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Quality of life, anxiety and depression in adult patients after add-on of levetiracetam and conversion to levetiracetam monotherapy

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Summary The aim of this study was to investigate the change of health related quality of life (HRQoL), anxiety and depression in adult patients in whom an adjunctive treatment with levetiracetam (LEV) was converted to a LEV monotherapy. A prospective, open, investigator initiated multicenter study enrolled 140 patients in whom LEV was added to the existing antiepileptic medication. A total of 65 patients who benefited from the 16-week add-on treatment with LEV (≥50% seizure reduction) were converted to LEV monotherapy (16-week follow-up). In LEV responders, HRQoL, anxiety and depression improved after add-on of LEV. The subsequent conversion to LEV monotherapy did not lead to a significant change in HRQoL, anxiety and depression. However, comparing baseline with LEV monotherapy, the improvements remained significant for most dimensions of HRQoL and for anxiety and depression. Patients' ratings of efficacy of LEV were related with their HRQoL after the conversion to monotherapy. Add-on therapy of LEV improved HRQoL, anxiety and depression in LEV responders. Conversion to a LEV

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monotherapy did not inevitably improve HRQoL in LEV responders, but the positive effect was maintained in the majority of the patients. The effects were highly related to seizure reduction.

Introduction

Antiepileptic monotherapy may have several advantages compared to polytherapy such as better tolerability, improved adherence, less interactions and lower cost (Guberman, 1998). When patients profit from the adjunctive treatment with a second antiepileptic drug (AED) in so far as good seizure control is achieved, it is therefore reasonable to attempt a conversion to a monotherapy. Several clinical trials have tested this method (Gilliam et al., 1998; Ben-Menachem and Falter, 2000).

Although health related quality of life (HRQoL) gains more and more importance as a patient-rated outcome measure, the impact of a conversion to a monotherapy on HRQoL has rarely been investigated. From the few studies dealing with this topic, no final conclusions can be drawn (Cramer et al., 2004; Deckers et al., 2001; Pirio Richardson et al., 2004). For levetiracetam (LEV), the influence of a conversion to a monotherapy on HRQoL has, to our knowledge, not been investigated up to now.

LEV is a newer AED with favorable pharmacological and pharmacokinetic characteristics. Its efficacy and tolerability have been shown in several studies, mainly as adjunctive treatment for partial epilepsies (Cereghino et al., 2000; Morrell et al., 2003) but also as add-on therapy for generalized epilepsies and as monotherapy for partial epilepsies (Brodie et al., 2007; De Smedt et al., 2007; Noachtar et al., 2008).

Adjunctive treatment with LEV has been shown to have a positive influence on HRQoL. In a randomized, placebo-controlled, double-blind study the improvements in HRQoL were larger in the LEV-groups than in the placebo-group with treatment responders ($\geq$50% seizure reduction) reporting the greatest increase (Cramer et al., 2000). The effects were stable in long-term follow-up (Cramer and Van Hammee, 2003). Other studies have confirmed the positive influence of adjunctive LEV on HRQoL (Steinhoff et al., 2007; Lopez-Gongora et al., 2008).

Anxiety and depression are common comorbid disorders in patients with epilepsy (Harden, 2002; Brandt et al., 2010b) and are negatively correlated with HRQoL (Cramer et al., 2005). For this reason it is useful to consider anxiety and depression in the context of HRQoL. The effects of LEV on anxiety and depression have only been investigated in small open-label studies (Mazza et al., 2008; Ciesielski et al., 2006) from which a positive influence of LEV on anxiety and depression can be concluded.

The aim of the present study is to investigate the change of HRQoL, anxiety and depression in patients in whom an adjunctive treatment with LEV was converted to a LEV monotherapy. The data was assessed in a prospective open multicenter study that was performed to determine the efficacy and tolerability of LEV as add-on treatment and as a monotherapy (Brandt et al., 2010a). Our main hypothesis was that HRQoL would improve under LEV add-on in comparison with antiepileptic treatment without LEV and that this effect would at least be maintained during the subsequent conversion to LEV monotherapy.

