Original article

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Quality of life in patients with partial-onset seizures under adjunctive therapy with zonisamide: results from a prospective non-interventional surveillance study

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ABSTRACT – This prospective, multicenter, non-interventional surveillance study (ZADE study) explored seizure outcome and tolerability of adjunctive treatment with zonisamide (ZNS) in a non-selected sample of patients with partial-onset seizures in everyday clinical practice. Changes in quality of life (QOL) and health status were also recorded. Clinical status was assessed before and 4 months after introduction of ZNS. The herein reported evaluation of QOL and health status was based on a representative subsample of 207 patients. In this subgroup, a reduced QOL had been apparent in 68% of patients at baseline. After introduction of ZNS, all measures improved, with ameliorations in QOL in up to 35% of patients. Major determinants for a better QOL outcome were (1) a better score at baseline, (2) a higher degree of seizure reduction, and (3) a lower number of concomitant AEDs. Tolerability was subjectively rated as good by 89% of patients. With a ZNS dose of 244.8±108 mg/d at study end, seizure frequency had dropped from 8.8±19.2 within 8 weeks before baseline to 3.6±9.1 seizures within the period of 8 weeks before study end. A total of 79% of patients responded to ZNS treatment with a ≥50% reduction in seizure frequency; 34% became seizure free. In conclusion, adjunctive treatment with ZNS seems to be efficacious and well tolerated. QOL improvement was predicted by baseline score, seizure outcome, and overall drug load, and is thus more likely a result of enhanced seizure control, rather than an intrinsic psychotropic effect of zonisamide.

Key words: zonisamide, non-interventional study, antiepileptic treatment, quality of life, efficacy, epilepsy

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The benzisoxazole derivate zonisamide (ZNS; Zonegran®) is a new-generation antiepileptic drug (AED). Following four randomised controlled trials on efficacy and safety in patients with pharmacoresistant epilepsies (Brodie *et al.*, 2005; Faught *et al.*, 2001; Sackellares *et al.*, 2004; Schmidt *et al.*, 1993), the drug was granted EU-wide approval for the adjunctive therapy of adults with partial seizures with or without secondary generalisation in 2005. As ZNS has a multimodal action (*e.g.* inhibition of voltage-gated Na^+ and T-type Ca^{2+} channels, enhancement of GABA activity) (Biton, 2007), and a low potential for pharmacokinetic interactions with other drugs (Sills and Brodie, 2007), ZNS can be of benefit as a complementary adjunctive treatment option for patients suffering from partial epilepsy. Due to its long elimination half-life of 60 hours, ZNS can be administered once daily after titration (Zonegran® SmPC, 2010).

The pivotal studies reported dose-dependent responder rates for all seizures of 25-52.5% as opposed to 9.8-22% with placebo (Brodie *et al.*, 2005; Faught *et al.*, 2001). The most common adverse events reported across all pivotal studies were dizziness, somnolence, and nausea, with incidences ranging between 4.2% and 18.3% (Brodie *et al.*, 2005; Faught *et al.*, 2001; Sackellares *et al.*, 2004; Schmidt *et al.*, 1993). According to clinical experience, tolerability of ZNS can be improved by choosing low initial doses and a slow up-titration schedule (Schulze-Bonhage, 2010). There is evidence that treatment with ZNS can be accompanied by increased subjective complaints about negative cognitive or psychiatric side effects (Arif *et al.*, 2009), leading to discontinuation of the drug in about 6% of patients in a case-control study (White *et al.*, 2010). However, a more severe epilepsy appeared to be a decisive determinant for negative side effects associated with ZNS in this study. So far, only one prospective study suggests dose-dependent negative cognitive side effects under ZNS monotherapy (100-400 mg/d) as assessed by standardised neuropsychological tests (Park *et al.*, 2008). Results from a recently published naturalistic study, with flexible dosing of ZNS and including patients with epilepsies less refractory than those enrolled in pivotal trials, demonstrated good efficacy of adjunctive ZNS, with 44.2% responders and 15.9% of patients rendered seizure-free at a mean dosage of 346 mg/d. ZNS was generally well tolerated in this study, with somnolence (3.2%), fatigue (1.8%), and insomnia (1.8%) being the most prominent reasons for study discontinuation (Dupont *et al.*, 2010).

Taking this as background, the objectives of this non-interventional study (NIS) entitled ZADE (acronym of the German title, Zonisamid im Alltag der Epilepsiepatienten [Zonisamide in the everyday life of patients with epilepsy]; ZNS-D-08-001) were (1) to determine seizure outcome and tolerability of adjunctive treatment with ZNS under conditions of practice in a common outpatient setting and (2) to evaluate the effects of the adjunctive treatment with ZNS on quality of life (QOL) and health status.

This report will mainly focus on subjective outcomes and QOL, since this aspect has not yet been evaluated in regard to ZNS. Clinical outcomes will be considered as far as they can be suggested to have a potential influence on QOL.

Methods

Study design

The study design of this phase IV trial was prospective, bi-national (Germany, Austria), multicentric, and non-interventional, and included outpatients with partial-onset seizures with or without secondary generalisation seen by medical specialists.

Exclusion criteria were a rapidly progressive neurological disorder (*e.g.* tumour, dementia, demyelinating disease), a psychiatric history, or substance abuse.

Patients were evaluated at baseline and had a follow-up examination after about four months following introduction of ZNS. The study was conducted in Germany and Austria between March 2008 and April 2009.

