Optimizing antiseizure medication treatment in glioma patients with epilepsy

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CHAPTER 3

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

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Abstract

Objective

This study aimed at estimating the cumulative incidence of AED treatment failure of first-line monotherapy levetiracetam versus 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 competing event. Patients were matched on baseline covariates potentially related to treatment assignment and outcomes of interest according to the nearest neighbour 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%CI=29-38%] versus 50% [95%CI=45-55%]; p<0.001). 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%] versus 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%] versus 15% [95%CI=11-18%]; p=0.636).

Significance

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

Keywords

Glioma, valproic acid, levetiracetam, antiepileptic drug, seizures

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.

Introduction

Gliomas are the most common malignant primary brain tumours and treatment options are multimodal.[1, 2] Seizures are a well-recognized symptom in glioma patients and occur frequently, either as presenting symptom or during the course of the disease.[3] The incidence of seizures is higher in slow-growing tumours.[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 codeleted 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 antitumour treatment, including surgical resection, radiotherapy, and chemotherapy.[6] Potential drug interactions between AEDs and chemotherapeutic drugs complicate seizure management in glioma patients and therefore cytochrome P450 (CYP450) enzyme-inducing AEDs, such as phenytoin and carbamazepine are generally not advised.[2] 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 glioma patients.[6-9] Valproic acid is a first-generation AED and has been used in the treatment of epilepsy for over 50 years.[10] It has a well-established reputation as a broad spectrum AED and has been associated with decreased psychiatric and behavioural adverse effects in epilepsy patients.[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 antitumoural 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 has been licensed around 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 behavioural 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 have not been sufficiently investigated in glioma patients yet. This retrospective observational study aimed to directly compare the effectiveness of first-line monotherapy levetiracetam versus valproic acid.

Methods

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 1st, 2004 and January 1st, 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 tumour-related epilepsy; 2) prophylactic or first-line AED treatment other than levetiracetam or valproic acid was initiated; 3) the tumour 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 institutions policy.

Patients' charts were examined to extract baseline sociodemographic data, tumour characteristics, information on anti-tumour treatment, radiological tumour progression data according to the Response Assessment in Neuro-Oncology (RANO) criteria,[19] and lastly 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.

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 one 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 case patients were lost to follow-up due to progressive disease, post-drop-out information (i.e. 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 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 versus 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 the plausibility to what extent the adverse effects were due to the AED.[22] If intolerable adverse effects were part of another (main) adverse effect (e.g. 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.

Statistics

Competing risks models, with death as 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 analysing treatment failure for any reason (treatment failure and death); 2) a model with five competing events when analysing 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 analysing 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 competing risk in the latter competing risk model. To assess the difference between the cumulative incidences the Gray's 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 tumour 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 analysed using the χ^2. Dosage at 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 standardised 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, tumour 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 <0.05 was considered statistically significant.

Results

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 tripletherapy (commonly levetiracetam combined with valproic acid and clobazam), and 1% (9/1435) received quadrupletherapy 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 forty 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%CI=21.4-32.0] versus 26.9 months [95%CI=21.6-32.2]; p=0.699). Median follow-up was equal to 86.2 months (95%CI=76.2-96.2).

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

	Before matching			After matching		
Characteristics	**LEV**	**VPA**	**SMD**	**LEV**	**VPA**	**SMD**
Patients included, no. (%)	776	659		429	429	
Age, no. (%)			0.219			0
≤40 years	136 (18)	180 (27)		83 (19)	82 (19)	
>40 years	640 (82)	479 (73)		346 (81)	347 (81)	
Sex, no. (%)			0			0.083
Male	506 (65)	426 (65)		280 (65)	262 (61)	
Female	270 (35)	233 (35)		149 (35)	167 (39)	
Tumour 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 codeletion	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 codeletion	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. (%)			0.468			0.027