Methods

Study design and patients

A prospective, open, investigator initiated, multicenter study enrolled 140 adult patients with focal or generalized epilepsy from 12 centers in Germany. Main inclusion criteria were at least two seizures during a baseline period of four weeks and a current treatment with one or two antiepileptic drugs. Main exclusion criteria comprised a current treatment with phenobarbital, primidone or bromide (because of the long half-life of these drugs which would have had an impact on the ability to withdraw them during the study) and a previous treatment with an adequate dose of LEV ($\geq$2000 mg/d). LEV was added for 16 weeks (LEV add-on). The target dose of 2000 mg/d could be adjusted within a range between 1000 mg/d and 4000 mg/d if efficacy was insufficient or intolerable adverse effects occurred. In patients treated with two AEDs, one was withdrawn in parallel (within the first three weeks) while the dose of the other AED was held stable during LEV add-on. Patients with $\geq$50% reduction of seizure frequency during the last four weeks of add-on phase compared to a four-week baseline period preceding the add-on of LEV should be converted to LEV monotherapy (16 weeks, including four weeks conversion period) (Fig. 1). The primary target group were those patients who entered the monotherapy phase ($N = 65$).

The primary endpoints of the current analysis were the change in HRQoL from baseline to LEV add-on and from LEV add-on to LEV monotherapy. Anxiety and depression were analyzed as secondary endpoints.

The primary objective was to examine the effect of add-on of LEV on HRQoL and especially of a subsequent conversion to LEV monotherapy on HRQoL.

Assessment of quality of life, depression and anxiety

The German version of the QOLIE-31 (Cramer et al., 1998) was used to assess epilepsy-specific HRQoL. This self-administered questionnaire consists of 30 items forming seven subscales (Seizure Worry, Overall QoL, Emotional Well-Being, Energy/Fatigue, Cognitive Functioning, Medication Effects, Social Functioning) which are weighted and summed up to obtain a total score, and a single Health Status Item. The raw scores are converted into 0—100 scores with higher values representing higher HRQoL. The German version of the QOLIE-31 has comparably favorable psychometric properties (May et al., 2001) with internal consistency reliability coefficients ranging from $\alpha = 0.76$ (Medication Effects and Social Functioning scales) to $\alpha = 0.90$ (Cognitive Functioning scale).

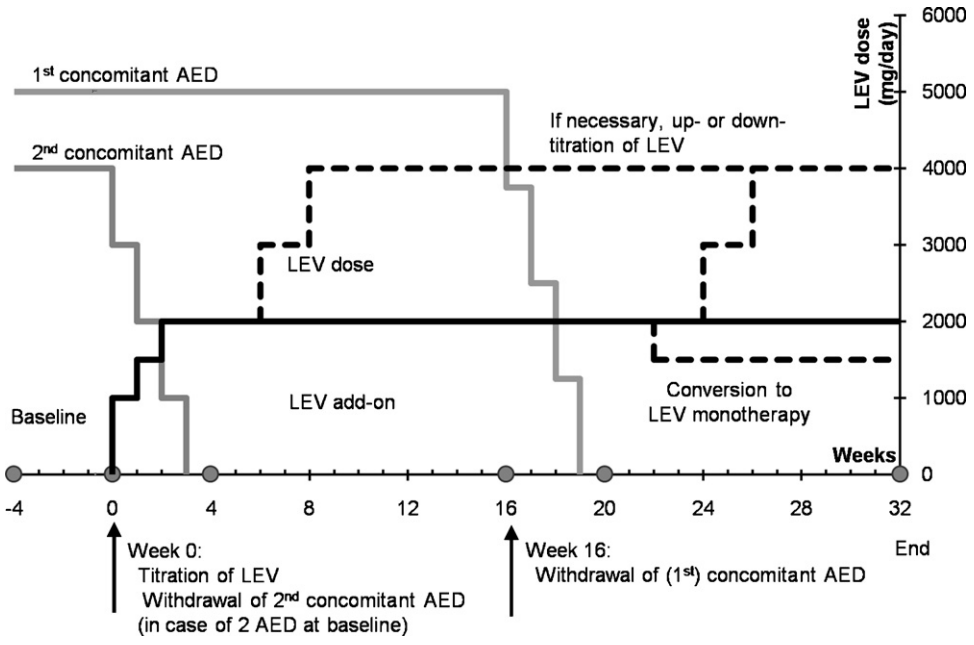

Figure 1 Study design.