Treatment with ZNS was initiated according to the Summary of Product Characteristics as add-on therapy starting with a dose of 50 mg/d, divided in two doses. The further titration schedule was at the physician's discretion. Physicians were asked to suggest a provisional end dose and to document individual steps of titration and the finally achieved end dose as well as type, dose, and eventual change of the co-medication.

Patients

A total number of 372 patients were recruited for the study. Due to patient drop-out, as a result of insufficient information on clinical parameters or incomplete assessment of QOL, either at baseline or follow-up, the number of evaluable patients decreased *(table 1)*. The following analysis comprises 207 patients with complete data sets. This represents 56% of the total sample only, however, it should be noted that a loss of patients for the analysis of the quality of life data mainly resulted from missing data at baseline or follow-up, rather than from drop-out which was evident in only 4% of all included patients.

Because of the significant loss of patients for the analysis, it appeared necessary to demonstrate whether or not this subset could be considered as representative of the total sample of the ZADE study with regards to baseline characteristics and clinical outcome, as reported elsewhere (Stefan *et al.*, 2010).

Table 1. Patients available for the QOL outcome analysis.

Total N	Lost to follow-up	Incomplete seizure information	Incomplete information on AEDs	Incomplete QOLIE assessment	Available for QOL analysis
372	13 (4%)	41 (11%)	65 (17%)	108 (29%)	**207 (56%)**

Table 2 lists the clinical characteristics of the sample for which all clinical data were available (n=365), and the respective characteristics of the subsample with QOL data (n=207). From this table, it can be seen that the groups' baseline conditions were very well matched. With respect to seizure outcome, both groups were comparable, as described in the "Results" section, such that the QOL subsample could be considered as representative of the entire study group.

Outcome measures

Seizure outcome

The observation period between inclusion/baseline (T1/Time 1) and the final visit at study end (T2/Time 2) was planned to be four months. Seizure outcome was assessed by changes in seizure frequency (all seizure types) by comparing the eight-week interval before inclusion with the eight weeks before the final study visit.

Subjective measures

Prior to and four months after the introduction of ZNS, a set of subjective measures was applied to assess patients' subjective perception of QOL, health status, and amount of available active time. Furthermore, at the final visit, both patient and physician had to rate ZNS therapy in regard to overall therapy satisfaction and tolerability.

Quality of life

Patient-weighted QOL in epilepsy was assessed by the QOLIE-10-P, an adapted and extended version of the brief questionnaire QOLIE-10 (Cramer *et al.*, 1996). The self-administered 10-item questionnaire covers different epilepsy- and treatment-related issues, including *energy, mood, mobility, work* and *social limitations, memory problems, physical* and *cognitive treatment effects, seizure worries*, and *general quality of life*. For each of the domains, the degree of impairment within the last four weeks has to be rated. Different from the original QOLIE-10 questionnaire, the scaling within the patient-weighted QOLIE-10-P varies between 4 and 6 points, thereby increasing the relative importance of *energy* and *mood* and decreasing the importance of *seizure worries*. In addition to the original version, the QOLIE-10-P separately assesses the perceived *burden of epilepsy*. Finally, a hierarchy of the relative importance of seven behavioural domains was requested *(energy, mood, daily activities, mental function, medication effects, seizure worries, general QOL)*.

In order to obtain a total QOL score, the polarity of different items was adjusted (*i.e.* after transformation, a higher score always indicates greater impairment) and a sum score of the 10 items belonging to the original QOLIE-10 was calculated to provide the total score. Accordingly, for the QOLIE-10 total score, a minimum of 10 and a maximum of 51 points could be achieved, with higher scores indicating greater impairment. The total scores in our sample of patients ranged between 13 and 50. Since on item level, values of 1 indicated no impairment, and values of 2 the mildest form of impairment, values exceeding half of the possible maximum value (>25) were arbitrarily defined as the cut-off score for suggesting impaired QOL.

Individual significant changes in the QOLIE-10 total score over time were evaluated in two respects: (1) as percentage of transitions from the "impaired" category into the "unimpaired" and vice versa; and (2) in terms of a difference score (T2-T1) exceeding one standard deviation of the QOL measure at baseline into positive or negative direction.

The *burden of epilepsy* score (range 1-5) and the hierarchy of relative importance (ranking 1-7 for each domain) were used as additional measures to the QOLIE-10 total score.

Health status and available active time

The patient as well as the physician were asked to rate the patient's overall health status on a 5-level scale from "very good" (1) to "bad" (5). In addition, patients were asked to provide an estimation of the available "active" time per day.

Tolerability and therapy satisfaction

Besides the recording of adverse events for the time of the study, tolerability of ZNS therapy was also assessed on a subjective level at the final visit. Patients and physicians were asked to rate the tolerability and therapy satisfaction on a 5-level scale from "very good" (1) to "bad" (5).

Table 2. Patient characteristics of the clinical and QOL study sample.

