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Effectiveness of Antiseizure Medication Triple Therapy in Glioma Patients With Refractory Epilepsy: An Observational Cohort Study

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Abstract

Background

About 10% of glioma patients with epilepsy need antiseizure medication (ASM) triple-therapy due to refractory epilepsy. Aim of this study was to evaluate whether levetiracetam combined with valproic acid and clobazam (LEV+VPA+CLB), a frequently prescribed triple-therapy, has favorable effectiveness compared to other triple-therapy combinations in glioma patients.

Methods

This was a multicenter retrospective observational cohort study, with as primary outcome the cumulative incidence of time to treatment failure for any reason, from start of ASM triple-therapy treatment. Secondary outcomes included cumulative incidences of: 1) time to treatment failure due to uncontrolled seizures; 2) time to treatment failure due to adverse effects; and 3) time to recurrent seizure. Patients were followed for a max. duration of 36 months.

Results

Out of n=1435 patients in the original cohort, n=90 patients received ASM triple-therapy after second-line ASM treatment failure due to uncontrolled seizures. LEV+VPA+CLB was prescribed to 48% (43/90) and other ASM triple-therapy to 52% (47/90) patients. The cumulative incidence of treatment failure for any reason of LEV+VPA+CLB did not significantly differ from other ASM triple-therapy combinations (12 months: 47% [95%CI, 31-62%] versus 42% [95%CI, 27-56%], p=0.892). No statistical significant differences for treatment failure due to uncontrolled seizures (12 months: 12% [95%CI, 4-25%] versus 18% [95%CI, 8-30%], p=0.445), due to adverse effects (12 months: 22% [95%CI, 11-36%] versus 15% [95%CI, 7-27%], p=0.446), or recurrent seizure (1 month: 65% [95%CI, 48-78%] versus 63% [95%CI, 47-75%], p=0.911) were found.

Conclusions

LEV+VPA+CLB might show equivalent effectiveness compared to other ASM triple-therapy combinations in glioma patients.

Classification of evidence

This study provides Class III evidence that for glioma patients with refractory epilepsy on triple-therapy ASMs, LEV+VPA+CLB demonstrated similar effectiveness and tolerability compared to other ASM triple-therapy combinations.

Introduction

Epileptic seizure management is an important aspect in the disease trajectory as preoperative seizures occur in up to ~75% of patients with diffuse gliomas.[1] Antiseizure medication (ASM) treatment is indicated once a first seizure has occurred.[2] However, drug resistant epilepsy (defined by the International League Against Epilepsy [ILAE] as patients without adequate seizure control after ≥2 trials with ASMs either in monotherapy or in combination) occurs in ~15% up to ~40% of glioblastoma and grade 2 glioma patients, respectively.[3, 4] Benzodiazepines and in particular clobazam (CLB) are commonly prescribed add-on ASMs in drug resistant epilepsy likely due to their ease of administration and ease of use. CLB does not require a careful titration and only needs to be taken once or twice a day.[5] CLB is a 1.5-benzodiazepine (nitrogen atoms are located at positions 1 and 5 of the diazepine ring) and is thought to have various mechanisms of action, but the major effect is potentiation of gamma aminobutyric acid (GABA)ergic neurotransmission. It has better tolerability compared to traditional 1.4-benzodiazepines. Due to its unique 1.5-pharmacological profile it is thought to give it a broader spectrum of anticonvulsive activity and possible synergistic efficacy when used with other ASMs.[6] CLB is frequently prescribed in brain tumor patients, but only one study evaluated its efficacy (30% seizure freedom within 6 months of initiation of CLB) and tolerability (6% experiencing intolerable adverse effects) as add-on ASM in the brain tumor population.[7, 8] Methodological issues, however, such as not taking into account the competing risk of death and lack of a comparison group, hamper reliable interpretation of results. In non-brain tumor-related epilepsy (BTRE) patients CLB seems to perform reasonably well (12-month retention of ~60-80% in patients with refractory epilepsy) compared to other ASMs, but large comparative efficacy trials are lacking.[9, 10] Four double-blind placebo-controlled randomized controlled trials (RCTs) have been conducted in the past decades, representing only n=197 patients, evaluating CLB as add-on in non-BTRE drug resistant epilepsy

patients. CLB may be effective in reducing seizure frequency in focal-onset seizures, but it should be noted that this finding is based on very low-quality evidence and all four included studies have an unclear risk of bias due to insufficient reporting of methodological details.[11]