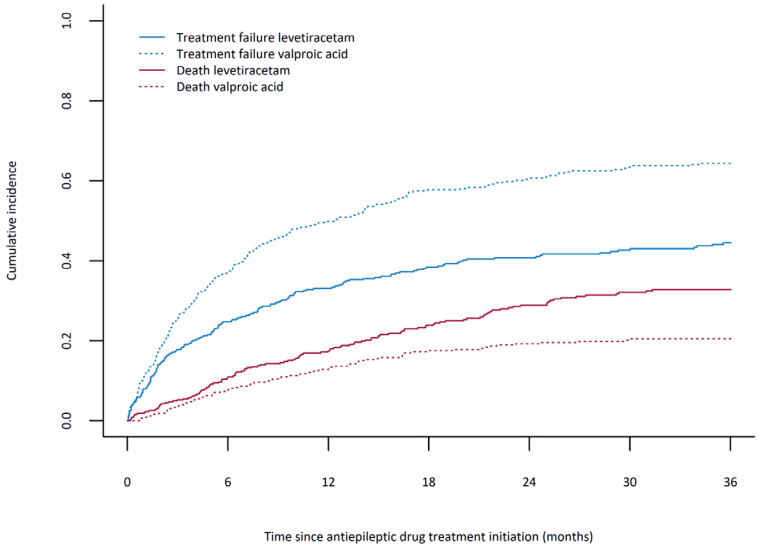
Table 1. Continued

	Before matching			After matching		
Characteristics	**LEV**	**VPA**	**SMD**	**LEV**	**VPA**	**SMD**
Yes	237 (31)	82 (12)		75 (17)	68 (16)	
No (including biopsy)	539 (69)	577 (88)		354 (83)	361 (84)	
Radiotherapy, no. (%)			0.313			0.058
Yes	190 (24)	77 (12)		64 (15)	56 (13)	
No	586 (76)	582 (88)		365 (85)	373 (87)	
Systemic therapy[a], no. (%)			0.412			0.062
Yes	181 (23)	56 (8)		54 (13)	47 (11)	
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)	
Tumour involvement of the temporal lobe			0.040			0.080
Yes	367 (47)	298 (45)		187 (44)	205 (48)	
No	409 (53)	361 (55)		242 (56)	224 (52)	
Tumour involvement of the frontal lobe			0.021			0.082
Yes	474 (61)	406 (62)		267 (62)	250 (58)	
No	302 (39)	253 (38)		162 (38)	179 (42)	
Karnofsky Performance Status, no. (%)			0.123			0.044
≥70	717 (92)	626 (95)		406 (95)	405 (94)	
<70	59 (8)	33 (5)		23 (5)	24 (6)	
History of a psychiatric disease[b], no. (%)			0.080			0.045
Yes	43 (6)	53 (8)		20 (5)	24 (6)	
No	733 (94)	606 (92)		409 (95)	405 (94)	
Seizure type[c], no. (%)			0.161			0.080
Focal	358 (46)	249 (38)		193 (45)	168 (39)	
Focal to bilateral tonic-clonic[d]	378 (49)	356 (54)		214 (50)	226 (53)	
Unknown	40 (5)	54 (8)		22 (5)	35 (8)	

[a]Yes versus 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; 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

Time to treatment failure

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



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 versus valproic acid.
CI=Confidence interval; CIF=Cumulative incidence function; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid

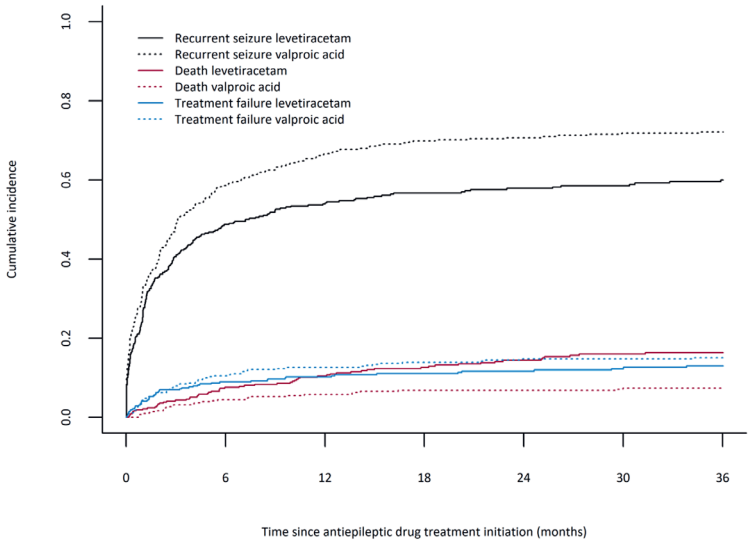
The cumulative incidence of treatment failure for any reason of levetiracetam was significantly lower compared to valproic acid (12 months: 33% [95%CI=29-38%] versus 50% [95%CI=45-55%]; p<0.001 [Figure 1]). When looking at the specific reasons of treatment failure, the cumulative incidence for treatment failure due to uncontrolled seizures for levetiracetam and valproic acid (12 months: 16% [95%CI=12-19%] versus 28% [95%CI=23-32%]; p<0.001) and treatment failure due to other reasons (12 months: 3% [95%CI=1-5%] versus 7% [95%CI=5-10%]; (p=0.004) 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%] versus 15% [95%CI=11-18%]; p=0.636) and withdrawal due to remission of seizures (36 months: 3% [95%CI=1-5%] versus 2% [95%CI=1-4%]; p=0.746 [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%] versus 19% [95%CI=15-24%]; p=0.043).