For the QOLIE-31, a minimum important change (MIC) of 11.76 was determined (Wiebe et al., 2002). This is the change in the QOLIE-31 total score that can be considered as clinically important. It was empirically derived by comparing patients' perceived change in HRQoL with their change in the QOLIE-31 total score.

The German version of the HADS (Herrmann et al., 1995) is a self-administered questionnaire designed as a screening tool for anxiety and depression in general medical settings. It consists of an anxiety and a depression subscale with seven items each. The HADS does not cover severe psychopathological symptoms in order to improve the acceptability and make it more sensitive to mild forms of psychiatric disorders. The subscale scores range between 0 and 21 with higher values representing higher levels of anxiety or depression. Two reviews give an overview of the psychometric properties of the HADS (Herrmann, 1997; Bjelland et al., 2002).

HRQoL, depression and anxiety were assessed at baseline (without LEV), after add-on of LEV (after 16 weeks) and after conversion to LEV monotherapy (after 32 weeks).

Change in efficacy and tolerability

At each study visit the patients were asked to rate the efficacy and tolerability of their antiepileptic medication on 4-point scales from 'very good' to 'unsatisfactory'. The difference in these scores between the study visits was categorized to obtain patient-rated measures of change in efficacy and tolerability. Additionally, the changes in seizure frequency and clinician-rated occurrence or absence of side effects were used as objective criteria of efficacy and AED tolerability. Seizure frequency was recorded in a seizure diary.

Statistical analyses

It was planned to include 150 patients in the LEV add-on phase, assuming that at least 50 patients would be eligible for the monotherapy period. Based on a sample size of $n = 50$ and an alpha error of 5% (two-sided) the power to detect an at least moderate effect ($d = 0.5$) of LEV monotherapy compared to LEV add-on-therapy (or baseline) was 0.93.

The intention-to-treat (ITT) population of the monotherapy period was defined as all patients who started the conversion to LEV monotherapy (LEV mono) after the end of the LEV add-on period. The per protocol (PP) population was defined as all patients included in the ITT population who had no major protocol deviations.

In a first step, the QOLIE-31 total score and both HADS scales were included in a multivariate analysis of variance (MANOVA) with repeated measures (baseline vs. LEV add-on) comparing responders of LEV add-on to non-responders (between subjects factor), followed by univariate ANOVAs. Simple effects analyses were performed to analyze change from baseline to LEV add-on for responders and non-responders separately. For the analysis of those patients in whom add-on LEV was converted to LEV mono (conversion group), all QOLIE-31 and HADS scales were included in a MANOVA with repeated measures (baseline, LEV add-on, LEV mono), followed by univariate analyses (ANOVAs). For those scales with significant ANOVAs, pairwise comparisons were performed for which the p-values were Bonferroni-adjusted to account for multiple tests. Effect sizes were calculated as the mean score change divided by the standard deviation of the score change with $d = 0.20—0.49$ being considered as a small effect, $d = 0.50—0.79$ as moderate and $d > 0.80$ as large (Cohen, 1988). Furthermore, it was analyzed in how far a change in QOLIE and HADS scores from LEV add-on to LEV mono depended on a change in efficacy or tolerability of

Table 1 Patient characteristics.

	Baseline sample ($N = 140$; ITT population)	Monotherapy group ($N = 65$; ITT population)
Mean age (years)	38.1 ± 14.5	36.9 ± 15.2
Gender (% female)	55.0	60.0
Duration of epilepsy (years)	17.7 ± 14.4	14.9 ± 13.4
Age at epilepsy onset	20.3 ± 15.0	22.0 ± 15.1
Classification of epilepsy (%)		
Partial	60.0	50.8
Generalized	30.0	38.5
Partial and generalized signs	7.9	7.7
Not specified	2.1	3.1
Etiology (%)		
Symptomatic	30.7	24.6
Cryptogenic	39.3	36.9
Idiopathic	27.9	35.4
Not specified	2.1	3.1
Baseline antiepileptic drug (%)		
Lamotrigine	45.7	44.6
Carbamazepine	22.1	27.7
Valproate	30.7	24.6
Oxcarbazepine	13.6	13.8
Other	20.0	12.3

Mean ± standard deviation if not otherwise specified. ITT, intention to treat.