Recently, we demonstrated in a large multicenter retrospective observational study that first-line monotherapy levetiracetam (LEV) has favorable efficacy compared to valproic acid (VPA), two commonly prescribed ASMs in the glioma population.[12] This finding is supported by a recent systematic review in which monotherapy LEV had the most favorable efficacy along with pregabalin (PGB) and phenytoin (PHT). However, the latter two ASMs were less well tolerated, reflected in higher treatment failure due to adverse effects rates.[8] If seizures are not adequately controlled on ASM monotherapy, the combination of LEV with VPA has favorable efficacy compared to other ASM dual therapy combinations with either LEV or VPA.[13] In ~10% of glioma patients with epilepsy treated with ASMs a third ASM is prescribed with the aim of reaching adequate seizure control.[12] With around 30 different ASMs available for use in clinical practice, more than 4000 triple-therapy combinations can be made, complicating the evaluation of ASM triple-therapy treatment.[14] Despite this plethora of combinations a frequently prescribed triple-therapy combination is LEV combined with VPA and CLB (LEV+VPA+CLB), because CLB is added to the dual therapy combination of LEV with VPA. Aim of this study was to evaluate whether LEV+VPA+CLB has favorable effectiveness in glioma patients with refractory epilepsy compared to other ASM triple-therapy combinations.

Methods

Study population and procedures

A more extensive description of the methodology has been previously published.[12] This was a multicenter retrospective observational study and all consecutive patients with a histological diagnosed World Health Organization (WHO) grade 2-4 diffuse glioma according to the WHO 2016 classification of central nervous system tumors,[15] between January 1st, 2004 and January 1st, 2018, and had undergone biopsy or surgical (re)resection were included. Participating centers were Erasmus Medical Center, Haaglanden Medical Center, and Amsterdam University Medical Centers (location VUMC). Patients receiving first-line monotherapy treatment with either LEV or VPA were included in the original cohort (n=1435).[12] Patients showing treatment failure due to uncontrolled seizures on their first-line LEV or VPA and receiving ASM dual therapy treatment were included in the subsequent study (n=355).[12, 13] Patients showing treatment failure on their ASM dual therapy treatment due to uncontrolled seizures and receiving ASM triple-therapy treatment subsequently were

included in the current study. We compared two groups: LEV+VPA+CLB versus other triple-therapy combinations. Patients were excluded if the add-on ASM was prescribed with the intention for a limited period of time (maximum term of 3 months). The following baseline (i.e. from the starting date of ASM triple-therapy initiation) information was collected from the patients' charts: sociodemographic data, tumor specific information, data on anti-tumor treatment, radiological progressive disease (at time of treatment failure due to uncontrolled seizures) based on the Response Assessment in Neuro-Oncology (RANO) criteria,[16] and ASM treatment information. In order to assess potential dose escalation and/or dose reduction differences between the two groups at time of ASM treatment failure the ASM load was calculated for each patient, since not all ASMs have similar defined daily dosages (DDD). ASM load is defined as the sum of the ratio between the prescribed daily dosage and the DDD of each individual ASM included in the ASM treatment combination (eTable 1).[17] For instance, the DDD of CLB is 20 milligram (mg) and of LEV and VPA 1500 mg. In case a patient is prescribed 10 mg CLB, 2500 mg LEV, and 2000 mg VPA each day, the ASM load is 3.5 ([10/20] + [2500/1500] + [2000/1500]).