		Total sample (n=365)	**QOL Study (n=207)**	**sign.**
Gender	n			
- Male		197 (54%)	113 (55%)	n.s.
- Female		166 (46%)	92 (45%)	
		[2 missing]		
Age (yrs.)	m (SD)	45.5 (14.9)	44.4 (14.2)	n.s.
		range: 16-87	range: 16-87	
		[3 missing]	[2 missing]	
Employment status employed/trainee	n			
- Yes		154 (44%)	89 (49%)	n.s.
- No		199 (56%)	104 (51%)	
		[12 missing]	[8 missing]	
Age at onset of epilepsy [yrs]	m (SD)	30.8 (19.2)	29.5 (17.0)	n.s.
		range: 0-84	range: 0-84	
		[9 missing]	[5 missing]	
Duration of epilepsy [yrs]	m (SD)	15.2 (14.9)	15.1 (13.8)	n.s.
		range: 0-78	range: 0-69	
		median: 10	median: 11	
		[6 missing]	[3 missing]	
Aetiology*,§	n			
- Symptomatic		191 (53%)	108 (53%)	n.s.
- Idiopathic		89 (25%)	47 (23%)	
- Cryptogenic		79 (22%)	49 (24%)	
		[6 missing]	[3 missing]	
Seizure type§	n			
- Simple partial		101 (28%)	46 (22%)	n.s.
- Complex partial		229 (63%)	133 (64%)	
- SGTCS		209 (57%)	130 (63%)	
- GTCS		51 (14%)	31 (15%)	
- Absences		9 (3%)	3 (1%)	
- Myoclonic		5 (1%)	2 (1%)	
- Tonic		5 (1%)	3 (1%)	
- Atonic		2 (1%)	1 (1%)	
Seizure frequency 8 week baseline	m (SD)	8.6 (18.3)	8.8 (19.2)	n.s.
		range: 0-180	range: 0-180	
		[11 missing]		

* Epilepsy classification according to Classification and Terminology of the International League Against Epilepsy, 1989.
§ As categorized by physician.
GTCS: generalized tonic-clonic seizures; n.s.: not significant; SGTCS: secondarily generalized tonic-clonic seizures.

Statistical analyses

Statistical evaluations were performed with the software package SPSS 17.0. Analyses comprised the comparison of baseline conditions in the evaluated sample on QOL with the total sample, descriptive statistics to report frequencies of subjective impairments, correlations to check for redundancy in the dependent measures, and stepwise regression analysis for the evaluation of determinants of QOL at baseline. Changes in subjective measures under therapy with ZNS were calculated by *t*-tests for dependent measures and alternatively by Wilcoxon signed-rank tests for related samples. Determinants of QOL at the end of the trial were evaluated by stepwise regression analysis.

Results

Clinical outcome

Before referring to the clinical outcome in more detail, it is important to note that 88 adverse events (AEs) were reported by 46 (12.6%) of all 365 patients treated with ZNS, the most frequent AEs being related to the central nervous (n=21) or gastrointestinal system (n=13). Ten AEs seen in eight patients (2.2%) were rated as "serious" (SAEs). One death due to acute heart failure occurred during the study interval, which was rated as "not related to ZNS". Twenty-two patients (6%) discontinued therapy with ZNS, mostly due to AEs. In a further 15 patients, therapy with ZNS was not continued beyond T2. The total retention rate was 90%.

Evaluation at baseline

At baseline, the final study group of 207 patients consisted of marginally more men (55%) than women, the patients' mean age was 44±14 years, and half of them (49%) were trainees or employed *(table 2)*. The mean age at the onset of epilepsy was late, at 29.5±17 years. Patients were categorized by the physicians as suffering from simple partial, complex partial, or secondary generalised seizures at baseline in 22%, 64% and 63% of cases, respectively. Generalised tonic-clonic seizures (15% of cases) were documented, as well as other seizure types (each 1%). The physicians categorised 53% of the epilepsies as symptomatic, 24% as cryptogenic, and 23% as idiopathic. The mean seizure frequency at baseline was 8.8±19.2; the median seizure frequency was 4 within the eight weeks before inclusion.

At baseline (T1), the majority of patients were on monotherapy (58%), and the most frequent polytherapy was a combination of two AEDs (34%).

The most frequently prescribed AEDs were carbamazepine (CBZ; 30%), valproate (VPA; 30%), lamotrigine (LTG; 26%), and levetiracetam (LEV; 18%) *(table 3)*. The major reason for therapy with ZNS was insufficient seizure control (93%), followed by problems with tolerability (19%) and compliance (4%) under current antiepileptic medication (multiple answers were possible).

On average, 2.5±1.7 AEDs had been prescribed in previous therapeutic attempts before the patients were included in this study *(table 3)*.

Titration

ZNS therapy started with 43.2±14.1 mg/d, and the mean end dose at T2 was 244.8±108.1 mg/d. The initially planned dose was reached in 85% of the patients, and the mean final dose remained below the dose planned at T1 (257.7±99.9 mg/d) *(table 3)*.

Follow-up evaluation

The time interval between T1 and T2 was 18.0±4.1 weeks.

ZNS was exclusively given as add-on therapy; all 120 patients (58%) on monotherapy at baseline changed to polytherapy within the observation period, treatment for 64% of 70 patients changed from two to three drugs, and 80% of 15 patients from three to four drugs. In only one patient, the total AED number was reduced. In 29 (14%) of all patients, the number of drugs remained stable because ZNS was given instead of a previous AED. In particular, physicians preferred to replace the newer-generation AEDs topiramate (TPM), LEV and oxcarbazepine (OXC) *(table 3)*.

Seizure outcome

Seizure frequency significantly dropped from 8.8±19.2 seizures in the eight weeks before baseline to 3.6±9.1 seizures in the eight weeks before the end of the study (t=4.76, $p<0.001$).

Thirty-four percent of the patients became seizure-free under ZNS, and an additional 45% showed a ≥50% reduction in seizure frequency *(table 3)*.

The results on seizure outcome correspond to the total sample (seizure frequency at T1: 8.2±17.0, at T2: 3.4±8.5, n=330; seizure-free patients at T2: 36% with seizure reduction ≥50%: 42.6%, n=322).

