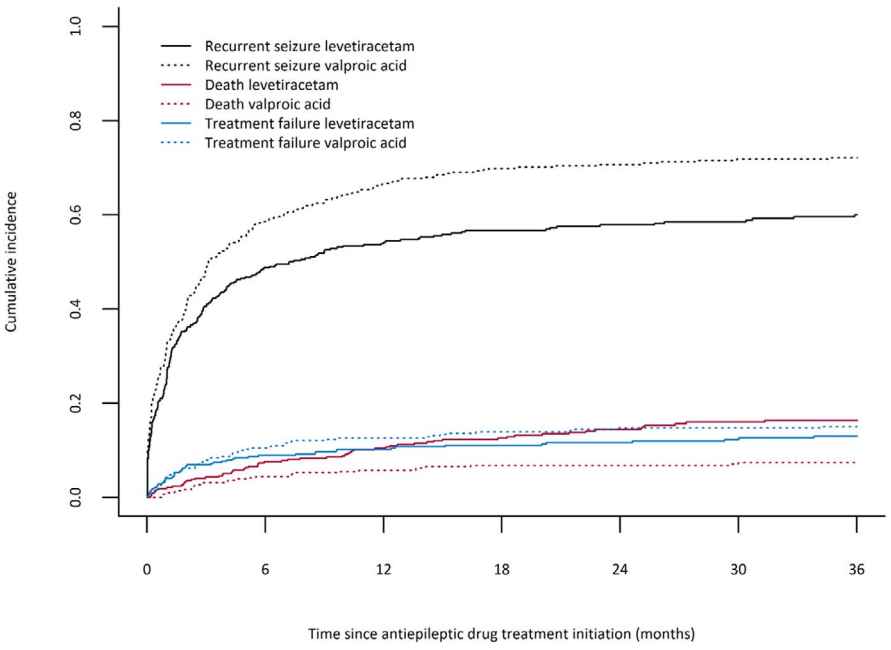
The cumulative incidence of treatment failure for any reason of low-grade (grade 2, $n = 213$) did not differ significantly from high grade (grade 3 or 4, $n = 645$) glioma patients (12 months: 38% [95% CI 31%–44%] vs 43 [95% CI 39%–47%]; $P = .891$). Neither did the cumulative incidences of treatment failure for any reason differ significantly for tumor involvement of the temporal lobe compared to no tumor involvement of the temporal lobe (12 months: 42% yes [95% CI 37%–47%) vs 41% no [95% CI 36%–45%); $P = .889$) or for tumor involvement of the frontal lobe compared to no tumor involvement of the frontal lobe (12 months: 43% yes [95% CI 38%–47%) vs 39% no [95% CI 34%–45%); $P = .252$).

3.3 | Time to recurrent seizure

The cumulative incidence of recurrent seizure was significantly lower for levetiracetam compared to valproic acid (12 months: 54% [95% CI 49%–59%] vs 67% [95% CI 62%–71%]; $P < .001$ [Figure 2]). No significant difference was found when comparing the cumulative incidence of recurrent seizure of low-grade with high-grade glioma patients (12 months: 60% [95% CI 53%–66%] vs 61% [95% CI 57%–64%); $P = .864$). Neither was a significant difference found for the cumulative incidence of recurrent seizure for tumor involvement of the temporal lobe (12 months: 60% yes [95% CI 55%–65%] vs 61% no [95% CI 56%–65%); $P = .738$) or tumor involvement of the frontal lobe (12 months: 62% yes [95% CI 57%–66%] vs 59% no [95% CI 53%–64%); $P = 273$).

3.4 | Adverse effects leading to intolerability

In the levetiracetam group, 110 adverse effects in 69 patients were observed, which led to treatment failure (Table 2). The three most common intolerable adverse effects were agitation (21/110 = 19%), fatigue (10/110 = 9%), and somnolence



Time in months	0	3	6	12	24	36	
No. at risk							
LEV, no.	426	196	137	95	52	0	
VPA, no.	423	164	101	57	28	0	
No. censored							
LEV, no.	0	13	18	23	34	70	
VPA, no.	0	11	19	19	21	41	
Event recurrent seizure							p<0.001
CIF (95%CI), LEV	0	41 (36-45)	49 (44-53)	54 (49-59)	58 (53-63)	60 (55-65)	
CIF (95%CI), VPA	0	48 (43-53)	58 (54-63)	67 (62-71)	71 (66-75)	72 (67-76)	
Event death							p<0.001
CIF (95%CI), LEV	0	4 (3-7)	8 (5-10)	10 (8-14)	14 (11-18)	16 (13-20)	
CIF (95%CI), VPA	0	3 (2-5)	4 (3-7)	6 (4-8)	7 (5-10)	7 (5-10)	
Event treatment failure[1]							p=0.387
CIF (95%CI), LEV		7 (5-10)	9 (6-12)	10 (7-13)	12 (9-15)	13 (10-17)	
CIF (95%CI), VPA		8 (6-11)	11 (8-14)	13 (10-16)	15 (11-18)	15 (12-19)	