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] versus 2000 mg [IQR=1500-2500]; p=0.005) at moment of treatment failure, while this was not true for treatment failure due to adverse effects (1000 mg [IQR=1000-1500] versus 1000 mg [IQR=1000-1000]; p=0.059). 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] versus 21% [24/106]; p=0.546) or in promotor methylated MGMT compared to non-methylated MGMT valproic acid patients (32% [9/28] versus 38% [23/60]; p=0.574). Neither did levetiracetam differ significantly from valproic acid with regard to radiological tumour progression at time of treatment failure due to uncontrolled seizures (36% [29/81] versus 26% [36/136]; p=0.147) nor use of chemotherapy at time of treatment failure due to adverse effects (30% [21/69] versus 36% [27/75]; p=0.479).

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%] versus 40% [95%CI=26-55%], 108 months: 41% [95%CI=23-59%] versus 54% [95%CI=38-68%]; p=0.243).

Of the 429 valproic acid patients 14% (59/429) switched to second-line monotherapy levetiracetam after treatment failure due to adverse effects, while 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%CI=15-37%] versus 44% [95%CI=28-59%], 36 months: 36% [95%CI=23-48%] versus 66% [95%CI=48-79%]; p=0.007).

The cumulative incidence of treatment failure for any reason of low-grade (grade 2,



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 versus 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 competing risk; CI=Confidence interval; CIF=Cumulative incidence function; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid

n=213) did not differ significantly from high grade (grade 3 or 4, n=645) glioma patients (12 months: 38% [95%CI=31-44%] versus 43 [95%CI=39-47%]; p=0.891). Neither did the cumulative incidences of treatment failure for any reason differ significantly of tumour involvement of the temporal lobe compared to no tumour involvement of the temporal

lobe (12 months: 42% yes [95%CI=37-47%) versus 41% no [95%CI=36-45%); p=0.889) nor of tumour involvement of the frontal lobe compared to no tumour involvement of the frontal lobe (12 months: 43% yes [95%CI=38-47%) versus 39% no [95%CI=34-45%); p=0.252).

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%] versus 67% [95%CI=62-71%]; p<0.001 [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%] versus 61% [95%CI=57-64%), p=0.864). Neither a significant difference was found for the cumulative incidence of recurrent seizure for tumour involvement of the temporal lobe (12 months: 60% yes [95%CI=55-65%] versus 61% no [95%CI=56-65%), p=0.738) nor tumour involvement of the frontal lobe (12 months: 62% yes [95%CI=57-66%] versus 59% no [95%CI=53-64%), p=273).

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 (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 4 patients due to intolerable psychiatric adverse effects, while this was in the valproic acid group in none of the 5 patients due to intolerable psychiatric adverse effects. Only a minority of the adverse effects were grade 3 or 4 (17% [19/110] with levetiracetam versus 20% [23/116] with valproic acid; p=0.625), also a minority did not improve after discontinuation of levetiracetam or valproic acid (both 18% [20/110 versus 21/116]; p=0.861).

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

Table 2. Adverse effects which led to treatment failure in 858 matched patients: levetiracetam versus valproic acid

Adverse effects which 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[2]	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

[a]A more detailed description of all adverse effects which led to treatment failure can be found in the supplementary, Table S2; [2]Includes adverse effects based on (laboratory) test results, e.g. decreased platelet count, increased alanine aminotransferase, or weight gain; CTCAE=Common Terminology Criteria for Adverse Events; No.=Number of patients

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.

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 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 the vast majority of cases, making it more likely 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 tumour-related epilepsy studies (i.e. AED monotherapy 6-month treatment failure due to adverse effects is between 10-14%).[29-31] This challenges the common view,[12, 32, 33] that glioma patients are more prone to intolerable adverse effects.[34] The common view that women with brain tumour-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, while 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 tumour grade or tumour location.