Determinants of seizure control

Patients who became seizure-free had fewer treatment attempts (historic AEDs plus medication at baseline) (2.9±1.1 *vs* 4.5±2.3, F=30.9, $p<0.001$), and also less AEDs at T1 (chi^2=19.2, df3, $p<0.001$). The relationship between number of AEDs and seizures was even stronger at T2 (chi^2=24.5, df2, $p<0.001$). In particular, 15 (11%) patients who did not become seizure-free were on at least three drugs at baseline (2.7% seizure-free patients). At T2, 60 (44%) patients with seizures versus eight (11%) seizure-free patients were on at least three drugs.

Subjective outcome including quality of life

Evaluation at baseline

Patients showed a mean baseline QOLIE-10 total score of 29.1±7.7 in the QOL questionnaire (median 30). By choosing a QOLIE-10 total score of > 25 as indicative for impaired quality of life, 68% of the patients fulfilled this criterion. Based on a 5-level scale, 49% rated the *burden of epilepsy* as significant (4) to very significant (5), and 22% reported a generally poor health status (4 or 5 points). Physicians rated the patients' general health marginally better than patients themselves, and indicated a poor health status (4 or 5 points) in 32 patients (16%) (z=-1.99, p=0.04).

Table 3. Clinical baseline (T1) and follow-up (T2) data of the QOL subsample.

		T1	T2	sign.
		(n=207)	(n=207)	
Medical history				
- Number of AEDs	mean (SD)	2.5 (1.7)		
	median	2		
	range	0-9		
AED treatment	n			
- Mono		120 (58%)	0 (0%)	***
- Poly		87 (42%)	207 (100%)	
- 2 AEDs		70 (34%)	139 (67%)	
- 3 AEDs		15 (7%)	55 (27%)	
- 4 AEDs		2 (1%)	13 (6%)	
Individual AEDs	n			
ZNS			207 (100%)	*
CBZ		62 (30%)	56 (27%)	
VPA		61 (30%)	60 (29%)	
LTG		53 (26%)	51 (25%)	
LEV		38 (18%)	7 (3%)	*
OXC		35 (17%)	19 (9%)	*
TPM		26 (13%)	17 (8%)	*
PHB		10 (5%)	6 (3%)	
PHT		7 (3%)	6 (3%)	
PGB		6 (3%)	4 (2%)	
CLB		4 (2%)	3 (1%)	
GBP		1 (1%)	1 (1%)	
ZNS dose		start dose	end dose	
	mean (SD)	43.2 (14.1)	244.8 (108.1)	***
	range	25-100	25-500	
Adverse events (AE)	n			n.s.
- Yes			16 (8%)	
- No			188 (92%) [3 missing]	
Seizure frequency (8 weeks interval)	mean (SD)	8.8 (19.2)	3.6 (9.1)	***
	median	4	1	
	range	0-180	0-90	
Seizure reduction with ZNS (n=204)	n			
- 100%			70 (34%)	
- ≥75%			39 (19%)	
- ≥50%			52 (26%)	
- <50% and worse			43 (21%) [3 remained seizure free]	

n: number; SD: standard deviation.
* $p<0.05$; *** $p<0.001$.
AED: antiepileptic drug; CBZ: carbamazepine; CLB: clobazam; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; n.s.: not significant; OXC: oxcarbazepine; PGB: pregabalin; PHB: phenobarbital; PHT: phenytoin; TPM: topiramate; VPA: valproic acid; ZNS: zonisamide.

The patients' ranking of the importance of seven behavioural domains showed that general QOL was most important (median rank of 2) followed by *daily activities*, *mental function* (median rank of 3), *energy*, *mood*, *seizure worries* (median rank of 4) and *medication effects* (median rank of 5).

According to correlation analysis, the subjective measures were not independent from each other. The scale *burden of epilepsy* of the QOLIE-10-P and the physicians' and patients' global health ratings showed mild correlations (physicians: r=0.26; patients: r=0.27, $p<0.001$), whereas a strong correlation was seen between the scale *burden of epilepsy* and the QOLIE-10 total score (r=0.63, $p<0.001$) on the one hand, and health ratings and the QOLIE-10 total score on the other (physicians: r=0.40; patients: r=0.44, $p<0.001$). Thus, the applied subjective measures are, in part, redundant and appear to converge in the QOLIE-10 total score. Patients' and doctors' health ratings were most strongly correlated (r=0.72, $p<0.001$).

Stepwise regression analysis showed that the patients' QOL at baseline (QOLIE-10 total score) could not be predicted by taking the variables age, gender, type of epilepsy, age at epilepsy onset, duration of epilepsy, seizure frequency, or the number of AEDs into consideration.

The present study design did not provide a control measure for the evaluation of the well known impact of mood on QOL, or change of QOL. However, mood was represented by one of the 10 questions of the QOLIE-10. In order to evaluate which subdomains determined the QOLIE-10 total score, an additional stepwise regression analysis was performed which included the QOLIE-10 total score as dependent, and the 10 individual questions as predictor variables. The same was performed with regard to the change of the QOLIE-10 total score over time.

As for the QOLIE-10 total score at baseline, the three domains which consecutively entered the prediction model (F=385, $p<0.001$) were (1) *social limitations* (t=11.8, $p<0.001$), (2) *cognitive treatment effects* (t=12.6, $p<0.001$) and (3) *general QOL* (t=10.0, $p<0.001$). These three variables explained 85% of the observed variance of the QOLIE-10 total score.

Follow-up evaluation

Ninety-four percent of the physicians and 89% of the patients rated the tolerability of ZNS treatment as at least "good" (63% *vs* 58% as "very good"). Both groups rated overall satisfaction with treatment as "good" in 86% cases (43% *vs* 47% as "very good"), and physicians reported a "good" to "very good" compliance in 96% for those patients still on ZNS at the end of the study. The correspondence of doctors' and patients' ratings of tolerability (r=0.79, $p<0.001$) and treatment satisfaction (r=0.76, $p<0.001$) were high and generally better when patients were seizure-free.