Outcomes

Time to treatment failure for any reason, a measure for ASM effectiveness that includes efficacy as well as tolerability,[18] was the primary outcome. It was estimated from the time of initiation of ASM triple-therapy until treatment failure, death, lost to follow-up, or reaching the end of study date (patients were followed for a max. duration of 36 months). We defined ASM treatment failure as the addition, withdrawal, or replacement of an ASM. We considered the following events not as treatment failure: the addition of an ASM pro re nata (i.e., when required), use of approved ASMs outside epilepsy (e.g., carbamazepine as treatment for trigeminal neuralgia), changing the dosage of the initial ASM triple-therapy combination, the addition of a temporary primary prophylactic ASM during a perioperative period, replacement of ASMs in the end-of-life phase with a non-oral route of administration (e.g., buccal clonazepam) due to dysphagia, or poor adherence <1 week. Evaluated secondary outcomes were: 1) time to treatment failure for specific reasons of treatment failure (i.e., adverse effects, uncontrolled seizures, withdrawal due to remission of seizures, or other reasons); 2) time to recurrent seizure, a measure for efficacy, similarly estimated as time to treatment failure (max. duration of follow-up of 36 months), until recurrent seizure, death, treatment failure (with the exception of treatment failure due to uncontrolled seizures), lost to follow-up, or reaching the end of study date; and 3) tolerability, which we defined according to the severity (grade 1-5) of adverse effects leading to ASM discontinuation (i.e.,

intolerability was based on clinical judgement of the treating physician) based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[19] Of each intolerable adverse effect it was evaluated whether it improved after ASM discontinuation based on laboratory results and information reported by clinicians in the patients' charts, in a period of approximately 1-2 months. Improvement of the intolerable adverse effect(s) after discontinuation of the ASM was seen as a valid reason to regard the suspected discontinued ASM as a likely causative (contributing) factor of the intolerable adverse effect(s).[20]

Statistics

Time to treatment failure and time to recurrent seizure were analyzed with a competing risks model comparing the cumulative incidences of LEV+VPA+CLB with other ASM triple-therapy.[21] The following three competing risks models were applied: 1) time to treatment failure for any reason (two competing events: outcome of interest and death); 2) time to treatment failure for specific reasons of treatment failure (five competing events: treatment failure due to adverse effects, uncontrolled seizures, withdrawal due to remission of seizures, other reasons, and death); 3) time to recurrent seizure (three competing events: outcome of interest, treatment failure before a recurrent seizure has occurred, and death). We reported the cumulative incidences at 1, 12, and/or 36 months after ASM initiation in the main text (including 95% confidence interval [CI]), because we regarded these time points as clinically most relevant. Gray's test was applied to assess the difference between the cumulative incidences.[22] Baseline demographic characteristics were analyzed with the χ^2 and ASM load at time of treatment failure was analyzed with the independent t-test. A power calculation and sample size estimation was performed for the original cohort only,[12] but not for the current study. Therefore, statistical analyses based on our small cohort should be regarded mainly as descriptive. All statistical tests were performed with *SPSS* version 25.0 and *R*.[23, 24] Statistical tests with regard to the competing risks models were performed with *R* by using the cmprsk library.[21] Statistical significance was set at a p-value of <0.05. P-values were only reported for time to treatment failure, time to recurrent seizure, baseline demographic characteristics, and ASM load at time of treatment failure and not for other comparisons, due to the descriptive nature of our study and to avoid (statistical) inference based on reported p-values.

Standard protocol approvals, registrations, and patient consents

The study protocol was approved by the medical ethics committee of each institution and informed consent of included patients was obtained according to the institutions policy.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Results

Patient characteristics

The baseline characteristics of the included patients are depicted in Table 1. A total of n=90 patients received ASM triple-therapy and were included in this study. LEV+VPA+CLB was prescribed to 48% (43/90) and other ASM triple-therapy combinations to 52% (47/90) patients equaling 22 different combinations (eTable 2). Patients in the LEV+VPA+CLB group had significantly more often a KPS ≥70, a history of a psychiatric disease, and solely focal seizures.

Time to treatment failure

During the 36 months follow-up a total of 49% (21/43) patients who used LEV+VPA+CLB and 45% (21/47) who used other triple-therapy combinations showed treatment failure. The cumulative incidence of treatment failure for any reason did not significantly differ between LEV+VPA+CLB and other triple-therapy combinations (12 months: 47% [95%CI=31-62%] versus 42% [95%CI=27-56%], p=0.892 [Figure 1]). Neither were there differences for treatment failure due to uncontrolled seizures (12 months: 12% [95%CI=4-25%] versus 18% [95%CI=8-30%], p=0.445), due to adverse effects (12 months: 22% [95%CI=11-36%] versus 15% [95%CI=7-27%], p=0.446), due to other reasons (12 months: 10% [95%CI=3-22%] versus 7% [95%CI=2-17%], p=0.924), or withdrawal due to remission of seizures (36 months: 5% [95%CI=1-16%] versus 2% [95%CI=0-11%], p=0.564 [eTable 3]).