FIGURE 2 Time to recurrent seizure, from antiepileptic drug treatment initiation, in 858 matched patients: levetiracetam vs valproic acid.[1] Patients who experienced treatment failure (due to adverse effects, withdrawal due to remission of seizures, or other reasons) before experiencing their recurrent seizure can no longer experience a recurrent seizure on their first-line monotherapy levetiracetam or valproic acid, and therefore, treatment failure was handled as a competing risk. CI, confidence interval; CIF, cumulative incidence function; LEV, levetiracetam; no., number of patients; VPA, valproic acid

(9/110 = 8% [Table S2]). In the valproic acid group, 116 adverse effects in 75 patients were observed, which led to treatment failure, with decreased platelet count (16/116 = 14%), weight gain (12/116 = 10%), and tremor (12/116 = 10%) as the three most common adverse effects. A total of 20% (4/20) of levetiracetam and 21% (5/24) of valproic acid patients with a history of psychiatric disease showed treatment failure due to adverse effects. In the levetiracetam group, this was in all four patients due to intolerable psychiatric adverse effects, whereas this was in the valproic acid group in none of the five patients due to intolerable psychiatric adverse effects. Only a minority of the adverse effects were grade 3 or 4 (17% [19/110] with levetiracetam vs 20% [23/116] with valproic acid; $P = .625$); also a minority did not improve after discontinuation of levetiracetam or valproic acid (both 18% [20/110 vs 21/116]; $P = .861$).

4 | DISCUSSION

The aim of this retrospective observational study was to compare the effectiveness of two of the most commonly prescribed AEDs in glioma patients with epilepsy: levetiracetam and valproic acid. The overall results indicate that levetiracetam shows better efficacy than valproic acid, reflected in lower cumulative incidences of treatment failure due to uncontrolled seizures and a recurrent seizure. However, tolerability was similar between the two AEDs, reflected in similar cumulative incidences of treatment failure due to adverse effects, and similar percentages of severe toxicity or improvement of adverse effects after AED discontinuation. Levetiracetam has thus shown better efficacy over valproic acid in glioma patients in our study, both as first-line and second-line AED treatment.

TABLE 2 Adverse effects that led to treatment failure in 858 matched patients: levetiracetam vs valproic acid

Adverse effects that led to treatment failure[a]	Levetiracetam	Valproic acid
Adverse effect categories based on the CTCAE v. 5.0	Adverse effects, no. (%)	Adverse effects, no. (%)
Blood and lymphatic system disorders	0 (0)	2 (2)
Eye disorders	3 (3)	0 (0)
Gastrointestinal disorders	6 (5)	8 (7)
General and administration site conditions	13 (12)	10 (9)
Hepatobiliary disorders	0 (0)	3 (3)
Investigations[b]	0 (0)	52 (45)
Metabolism and nutrition disorders	1 (1)	0 (0)
Nervous system disorders	30 (27)	31 (27)
Psychiatric disorders	51 (46)	3 (3)
Reproductive system and breast disorders	0 (0)	1 (1)
Respiratory, thoracic and mediastinal disorders	1 (1)	0 (0)
Skin and subcutaneous tissue disorders	3 (3)	4 (3)
Unknown	2 (2)	2 (2)
Total number of adverse effects	110 (100)	116 (100)
Total number of patients who showed treatment failure due to adverse effects	69	75

CTCAE, Common Terminology Criteria for Adverse Events; no., number of patients.

[a]A more detailed description of all adverse effects that led to treatment failure can be found in the supplementary, Table S2.

[b]Includes adverse effects based on (laboratory) test results, for example, decreased platelet count, increased alanine aminotransferase, or weight gain.