According to t-tests for dependent measures, QOL, as assessed by the QOLIE-10 total score and all of its subscales, demonstrated significant improvement between T1 and T2 *(table 4)*. The mean QOLIE-10 total score dropped from 29.1 to 23.5, and the median from 30 to 23. The effect sizes, which are depicted in descending order in *figure 1*, demonstrate that changes were most prominent in regard to *general QOL* and *seizure worries*, followed by *energy*, *work* and *social limitations,* and were less significant with regard to *mood* and mental capabilities (*cognitive treatment effects* and *memory*).

As could be expected from inference statistics, the number of patients with increased QOLIE-10 total scores indicating reduced quality of life dropped from 68% to 37% at follow-up *(table 4)*.

On an individual level, 73 patients (35%) changed the category from an "impaired" to "unimpaired" QOLIE-10 total score, and 54 (26%) showed improvement of the QOLIE-10 total score of more than one standard deviation (difference score >8 points). A change in category from "unimpaired" to "impaired" was seen in nine (4%) of the patients, and negative changes exceeding one standard deviation indicated significant worsening of QOL in only seven (3%) of the patients *(table 4)*. Counting only the overlap of change indices, 44 patients (21%) improved, and six (3%) deteriorated.

Improvements in subjective ratings were evident not only with regard to the QOLIE-10 total score, but also to the ratings on the overall health status by patients and doctors, to the amount of "active" time (on average, one hour more), and with regard to the perceived *burden of epilepsy (table 4)*.

Significant changes in the ranking of the importance of the rated domains were seen for *general QOL* and *seizure worries*, which became less important in the hierarchy.

Comparing the effect sizes of the major dependent subjective measures, the greatest effect was obtained for *burden of epilepsy*, followed by the doctors' rating of the patient's health status, the QOLIE-10 total score, and the patients' own health rating. The variable "available active time" showed the least significant improvement *(figure 2)*.

Variables affecting QOL outcome

Seizure outcome, drug load, and drug tolerability were the factors that theoretically could be expected to have an impact on QOL under the treatment with ZNS.

As already mentioned, 34% of the patients became seizure-free for the last eight weeks of the observation period, and another 45% had ≥50% seizure reduction. When relating the QOL changes to the different

Table 4. Change of subjective outcomes under the treatment with zonisamide (ZNS).

t-tests for dependent measures [questionnaire, ratings, rankings)					
QOLIE		**T1**	**T2**	**T/sign.**	**d**
QOLIE-10 total score	m (SD) median	29.1 (7.7) range: 13-50 30	23.5 (6.8) range: 11-48 23	11.9 ***	0.77
Energy	m (SD)	3.7 (1.2)	3.0 (1.1)	9.0 ***	0.61
Mood	m (SD)	3.1 (1.1)	2.6 (1.1)	5.4 ***	0.45
Mobility	m (SD)	2.5 (1.3)	2.0 (1.1)	6.1 ***	0.42
Work limitations	m (SD)	3.0 (1.2)	2.3 (1.0)	8.7 ***	0.58
Social limitations	m (SD)	2.9 (1.2)	2.2 (1.1)	8.7 ***	0.61
Memory problems	m (SD)	2.9 (1.1)	2.5 (1.2)	5.3 ***	0.34
Physical treatment effects	m (SD)	2.5 (1.1)	2.0 (1.0)	6.6 ***	0.51
Cognitive treatment effects	m (SD)	2.5 (1.1)	2.0 (1.0)	7.1 ***	0.48
Seizure worries	m (SD)	3.0 (0.9)	2.4 (0.9)	8.2 ***	0.67
General QOL	m (SD)	3.0 (0.9)	2.4 (0.8)	10.5 ***	0.70
QOLIE categories				**Chi^2/sign.**	
Impaired (QOLIE-10 total score >25)	n	141 (68%)	77 (37%)	23.0 ***	
Individual change QOLIE-10 total score (>/< m±1SD) - improved - worsened	n		 54 (26%) 7 (3%)		
Individual change QOLIE-10 total score (category) - improved - worsened	n		 73 (35%) 9 (4%)		
Analogue ratings		**T1**	**T2**	**T/sign.**	**d**
Health rating [physicians]	m (SD)	2.7 (0.8) [2 missing]	2.1 (0.7)	11.0 ***	0.80
Poor health rating [physicians]	%	16%	2%		
Health rating [patients]	m (SD)	2.8 (0.9) [2 missing]	2.2 (0.8)	10.8 ***	0.70

Table 4. (*Continued*)

t-tests for dependent measures [questionnaire, ratings, rankings)					
QOLIE		**T1**	**T2**	**T/sign.**	**d**
Poor health rating [patients]	%	22%	6%		
Active time [hours]	m (SD)	11.1 (6.0) [48 missing]	12.2 (5.5)	- 3.7 ***	0.19
Burden of epilepsy	m (SD)	3.3 (1.0) [3 missing]	2.4 (1.0)	10.83 ***	0.90
Significant burden	%	49%	13%		
Hierarchy Rating	**median**	**T1**	**T2**	**Z/sign.**	
General QOL	rank	2	2	Z= -2.2 *	
Daily activities	rank	3	3		
Mental function	rank	3	3		
Energy	rank	4	4		
Seizure worries	rank	4	5	Z= -2.9 **	
Mood	rank	4	4		
Medication effects	rank	5	5		

QOL: quality of life; * $p<0.05$; ** $p<0.01$; *** $p<0.001$; d: effect size Cohen's *d*.