AED treatment. MANOVA was used to compare score changes between groups with different degrees of change in patient-rated efficacy or tolerability, respectively. The size of these effects was expressed as the amount of explained variance (η^2) with $\eta^2 = 0.01—0.05$ being considered as a small effect, $\eta^2 = 0.06—0.13$ as moderate and $\eta^2 > 0.14$ as large (Cohen, 1988).

The criterion for statistical significance was set at 5%. For all analyses, two-sided significance levels are reported. SPSS 18.0 was used for statistical analysis.

Results

A total of 140 patients were included in the study (Table 1). In 67 patients, LEV was withdrawn during or at the end of the LEV add-on period, mostly due to lack of efficacy or tolerability (Fig. 2). Ten patients had to be discontinued because of lack of tolerability. These included psychiatric problems (aggression, mood disorders, depression, and anxiety) in eight cases (5.7%) with one patient experiencing suicidal ideation. Of the 69 patients for whom a subsequent conversion to a LEV mono was intended, four were excluded from the analysis because they had already been converted to LEV mono during the LEV add-on period. Thus the ITT population for the monotherapy group comprised 65 patients. Sixteen of these patients had at least one major protocol deviation (e.g. renewed taking of a second AED, <50% reduction in seizure frequency under LEV add-on). Therefore the PP population comprised 49 patients.

Characteristics of the ITT population are described in Table 1. Baseline seizure frequencies are given in Tables 2 and 3. In the monotherapy group, mean seizure frequency decreased significantly from baseline (median 5.0 per 4 weeks) to the end of the study/LEV mono (median 0.0 per 4 weeks; Wilcoxon's test, $p < .001$) (Table 3).

The study population represents a mixed group of patients with partial as well as generalized epilepsies. The proportion of responders to LEV add-on (≥50% seizure reduction) was higher in patients with generalized epilepsy (76%) than in patients with partial epilepsy (51%). However, the study population was not split up for the analysis of QOLIE-31 and HADS because the change in QOLIE-31 and HADS scores was not dependent on the epilepsy syndrome (MANOVA; $p > .05$). Furthermore, the monotherapy group and the group of patients not entering the monotherapy phase did not differ significantly concerning the epilepsy syndrome.

For the comparison of responders and non-responders to LEV add-on, missing seizure frequencies were replaced with the last observed value ('last observation carried forward', LOCF). Further missing values were not replaced. LOCF was not considered useful for the comparison of LEV add-on and LEV mono because it might have masked deteriorations in the outcome measures during the conversion.

Effects of LEV add-on on HRQoL, depression and anxiety

The overall improvement from baseline to of LEV add-on was significant for the QOLIE-31 total score (within subjects effect: $F(1,111) = 16.3$, $p < .001$) and HADS anxiety ($F(1,116) = 7.1$, $p = .009$; MANOVA, Pillai's trace: $F(3,107) = 7.4$, $p < .001$).

Of the 140 patients entering the LEV add-on period, 83 were responders with ≥50% seizure reduction from baseline to LEV add-on. Responders and non-responders differed significantly with respect to their change in the QOLIE-31 total score (ANOVA, interaction: $F(1,111) = 12.3$, $p = .001$), HADS anxiety ($F(1,116) = 7.5$, $p = .007$) and HADS depression ($F(1,116) = 12.8$, $p = .001$; MANOVA, Pillai's trace: $F(3,107) = 4.2$, $p = .008$) (Table 2). Simple effects analyses revealed significant improvements from baseline to LEV add-on for responders ($p < .001$ for QOLIE-31 and HADS anxiety, $p = .002$ for HADS depression) whereas non-responders did not change in QOLIE-31 and HADS anxiety (both $p > .10$) and their HADS depression scores increased ($p = .041$). Further simple effects analyses showed no difference between the two groups at baseline ($p = .356$).