Mean ASM load of LEV+VPA+CLB was significantly higher compared to other triple-therapy combinations at moment of treatment failure due to uncontrolled seizures (4.33 [SD=1.03] versus 3.21 [SD=0.48] ASM load, p=0.029), but no significant differences were found between LEV+VPA+CLB and other triple-therapy combinations for treatment failure due to adverse effects (2.89 [SD=0.54] versus 3.42 [SD=0.58] ASM load, p=0.062). Radiological progressive disease (i.e. tumor progression) at time of treatment failure due to uncontrolled seizures was present in 40% (2/5) of patients who used LEV+VPA+CLB compared to 13% (1/8) who used other triple-therapy combinations.

Time to recurrent seizure

Already one month after initiation of ASM triple-therapy the majority of the patients had experienced a recurrent seizure, but no significant differences for the cumulative incidences of a recurrent seizure were found between LEV+VPA+CLB and other triple-therapy combinations (1 month: 65% [95%CI=48-78%] versus 63% [95%CI=47-75%], p=0.911 [Figure 2]).

Intolerable adverse effects

Sixteen intolerable adverse effects occurred in 10/43 LEV+VPA+CLB patients, while there were 9 intolerable adverse effects in 8/47 other triple-therapy patients (Table 2). CLB was discontinued in 5 (50%, in all 5 due to somnolence [eTable 4]), VPA in 3 (30%), and LEV in 2 (20%) of the 10 LEV+VPA+CLB patients. The most common intolerable adverse effects in LEV+VPA+CLB and other triple-therapy combinations were somnolence (6/16=38%) and decreased platelet count (2/9=22%), respectively. One patient in both LEV+VPA+CLB and other triple-therapy combinations experienced a grade 3 or 4 adverse effect (6% versus 11%). In patients using LEV+VPA+CLB 75% (12/16) of adverse effects improved versus 44% (4/9) in patients using other triple-therapy combinations.

Classification of evidence

This study provides Class III evidence that for glioma patients with refractory epilepsy on triple-therapy ASMs, LEV+VPA+CLB demonstrated similar effectiveness and tolerability compared to other ASM triple-therapy combinations.

Discussion

This study aimed to compare the effectiveness of triple ASM treatment in glioma patients with drug resistant epilepsy, in particular LEV+VPA+CLB versus other ASM triple-therapy combinations. No differences were found between the two studied triple-therapy groups on efficacy or tolerability outcomes. On the other hand, the ASM load at moment of treatment failure due to uncontrolled seizures was significantly higher for LEV+VPA+CLB, meaning dose escalation was probably less optimal in the other ASM triple-therapy combinations, possibly increasing (prematurely) treatment failure due to uncontrolled seizures in the latter group. This might be (partly) explained by the difference in ease of administration as many ASMs need more careful titration and dose escalation is more slowly compared to CLB. Altogether, the combination of LEV+VPA+CLB

might perform equivalent compared to other ASM triple-therapy combinations in glioma patients. The addition of a third ASM to the treatment regimen might help to a limited extent in this difficult-to-treat population.

To our knowledge, this is the second study evaluating CLB as add-on ASM treatment in glioma patients. After 3 and 6 months follow-up the cumulative incidence of LEV+VPA+CLB patients for a recurrent seizure was 75% (i.e., 25% seizure freedom) and treatment failure due to adverse effects was 15% and 17%, respectively, of which half was thought to be attributable to CLB (~8%) by the treating physician given CLB was discontinued. Efficacy and tolerability in our study were comparable to the study of Brahmbhatt et al. (2021), who found a seizure freedom of 30% at 6 months follow-up and treatment failure due to adverse effects of 6% in glioma patients with epilepsy who received add-on CLB and of which the majority received ASM triple-therapy.[7] When comparing seizure freedom (12-20%) and treatment failure due to adverse effects (8-19%) after 3 months follow-up in non-BTRE patients receiving CLB as add-on,[11] CLB does seem to perform quite similar in glioma patients. The vast majority of glioma patients in our cohort experienced a recurrent seizure within 1 month, while according to our definition this implied treatment failure in only a minority of these patients. Given this cohort entails a population with drug resistant epilepsy, having recurrent seizures seems to be more accepted by both the treating physician and the patient and does not necessarily lead to a change in ASM treatment regimen.