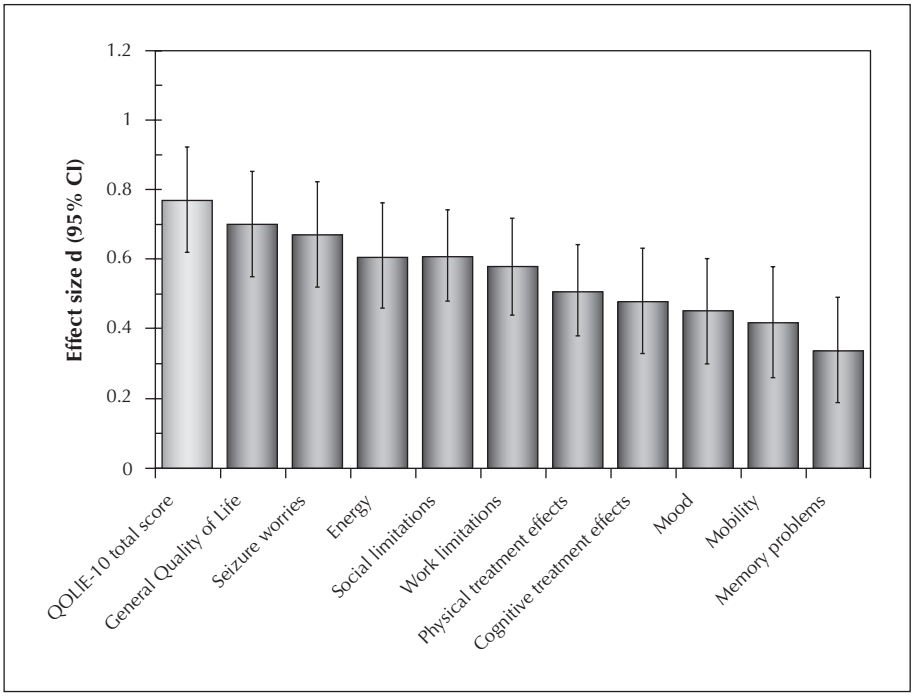

Figure 1. Effect sizes (descending order) of ZNS treatment on QOLIE-10-P and its subscales.

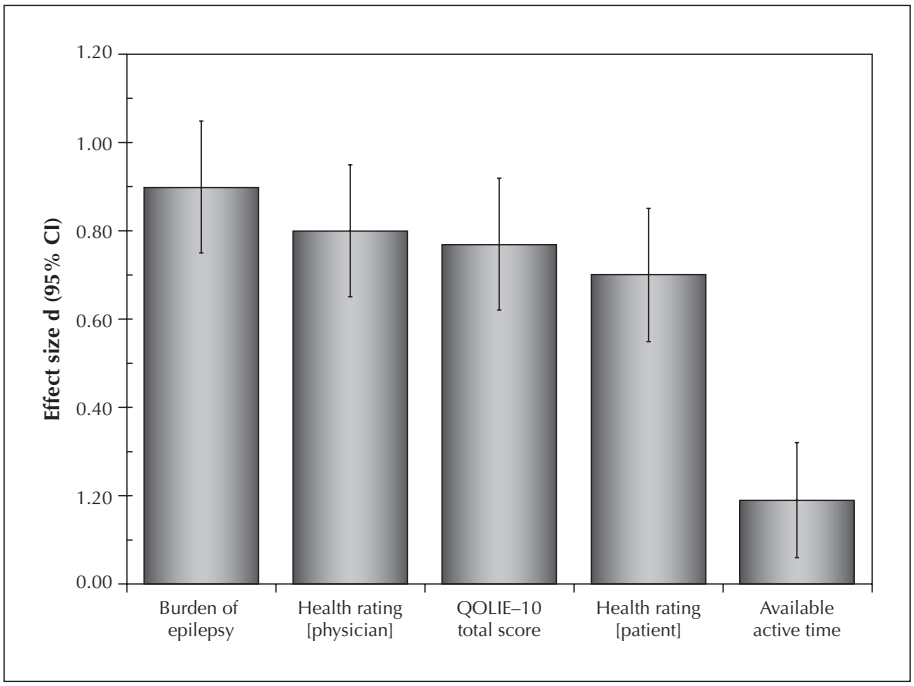

Figure 2. Effect sizes (descending order) of ZNS treatment on dependent measures.

degrees of seizure reduction (100%, ≥75%, ≥50%, <50% or worse), all seizure outcome groups significantly improved in QOL (paired *t*-tests with T between 3.1 and 11.0, p<0.001). Most prominently, improvement was seen in the seizure-free group and the group with ≥ 75% improvement of residual mild to very mild impairment of QOL *(figure 3)*. However, improvement in QOL was also observed in groups which responded less well or showed an unchanged or even worsened seizure situation at T2.

Stepwise multiple regression analysis for QOL outcome prediction indicated that QOL at baseline, seizure control, a lower total number of AEDs at T2 and fewer failed treatment attempts prior to this trial, were indicative of a better outcome. In addition, epilepsies rated as idiopathic appeared to have a better QOL outcome *(table 5)*.

When controlling for how much the ratings of change in the individual subdomains of QOL determined change in the QOLIE-10 total score, change in *social limitations* (*t*=11.8, p<0.001) followed by changes in *general QOL* (*t*=11.5, p<0.001) and *cognitive treatment effects* (*t*=10.1, p<0.001) entered the regression model first and explained 79% of the variance (*F*=255.6, p<0.001).