This is the first study that investigated the effectiveness of levetiracetam compared with valproic acid in glioma patients, 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% versus 66%), but comparable seizure freedom percentages (43% versus 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]

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-tumour 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 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 why 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 our study was not designed under ideal circumstances (i.e. no randomisation, not placebo controlled, no blinding), this study should be interpreted as an effectiveness study and not as an efficacy trial.[42]

Conclusion

Our results suggest that first-line monotherapy levetiracetam may have favourable efficacy compared to valproic acid, while 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 which AED is preferred in glioma patients.

Author's 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, 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.

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

Conflicts of interest statement
All authors declare no competing interests.

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Ethical publication statement
We confirm that we have read the Journal's guidelines for ethical publication and affirm that this manuscript is consistent with these guidelines.

Ethics committee approval
The institutional review board approved the study. If necessitated by the medical ethics committee of the institution (Amsterdam University Medical Center and Erasmus Medical Center), patients provided written informed consent.

Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supplementary material

Table S1. Demographic characteristics of the matched versus the non-matched patients

Characteristics	Matched	Non-matched	P-value
Patients included, no. (%)	858	577	
Age, no. (%)			0.002
≤40 years	165 (19)	151 (26)	
>40 years	693 (81)	426 (74)	
Sex, no. (%)			0.085
Male	542 (63)	390 (68)	
Female	316 (37)	187 (32)	
Tumour grade and pathology, no. (%)			0.052
Grade 2	213 (25)	158 (27)	
Grade 3	88 (10)	78 (14)	
Grade 4	557 (65)	341 (59)	
Surgical resection, no. (%)			<0.001
Yes	143 (17)	176 (31)	
No (including biopsy)	715 (83)	401 (69)	
Radiotherapy, no. (%)			<0.001
Yes	120 (14)	147 (25)	
No	738 (86)	430 (75)	
Systemic therapy[1], no. (%)			<0.001
Yes	101 (12)	136 (24)	
No	757 (88)	441 (76)	
Tumour involvement of the temporal lobe			0.545
Yes	392 (46)	273 (47)	
No	466 (54)	304 (53)	
Tumour involvement of the frontal lobe			0.311
Yes	517 (60)	363 (63)	
No	341 (40)	214 (37)	
Karnofsky Performance Status, no. (%)			0.078
≥70	811 (95)	532 (92)	
<70	47 (5)	45 (8)	
History of a psychiatric disease[a], no. (%)			0.004
Yes	44 (5)	52 (9)	
No	814 (95)	525 (91)	
Seizure type, no. (%)			0.813
Focal	360 (42)	247 (43)	
Focal to bilateral tonic-clonic[b]	440 (51)	294 (51)	
Unknown	58 (7)	36 (6)	

[a]History of a psychiatric disease included depression, anxiety, or psychotic disorders; [b]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; No.=Number of patients