Choice of a particular ASM treatment regimen should not only depend on efficacy, but drug-related properties including pharmacokinetics, tolerability, safety, drug interactions, and ease of administration are of importance as well. CLB is generally considered as a safe ASM in (non-)BTRE, with dose-dependent adverse effects and severe adverse effects being very rare, and with an incidence rate of 1.6 per 1000 person-years the risk of benzodiazepine dependence low.[5, 25] No enzyme inducing or inhibiting properties have been found for CLB and the drug levels of other ASMs did not change when CLB was added in pharmacokinetic studies. Common adverse effects include somnolence, dizziness, and ataxia.[5] The additional anxiolytic properties of CLB might be a favorable side effect, as ~25% of patients with glioma experiences symptoms of anxiety.[26]

It is the first time that a fixed and regularly prescribed combination of three ASMs is examined in BTRE patients. The major mechanism of action of CLB is potentiation of GABAergic neurotransmission, which is a mechanism of action for VPA as well. Since rational polytherapy advises to combine ASMs with different mechanisms of action, CLB might not be the best choice to combine with LEV+VPA. For example, perampanel (PER) and lacosamide (LCM) might serve as efficacious add-on ASMs.[8], being a non-competitive α-amino□3□hydroxy□5□methyl□4□isoxazolepropionic acid (AMPA) glutamate receptor antagonist,[27] voltage-gated

natrium channels inactivator, respectively.[28] PER combined with LEV does not seem to affect clearance and neither increased psychiatric adverse effects, such as agitation (the most intolerable adverse effect in LEV glioma patients),[12] compared to other ASM combinations.[29] Altered glutamate homeostasis seems to play an important role in the epileptogenesis in gliomas, making PER a rational treatment choice.[30] LCM showed a synergistic effect with LEV and a tendency toward synergism with VPA in pre-clinical models.[31] As LCM has the advantage of having no interactions with other (antineoplastic) drugs and of a quick titration, unlike for example lamotrigine (LTG), it is considered a suitable (add-on) ASM in the glioma population. Our cohort is based on triple-therapies prescribed in the past two decades. We suspect prescribed triple-therapies in the last few years differ (partly) from previously prescribed triple-therapies and think the proportion of LCM as add-on ASM in the triple-therapy regimens is larger, while CLB might be smaller.

Given only 10% of glioma patients with epilepsy need ASM triple-therapy,[12] recruiting a sufficiently large sample of patients that is needed to provide reliable results on the effectiveness of a specific ASM combination remains a major challenge. Due to the small cohort we were not able to use matching techniques or multivariable regression analysis to take confounders into account. Therefore, (unknown) confounders were not equally distributed across the two studied treatment groups and could have influenced the outcomes. In a retrospective study design combined with a patient population with refractory epilepsy time to recurrent seizure seems the best efficacy outcome, despite its limitations as at 3 months the number of patients at risk was already low. Ideally, when evaluating the comparative efficacy of ASMs in patients with refractory epilepsy (meaning a high seizure frequency) prospectively assessed outcomes assessing seizure severity should be included.

Conclusion

In this retrospective observational study LEV+VPA+CLB treatment in epileptic refractory glioma patients might show similar effectiveness compared to other ASM triple-therapy combinations. Prospective studies are needed to determine which ASMs are the most effective and tolerable add-on treatment options for glioma patients with refractory epilepsy.