Effects of conversion to LEV monotherapy on HRQoL, depression and anxiety (ITT population)

For the ITT population (monotherapy group), QOLIE-31 scale scores differed significantly between baseline (without LEV), LEV add-on and LEV mono (MANOVA [including the two HADS scales], Pillai's trace, $F(20,35) = 4.7$, $p < .001$). Univariate analyses revealed significant differences between the three study visits for the total score ($p < .001$) as well as for all subscales and the Health Status Item (all $p < .01$) (Table 3, Fig. 3).

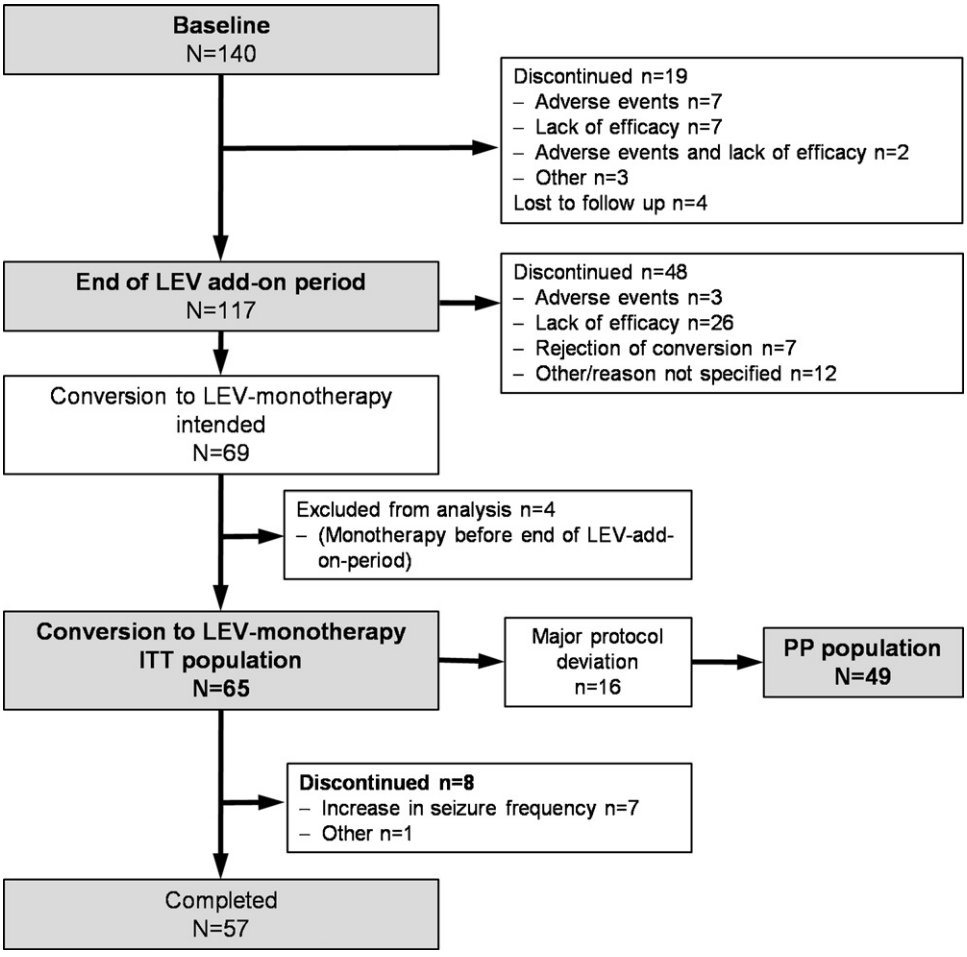

Figure 2 Patient disposition.

Pairwise comparisons confirmed that the scores increased significantly from baseline to LEV add-on (all $p < .05$). The effect was largest for Seizure Worry ($d = 1.10$). For the total score and the other subscales, effect sizes were small to moderate ($d = 0.36—0.78$) (Table 3).