Several factors need to be taken into consideration when interpreting these results. Median dosage at the time of treatment failure due to uncontrolled seizures was significantly higher for levetiracetam. This might indicate less adequate dose escalation of valproic acid, given that both drugs have similar defined daily dosages, which may partly explain the higher percentage of treatment failure due to uncontrolled seizures of valproic acid. Possible reasons for the lower median dosage at moment of treatment failure due to uncontrolled seizures of valproic acid might be the narrower therapeutic index of valproic acid, the unpredictable relationship between dosage and serum concentration of valproic acid, and a possible preference of physicians for levetiracetam. Due to its lack of hepatic metabolism and no known pharmacological interactions, physicians might have prematurely added levetiracetam as second-line AED. Treatment failure due to adverse effects could also be attributed to other medications, such as dexamethasone or chemotherapeutic agents. However, after discontinuation of the AED, the adverse effects improved in most cases, making it more likely that these adverse effects were indeed attributable to the AED. Six-month treatment failure due to adverse effects percentages of levetiracetam (12%) and valproic acid (11%), as well as the frequency of types of adverse effects, were very much alike in other non-brain tumor-related epilepsy studies (ie, AED monotherapy 6-month treatment failure due to adverse effects is between 10% and 14%).[29–31] This challenges the common view[12,32,33] that patients with glioma are more prone to intolerable adverse effects.[34] The common view that women with brain tumor–related epilepsy are more prone to adverse effects was confirmed by this study.[9] Although intolerability percentages between levetiracetam and valproic acid were comparable, the type of adverse effects differed substantially. The most frequently occurring adverse effects in patients on levetiracetam was agitation, whereas this was a decreased platelet count in those on valproic acid, which is in line with previous reports.[6,35] Other common views in the field of neuro-oncology, the potential survival benefit of valproic acid, worse seizure control in temporal lobe, frontal lobe, and low-grade gliomas,[12,32,36–40] are challenged by this study. We found no survival difference between valproic acid and levetiracetam or difference in seizure recurrence with regard to tumor grade or tumor location.

This is the first study that investigated the effectiveness of levetiracetam compared with valproic acid in patients with glioma, taking into account relevant methodological issues. We matched the two groups appropriately on measured potential confounders to mimic the randomized controlled trial (RCT) design as far as possible. A previous study found lower treatment failure percentages of levetiracetam compared to valproic acid (41% vs 66%), but

comparable seizure freedom percentages (43% vs 41%). However, only glioblastoma patients were included and no formal statistical analysis was conducted, including competing risks analysis and a pre-specified maximum duration of follow-up for the AEDs, to ensure comparability between the two AED groups.[6, 41]

4.1 | Limitations

Valproic acid used to be the preferred choice as first-line AED monotherapy in glioma patients in the beginning of the century, at least in The Netherlands, but over the years has been overtaken by levetiracetam. This disparity in calendar period could theoretically introduce bias. However, given that the anti-tumor treatments for glioma, which have shown to have an advantageous effect on seizure control,[6] has remained fairly comparable over the past 15 years, we believe this had a negligible effect on the outcomes. Due to the retrospective nature of this study we did not have information on serum levels at the moment of treatment failure of both drugs, which would have been a more reliable estimate. In our study, only patients who were prescribed first-line valproic acid or levetiracetam were included. Unfortunately, the reason and whether a specific AED was prescribed as first or maybe as second choice cannot be determined due to our retrospective design. Although we accounted for confounding by matching according to the nearest neighbor propensity score matching technique, in a retrospective design it is impossible to account for unmeasured confounders. Residual confounding might therefore still be present. Given that our study was not designed under ideal circumstances (ie, no randomization, not placebo controlled, no blinding), this study should be interpreted as an effectiveness study and not as an efficacy trial.[42]

5 | CONCLUSION

Our results suggest that first-line monotherapy levetiracetam may have favorable efficacy compared to valproic acid, whereas the two AEDs seem similarly tolerated in glioma patients with epilepsy. Therefore, given the available evidence, levetiracetam seems the preferred choice for first-line AED treatment in glioma patients with no history of certain psychiatric diseases. Currently an RCT is ongoing (ClinicalTrials.gov Identifier: NCT03048084) comparing efficacy and tolerability of first-line monotherapy levetiracetam with valproic acid in glioma patients, and may provide more insight into the question of which AED is preferred in patients with glioma.

CONFLICTS OF INTEREST

None of the authors declare a conflict of interest. We confirm that we have read the Journal's guidelines for ethical publication and affirm that this manuscript is consistent with these guidelines.

ACKNOWLEDGMENTS

We acknowledge the contribution of Marijke Coomans with her input in the design of the figures.

AUTHOR CONTRIBUTION

PBvdM, LD, MJvdB, MJBT, and JAFK designed the study. Data collection was performed by PBvdM. PBvdM performed data-analysis with input from LD, MF, and JAFK. PBvdM wrote the first and successive versions of the manuscript. All authors (PBvdM, LD, MF, MJV, MCMK, MJvdB, MJBT, and JAFK) contributed to the interpretation of the results, intellectual content, and critical revisions to the drafts of the paper, and approved the final version. PBvdM had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Meer PB, Dirven L, Fiocco M, et al. First-line antiepileptic drug treatment in glioma patients with epilepsy: Levetiracetam vs valproic acid. *Epilepsia*. 2021;62:1119–1129. https://doi.org/10.1111/epi.16880