http://links.lww.com/WNL/C610

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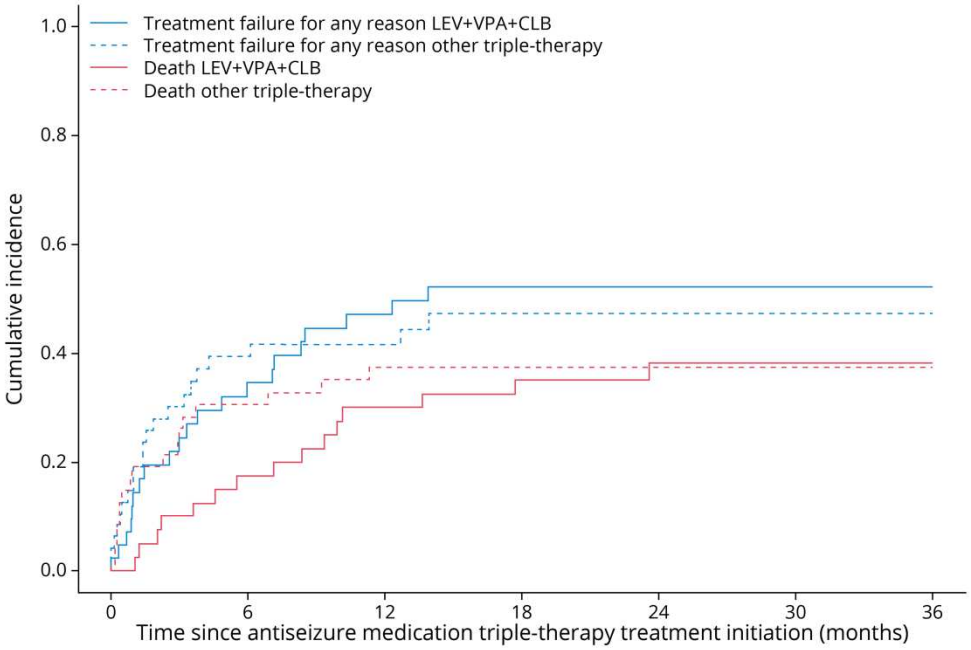
Table 1. Demographic characteristics of the patients at baseline antiseizure medication triple-therapy treatment

	Antiseizure medication treatment		
Characteristics	**LEV+VPA+CLB**	**Other triple-therapy**	**p-value**
Patients included, no. (%)	43	47	
Age, no. (%)			0.508
≤40 years	11 (26)	15 (32)	
>40 years	32 (74)	32 (68)	
Sex, no. (%)			0.810
Male	32 (74)	36 (77)	
Female	11 (26)	11 (23)	
Tumor grade and pathology, no. (%)			0.098
Grade 2	15 (35)	16 (34)	
Diffuse astrocytoma NOS	4 (9)	6 (13)	
Diffuse astrocytoma IDH-mutant	4 (9)	3 (6)	
Oligodendroglioma NOS	3 (7)	1 (2)	
Oligodendroglioma IDH-mutant 1p/19q codeletion	4 (9)	5 (11)	
Oligoastrocytoma NOS	0 (0)	1 (2)	
Grade 3	2 (5)	9 (19)	
Anaplastic astrocytoma NOS	0 (0)	7 (15)	
Anaplastic oligodendroglioma NOS	0 (0)	1 (2)	
Anaplastic oligodendroglioma IDH-mutant 1p/19q codeletion	2 (5)	1 (2)	
Grade 4	26 (60)	22 (47)	
Diffuse astrocytoma wildtype	0 (0)	1 (2)	
Anaplastic astrocytoma wildtype	1 (2)	1 (2)	
Glioblastoma NOS	17 (40)	14 (30)	
Glioblastoma wildtype	6 (14)	6 (13)	
Glioblastoma IDH-mutant	2 (5)	0 (0)	
Surgical resection, no. (%)			0.360
Yes	33 (77)	32 (68)	
No (including biopsy)	10 (23)	15 (32)	
Radiotherapy, no. (%)			0.456
Yes	28 (65)	27 (57)	
No	15 (35)	20 (43)	
Systemic therapy, no. (%)			0.514
Yes	24 (56)	23 (49)	
Temozolomide (+ additional agents)	20 (47)	22 (47)	
Temozolomide rechallenge	0 (0)	2 (4)	
PCV[1]	4 (9)	0 (0)	
Lomustine	5 (12)	3 (6)	
Other	2 (5)	3 (6)	
No	19 (44)	24 (51)	
Tumor involvement in the temporal lobe			0.329
Yes	14 (33)	20 (43)	
No	29 (67)	27 (57)	
Tumor involvement in the frontal lobe			0.699
Yes	30 (70)	31 (66)	
No	13 (30)	16 (34)	
Karnofsky Performance Status, no. (%)			0.011
≥70	42 (98)	38 (81)	
<70	1 (2)	9 (19)	
History of a psychiatric disease[2], no. (%)			0.018
Yes	7 (16)	1 (2)	
No	36 (84)	46 (98)	
Seizure type, no. (%)			0.222
Focal	13 (30)	9 (19)	
Focal to bilateral tonic-clonic[3]	30 (70)	38 (81)	