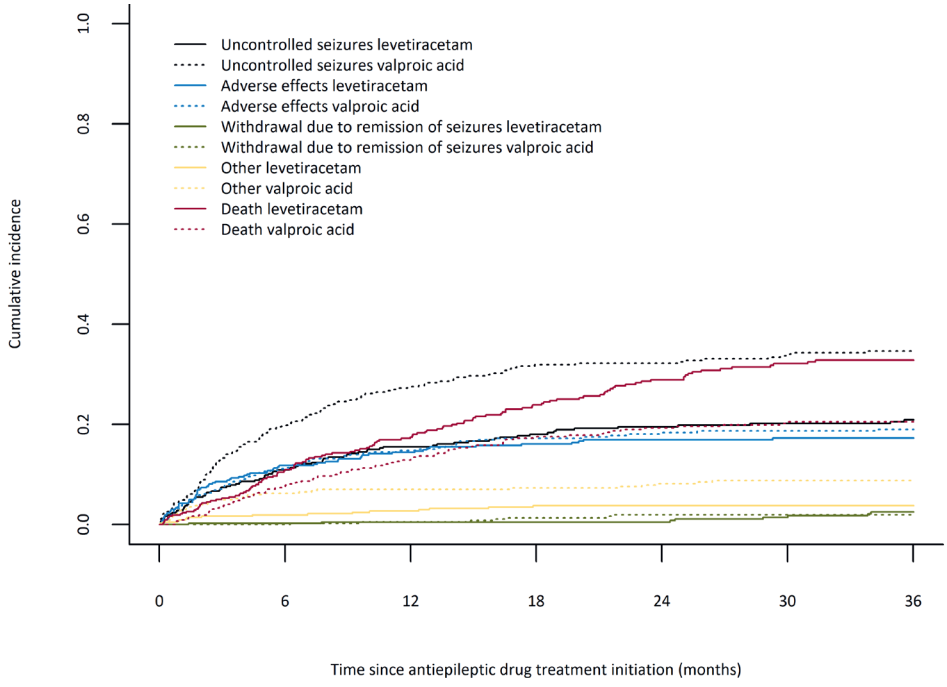

Figure S1. Time to treatment failure for specific reasons of treatment failure, from antiepileptic drug treatment initiation, in 858 matched patients: levetiracetam versus valproic acid

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	
Treatment failure							
Event uncontrolled seizures							p<0.001
CIF (95%CI), LEV	0	7 (5-10)	11 (8-14)	16 (12-19)	20 (16-24)	21 (17-25)	
CIF (95%CI), VPA	0	13 (10-16)	20 (16-24)	28 (23-32)	32 (28-37)	35 (30-39)	
Event adverse effects							p=0.636
CIF (95%CI), LEV	0	9 (6-12)	12 (9-15)	14 (11-18)	17 (13-21)	17 (14-21)	
CIF (95%CI), VPA	0	8 (5-11)	11 (8-14)	15 (11-18)	18 (15-22)	19 (15-23)	
Event withdrawal due to remission of seizures[a]							p=0.746
CIF (95%CI), LEV	0	0 (0-1)	0 (0-1)	0 (0-2)	0 (0-2)	3 (1-5)	
CIF (95%CI), VPA	0	0 (-)	0 (-)	0 (0-2)	2 (1-4)	2 (1-4)	
Event other reasons[b]							p=0.004
CIF (95%CI), LEV	0	2 (1-3)	2 (1-4)	3 (1-5)	4 (2-6)	4 (2-6)	
CIF (95%CI), VPA	0	5 (3-7)	6 (4-9)	7 (5-10)	8 (6-11)	9 (6-12)	
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)	

[a]Withdrawal due to remission of seizures was defined as discontinuation of the antiepileptic drug with consent of the medical doctor, regardless of the term being treated with the antiepileptic drug; [b]Other encompassed treatment failure due to unknown reasons (n=22), due to poor adherence (n=13), due to possible interaction with temozolomide (n=7), due to increased risk of bleeding (n=4), due to participation in a trial (n=1), due to porphyria (n=1), due to no rectal administration available (n=1), due to an estimated glomerulation filtration rate 17 milliliters/minute (n=1); LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid

Table S2. Adverse effects which led to treatment failure in detail in 858 matched patients

Adverse effects according to the CTCAE 5.0	Levetiracetam							Valproic acid						
	Grade, no.				Improved, no.[a]			Grade, no.				Improved, no.[a]		
	1,2	3,4	?	Total	Yes	No	?	1,2	3,4	?	Total	Yes	No	?
Blood and lymphatic system disorders														
Anemia	-	-	-	-	-	-	-	-	1	-	1	1	-	-
Perioperative bleeding	-	-	-	-	-	-	-	-	1		1	1	-	-
Total	-	-	-	-	-	-	-	-	2	-	2	2	-	-
Eye disorders														
Blurred vision	2	-	-	2	2	-	-	-	-	-	-	-	-	-
Photophobia	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Total	3	-	-	3	3	-	-	-	-	-	-	-	-	-
Gastrointestinal disorders														
Diarrhea	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Dyspepsia	3	-	-	3	3	-	-	4	-	-	4	3	1	-
Nausea	2	-	-	2	1	-	1	3	-	-	3	3	-	-
Vomiting	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Total	6	-	-	6	5		1	8			8	7	1	
General and administration site conditions														
Edema limbs	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Fatigue	10	-	-	10	6	4	-	7	1	-	8	3	3	2
Gait disturbance	2	-	-	2	1	1	-	1	-	-	1	1	-	-
Malaise	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Total	13	-	-	13	8	5	-	9	1	-	10	5	3	2
Hepatobiliary disorders														
Hepatic failure	-	-	-	-	-	-	-	-	3	-	3	2	1	-
Total	-	-	-	-	-	-	-	-	3	-	3	2	1	-
Investigations														
ALAT increased	-	-	-	-	-	-	-	5	2	-	7	5	2	-
Ammonia increased	-	-	-	-	-	-	-	2	-	-	2	2	-	-
ASAT increased	-	-	-	-	-	-	-	4	-	-	4	3	1	-
Blood LDH increased	-	-	-	-	-	-	-	3	-	-	3	3	-	-
GGT increased	-	-	-	-	-	-	-	1	2	-	3	2	1	-
INR increased	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Neutrophil count decreased	-	-	-	-	-	-	-	3	-	-	3	3	-	-
Platelet count decreased	-	-	-	-	-	-	-	10	6	-	16	12	4	-
Weight gain	-	-	-	-	-	-	-	11	1	-	12	5	3	4
White blood cell decreased	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Total	-	-	-	-	-	-	-	41	11	-	52	37	11	4
Metabolism and nutrition disorders														
Anorexia	-	1	-	1	-	1	-	-	-	-	-	-	-	-
Total	-	1	-	1	-	1	-	-	-	-	-	-	-	-
Nervous system disorders														
Anosmia		-	-	-	-	-	-	1	-	-	1	-	-	1
Bradyphrenia	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Cognitive disturbance		-	-	-	-	-	-	1	-	-	1	-	1	-
Concentration impairment	2	-	-	2	-	2	-	-	-	-	-	-	-	-