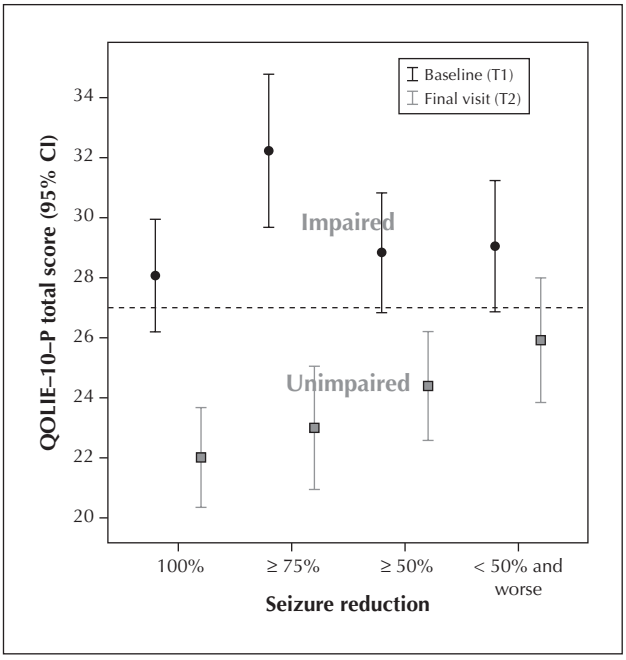

Figure 3. Improvement of quality of life (QOL) after introduction of zonisamide (ZNS) by degree of seizure reduction.

Discussion

Following the European double-blind, placebo-controlled marketing authorisation studies, which had proven the safety and efficacy of ZNS within a fixed treatment schedule, this non-interventional uncontrolled study was set up to assess seizure outcome and tolerability together with subjective ratings on treatment satisfaction and QOL under adjunctive

Table 5. Predictors of subjective outcomes at the four-month follow-up (stepwise multiple regression analyses).

	Dependent measures (better outcomes)					
	QOLIE-10 total score	**Energy**	**Mood**	**Mobility**	**Work limitations**	**Social limitations**
Model	F=33.1 R^2=0.39	F=67.0 R^2=0.24	F=27.1 R^2=0.21	F=23.2 R^2=0.31	F=113.1 R^2=0.36	F=51.7 R^2=0.34
Predictive variables						
Baseline	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Seizure control	↑↑			↑		
No. of AEDs	↓			↓		
Previous AEDs						↓
Idiopathic	↑					
Symptomatic				↓		
ZNS dose			↓			
Age at onset						

	Dependent measures (better outcomes)					
	Memory problems	**Physical treatment effects**	**Mental treatment effects**	**Seizure worries**	**General Quality of Life**	**Burden of epilepsy**
Model	F=57.3 R^2=0.35	F=20.1 R^2=0.22	F=34.4 R^2=0.25	F=30.1 R^2=0.22	F=26.9 R^2=0.34	F=18.8 R^2=0.26
Predictive variables						
Baseline	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑	↑↑↑
Seizure control		↑↑		↑↑↑	↑↑	↑↑↑
No. of AEDs			↓		↓↓	↓↓
AEDs in history	↓					
Idiopathic						↓↓
Symptomatic					↓	
ZNS dose						
Age at onset		↑↑				

↑↑↑ $p<0.001$
↑↑ $p<0.01$
↑ $p<0.05$
Predictor variables: baseline rating, sex, age, occupational status, age at onset, duration >5 years, type of epilepsy, previous AEDs in medical history, ZNS end dose, number of AEDs at T2, change of number of AEDs (difference T2-T1).
AED: antiepileptic drug; QOLIE: Quality Of Life In Epilepsy; ZNS: zonisamide.

treatment with ZNS in a common practice setting. In contrast to the double-blind randomised study by Brodie *et al*. (2005), as well as the open-label study by Dupont and co-workers (2010), the present sample comprised patients with less severe, and presumably easier-to-treat epilepsies. Median seizure frequency at baseline was low with four seizures in eight weeks, and 92% of the patients were taking one or two AEDs. The patients in this trial also had epilepsies with a later onset and shorter duration (a difference of seven to eight years) and a ZNS end dose (244.8 mg) about 100 mg lower than that in the Dupont trial. Compared to the study of Brodie *et al*. (2005), only 42% *vs* about 70-73% were on AED polytherapy.

Corresponding to this, the seizure outcome of this trial was impressive, with 34% seizure-free patients and additional 45% responders with a ≥50% seizure reduction (over an eight-week observation period). Comparatively high responder rates have also been reported in other open surveillance trials performed in similar common outpatient settings (Helmstaedter and Witt, 2008, 2010). In contrast, responder rates in the ZNS authorisation studies with more refractory epilepsies ranged between 25 and 52.5%. In the present study, the follow-up interval of four months was relatively short. In addition, taking into consideration the fact that seizure frequency in some patients was low at baseline, the observed seizure control should be put into perspective. Furthermore, it is important to keep in mind that surveillance trials, such as the one presented here, follow an uncontrolled, unblinded, and non-randomised study design. Thus, effects of other factors in addition to the introduction of ZNS on seizure frequency cannot be excluded.

The physicians' decision to treat with ZNS was mainly driven by insufficient seizure control followed by tolerability problems with current medication. The physicians' most frequent treatment schedule was to add ZNS to the pre-existing treatment rather than switching drugs. Understandably, this accounted for all patients who were on monotherapy at the time of inclusion, but it also accounted for 66% of those patients who were already taking two or three drugs at baseline. The number of drugs was only reduced in one of two patients who were already taking four concomitant drugs at baseline.