[1]PCV=Procarbazine, Lomustine, and Vincristine; [2]History of a psychiatric disease included depression, anxiety, or psychotic disorders; [3]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; CLB=Clobazam; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid

Figure 1. Time to treatment failure for any reason: LEV+VPA+CLB versus other triple-therapy

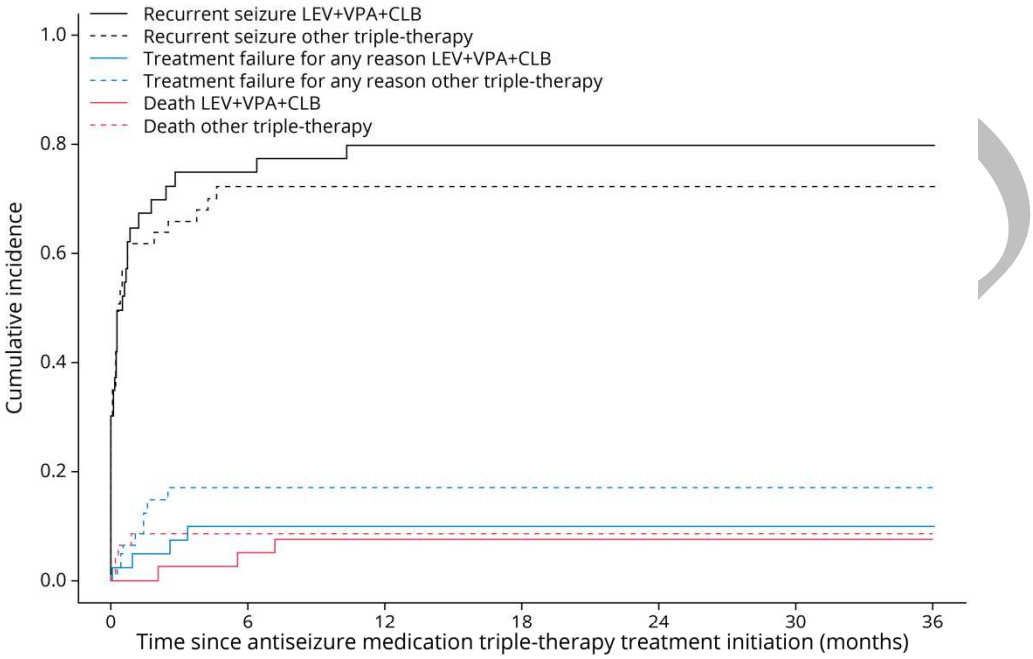
[1]Number of patients at risk refers to the number of patients who have not experienced an event (i.e. the event treatment failure of the event death) at that particular timepoint (e.g. 3 months) and who are still at risk for experiencing an event (i.e. not censored); CI=Confidence interval; CIF=Cumulative incidence function; CLB=Clobazam; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid



Time in months	0	1	3	6	12	36	
Number at risk[1]							
LEV+VPA+CLB	43	35	26	19	9	0	
Other triple-therapy	47	29	19	13	8	0	
Number censored							
LEV+VPA+CLB	0	2	3	3	3	7	
Other triple-therapy	0	1	2	2	3	9	
Event treatment failure for any reason							$p = 0.892$
CIF (95% CI), LEV+VPA+CLB	0	15 (6–27)	25 (13–39)	35 (20–49)	47 (31–62)	52 (35–67)	
CIF (95% CI), other triple-therapy	0	17 (8–29)	30 (18–44)	39 (25–54)	42 (27–56)	47 (32–62)	
Event death							$p = 0.623$
CIF (95% CI), LEV+VPA+CLB	0	0 (–)	10 (3–22)	18 (8–31)	30 (17–45)	38 (23–54)	
CIF (95% CI), other triple-therapy	0	19 (9–32)	26 (14–39)	31 (18–44)	38 (23–52)	38 (23–52)	