Table S2. Continued

Adverse effects according to the CTCAE 5.0	Levetiracetam							Valproic acid						
	Grade, no.				Improved, no.[a]			Grade, no.				Improved, no.[a]		
	1,2	3,4	?	Total	Yes	No	?	1,2	3,4	?	Total	Yes	No	?
Depressed level of consciousness	2	-	-	2	2	-	-	1	-	-	1	1	-	-
Dizziness	5	-	1	6	4	2	-	2	-	-	2	2	-	-
Encephalopathy	-	-	-	-	-	-	-	-	2	-	2	1	-	1
Headache	3	-	-	3	2	-	1	2	-	-	2	1	-	1
Lethargy	2	-	-	2	-	2	-	2	-	-	2	1	-	1
Memory impairment	2	-	-	2	-	2	-	3	-	-	3	-	2	1
Somnolence	9	-	-	9	7	-	2	4	-	-	4	2	1	1
Syncope	-	-	-	-	-	-	-	-	1	-	1	1	-	-
Tremor	3	-	-	3	1	1	1	11	1	-	12	9	1	2
Total	29	-	1	30	17	9	4	27	4	-	31	18	5	8
Psychiatric disorders														
Agitation	18	2	1	21	14	3	4	-	-	-	-	-	-	-
Anxiety	3	-	-	3	3	-	-	-	-	-	-	-	-	-
Apathy	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Delirium	-	-	-	-	-	-	-	-	1	-	1	-	-	1
Depression	4	3	-	7	5	1	1	-	-	-	-	-	-	-
Hallucinations	1	2	-	3	3	-	-	-	1	-	1	1	-	-
Insomnia	2	2	-	4	4	-	-	1	-	-	1	-	-	1
Mood swings	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Personality change	1	3	-	4	3	1	-	-	-	-	-	-	-	-
Psychosis	-	5	-	5	5	-	-	-	-	-	-	-	-	-
Suicidal ideation	1	1	-	2	2	-	-	-	-	-	-	-	-	-
Total	32	18	1	51	41	5	5	1	2	-	3	1	-	2
Reproductive system and breast disorders														
Irregular menstruation	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Total	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Respiratory, thoracic and mediastinal disorders														
Laryngeal inflammation	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Total	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Skin and subcutaneous tissue disorders														
Alopecia	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Eczema	1	-	-	1	-	-	1	-	-	-	-	-	-	-
Pruritis	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Rash	1	-	-	1	1	-	-	1	-	2	3	3	-	-
Total	3	-	-	3	2	-	1	2	-	2	4	4	-	-
Unknown														
Unknown	-	-	2	2	1	-	1	-	-	2	-	-	-	2
Total	-	-	2	2	1	-	1	-	-	2	-	-	-	2
Total all adverse effects	87	19	4	110	78	20	12	89	23	4	116	77	21	18

?=Unknown; [a]=Improvement after discontinuation of the current therapy with levetiracetam or valproic acid; CTCAE=Common Terminology Criteria for Adverse Events; ALAT=Alanine Aminotransferase; ASAT=Aspartate Aminotransferase; GGT=Gamma-Glutamyl Transferase; INR=International Normalized Ratio; LDH=Lactate Dehydrogenase; No.=Number of patients