Nonetheless, treatment satisfaction and tolerability of the adjunctive treatment with ZNS were positively rated in 86-94% by doctors and patients. The results obtained with regard to QOL under ZNS treatment were similarly positive. At baseline, the extended version of the widely used and well accepted QOL questionnaire, QOLIE-10 (QOLIE-10-P), indicated reduced QOL within the last four weeks in about two thirds of the patients (68%). Since there is no normative data for the QOLIE-10-P in epilepsy, nor any external criterion to conclude an impairment, and since the cut-off value for impairment was arbitrarily set at 50% of the maximum achievable score, the result can only be a relative one. The relative validity of this classification, however, is indicated by the fact that half of the patients also perceived a significant *burden of epilepsy*. General health was rated better than specific epilepsy-related QOL measures, such that only 22% of the patients complained about a poor health status.

At follow-up under treatment with ZNS, QOL was rated significantly better than before, and the rate of patients with impaired QOL dropped from 68 to 37%. Since, as already mentioned, this number is relative, the change in terms of shifting between categories, or the number of patients with a difference of more than one standard deviation, may be better indicators of how much QOL changed over time. Accordingly, between 26 and 35% of the patients individually improved, and 3-4% deteriorated in QOL. The overlap of both categories was 21% for improvements and 3% for worsening, so that at least one fifth of patients significantly profited with regard to QOL following adjunctive treatment with ZNS. Additional positive changes were observed for general health ratings, the rating of the *burden of epilepsy*, available active time, and the ranking of *general QOL* and *seizure worries*. All subjective measures/ratings were highly intercorrelated, indicating that they pick up similar rather than different behavioural domains. However, high intercorrelations of the items can, in part, also be explained by the fact that different areas of interest had been addressed only by one question. Patients' ratings were correlated with physicians' ratings, but this is not surprising given that the ratings cannot be assumed to have been made independently.

It is a fact that self reported depression and QOL ratings are highly correlated and that depression can explain up to 50% of the variance in QOL (Hoppe *et al.*, 2007; Marino *et al.*, 2009). The design of this study did not provide an assessment of depression in addition to QOL, but according to regression analyses, both the QOLIE-10 total score at baseline and its change over time were mainly predicted by scores of *social limitations*, *cognitive treatment effects* and *general QOL* whereas *mood* or *seizure worries* played a minor role. These variables explained about 80 to 85% of the variance of the QOLIE-10 total score at baseline and its change over time.

It is difficult to conclude any negative effects of the treatment of ZNS on QOL based on the present findings. Moreover, ZNS as adjunctive treatment was mostly accompanied by an increase in total drug load. However, ZNS has recently been associated with negative cognitive side effects (Park *et al.*, 2008).

The important question related to QOL outcome at the end of this trial is whether this can be attributed to the drug, the success of the therapy, or other variables. Regression analysis identified three major variables that account for QOL at T2: (1) a better outcome with higher baseline scores; (2) a better outcome with better seizure control; and (3) a better outcome with fewer antiepileptic drugs at T2. In addition, better outcome in patients classified as idiopathic, better outcome in patients with fewer previous AEDs, and better outcome with a later onset of epilepsy was indicated within a complex model that took various variables into account. In this context, it should be noted that the presence of partial seizures was a prerequisite for inclusion in the study. Still, 23% of patients were classified as having idiopathic epilepsies. As this was a

naturalistic observational study, and no confirmation of aetiology was required, it is difficult to estimate whether, or to what extent, the finding of a differential outcome depending on aetiology could be affected by classification mismatch. Altogether, the regression models explained between 21 and 39% of the variance, and they reflect non-specific effects that do not allow any conclusion with regard to ZNS. The winners are those with better baseline conditions and greater therapeutic success. The finding that QOL significantly improved also in patients with poor seizure control puts the findings into perspective. Calculations of effect sizes in this and a recent other NIS demonstrate that effect sizes for more objective measures are weaker than those for subjective opinion-based ratings (Helmstaedter and Witt, 2010). The negative effect of a higher total drug load on QOL may reflect more severe forms of epilepsy, but this may also be interpreted as suggesting that keeping the total number of AEDs low, by exchanging drugs, may be positive for QOL. As demonstrated by this finding, the QOLIE-10-P is sensitive to adverse effects of AEDs. However, only two questions of the QOLIE-10-P explicitly address side effects. Consequently, the inventory assesses medication effects in a much less differentiated way than scales which have been constructed and validated for monitoring adverse AED effects, such as the Aldenkamp and Baker Neuropsychological Assessment Scale (ABNAS) (Aldenkamp *et al*., 2002; Brooks *et al*., 2001), the Side Effect and Life Satisfaction Scale (SEALS; Gillham *et al*., 1996; Gillham *et al*., 2000), the Adverse Event Profile (AEP) (Baker *et al*., 1994), or the Portland Neurotoxicity Scale (PNS) (Salinsky and Storzbach, 2005). In regard to this, one must keep in mind that the choice of a screening tool, such as the QOLIE-10-P, in such a large observational study followed pragmatic considerations.

Concluding the present findings, this study proves satisfactory seizure control and good tolerability of adjunctive treatment with ZNS in a group of patients commonly seen by practitioners, to be rated as easy-to-treat. QOL, as assessed by the QOLIE-10-P questionnaire, improved as a function of better baseline conditions, seizure control, and a lower total drug load, which together with other variables explained up to 39% of the QOL ratings at the end of the trial. The positive effects are unlikely to be attributable to eventual positive psychotropic effects of ZNS; more importantly, no negative effects could be discerned. □

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