Figure 2. Time to recurrent seizure: LEV+VPA+CLB versus other triple-therapy

[1]Number of patients at risk refers to the number of patients who have not experienced an event (i.e. the event treatment failure of the event death) at that particular timepoint (e.g. 3 months) and who are still at risk for experiencing an event (i.e. not censored); [2]Patients who experienced treatment failure (due to adverse effects, withdrawal due to remission, 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; CLB=Clobazam; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid



Time in months	0	1	3	6	12	36	
Number at risk[1]							
LEV+VPA+CLB	43	12	6	4	1	0	
Other triple-therapy	46	10	3	0	0	0	
Number censored							
LEV+VPA+CLB	0	2	2	2	2	3	
Other triple-therapy	0	0	0	0	0	0	
Event treatment failure for any reason							
CIF (95% CI), LEV+VPA+CLB	0	0	0	0	0	0	
CIF (95% CI), other triple-therapy	1	1	1	1	1	1	
Event death							$p = 0.911$
CIF (95% CI), LEV+VPA+CLB	0	65 (48–78)	75 (58–86)	75 (58–86)	80 (62–90)	80 (62–90)	
CIF (95% CI), other triple-therapy	0	63 (47–75)	67 (51–79)	67 (51–79)	67 (51–79)	67 (51–79)	
Event death							$p = 0.214$
CIF (95% CI), LEV+VPA+CLB	0	0 (–)	3 (0–12)	5 (1–16)	8 (2–20)	8 (2–20)	
CIF (95% CI), other triple-therapy	0	9 (3–19)	9 (3–19)	9 (3–19)	9 (3–19)	9 (3–19)	
Event treatment failure[2]							$p = 0.322$
CIF (95% CI), LEV+VPA+CLB	0	5 (1–15)	7 (2–18)	10 (3–22)	10 (3–22)	10 (3–22)	
CIF (95% CI), other triple-therapy	0	6 (2–16)	17 (8–30)	17 (8–30)	17 (8–30)	17 (8–30)	

Table 2. Adverse effects which led to treatment failure (including grade 1 to 5): LEV+VPA+CLB versus other triple-therapy

Adverse effects which led to treatment failure	**LEV+VPA+CLB**	**Other triple-therapy**
Adverse effect categories based on the CTCAE v. 5.0	*Adverse effects, no. (%)*	*Adverse effects, no. (%)*
Eye disorders	0 (0)	1 (11)
General and administration site conditions	4 (25)	1 (11)
Investigations	0 (0)	3 (33)
Nervous system disorders	7 (44)	2 (22)
Psychiatric disorders	4 (25)	1 (11)
Skin and subcutaneous tissue disorders	1 (6)	0 (0)
Unknown	0 (0)	1 (11)
Total number of adverse effects	16 (100)	9 (100)
Total number of patients who showed treatment failure due to adverse effects	10	8

CTCAE=Common Terminology Criteria for Adverse Events; CLB=Clobazam; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid

Appendix 1. Authors

Name	Location	Contribution
Pim B. van der Meer	Leiden University Medical Center, Leiden	Design, data collection, data-analysis, interpretation of results, intellectual content, wrote first and successive versions, and approved the final version. PBvdM had full access to all the data in the study and had final responsibility to submit for publication.
Linda Dirven	Leiden University Medical Center, Leiden; Haaglanden Medical Center, The Hague	Design, input in data-analysis, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Marta Fiocco	Leiden University Medical Center, Leiden	Input in data-analysis, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Maaike J. Vos	Haaglanden Medical Center, The Hague	Interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Mathilde C.M. Kouwenhoven	Amsterdam University Medical Centers, Location VUmc, Amsterdam	Interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Martin J. van den Bent	Erasmus Medical Center Cancer Institute, Rotterdam	Design, interpretation of results, intellectual content, critical

		revisions to the drafts of the paper, and approved the final version.
Martin J.B. Taphoorn	Leiden University Medical Center, Leiden; Haaglanden Medical Center, The Hague	Design, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Johan A.F. Koekkoek	Leiden University Medical Center, Leiden; Haaglanden Medical Center, The Hague	Design, input in data-analysis, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.

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