The following conversion to a LEV monotherapy did not lead to significant change in any of the QOLIE-31 scales (all $p > .05$). Comparing baseline scores with LEV mono, the improvements remained significant except for Emotional Well-Being ($p = .096$) and Medication Effects ($p = .051$, all

Table 2 Mean QOLIE-31 and HADS scores, seizure frequencies and LEV doses (baseline and LEV add-on).

		All patients[a]	Non-responders[b]	Responders
QOLIE-31 total score	Baseline	54.5 ± 16.1	52.7 ± 16.8	55.6 ± 15.6
	LEV add-on	60.7 ± 17.1**	53.3 ± 16.2	65.3 ± 16.1**
HADS anxiety	Baseline	7.6 ± 4.0	7.6 ± 4.1	7.5 ± 4.0
	LEV add-on	6.5 ± 4.1**	7.6 ± 4.1	5.8 ± 3.9**
HADS depression	Baseline	5.4 ± 3.5	5.0 ± 4.0	5.6 ± 3.2
	LEV add-on	5.0 ± 4.2	6.1 ± 4.4*	4.4 ± 3.9**
Seizure frequency[c]	Baseline	36.2 ± 123.1	53.9 ± 180.8	24.9 ± 62.2
	LEV add-on	32.7 ± 161.3	79.3 ± 252.6	2.9 ± 9.5
Mean LEV dose	LEV add-on	2290.1 ± 815.6	2490.4 ± 1007.3	2158.2 ± 633.2

[a] All patients with the respective value for baseline and LEV add-on; ANOVA within subjects effect (only QOLIE-31 and HADS): $^{**}p < .01$.
[b] QOLIE-31: responders $n = 70$, non-responders $n = 43$; HADS: responders $n = 73$, non-responders $n = 45$; simple effects analysis (only QOLIE-31 and HADS): $^{*}p < .05$. $^{**}p < .01$.
[c] Number of seizures per 4 weeks.

Table 3 Mean QOLIE-31 and HADS scores, seizure frequencies and LEV doses for the LEV monotherapy group.

	Baseline[a]	LEV add-on	LEV mono	p[b]	Effect size d	
					Adj. LEV[c]	LEV mono[d]
Seizure worry	44.6 ± 28.7	65.4 ± 23.2	60.8 ± 25.1	**<.001**	1.10**	0.56**
Overall QoL	56.5 ± 14.8	67.5 ± 15.3	63.0 ± 16.6	**<.001**	0.55**	0.33*
Emotional well-being	62.9 ± 16.4	69.6 ± 17.2	67.3 ± 16.0	**.002**	0.46**	0.28
Energy/fatigue	49.2 ± 15.6	56.1 ± 18.5	56.7 ± 15.5	**.002**	0.36*	0.41**
Cognitive functioning	56.9 ± 22.3	66.5 ± 21.1	68.2 ± 20.0	**<.001**	0.51**	0.57**
Medication effects	56.8 ± 23.3	70.3 ± 22.4	66.6 ± 23.2	**.001**	0.47**	0.32
Social functioning	57.4 ± 25.3	71.7 ± 22.6	70.5 ± 21.1	**<.001**	0.60**	0.47**
Health status item	58.6 ± 16.7	68.8 ± 14.7	65.2 ± 16.8	**<.001**	0.52**	0.34*
QOLIE-31 total score	56.3 ± 14.7	67.0 ± 14.9	65.8 ± 14.6	**<.001**	0.78**	0.59**
HADS anxiety	7.4 ± 3.9	5.6 ± 3.9	5.7 ± 3.7	**<.001**	−0.63**	−0.54**
HADS depression	5.3 ± 3.2	3.8 ± 3.3	4.1 ± 3.3	**<.001**	−0.55**	−0.40**
Seizure frequency[e]	14.6 ± 27.9	3.8 ± 11.0	4.8 ± 14.1	**<.001**	−0.50**	−0.49**
Mean LEV dose	–	2069.2 ± 329.3	2388.5 ± 694.6			

QOLIE-31/HADS: $N = 57–61$; seizure frequency and LEV dose: $N = 65$.
[a] Mean ± standard deviation (SD).
[b] ANOVA, Greenhouse–Geisser corrected ($p < .05$ in boldface).
[c] mean difference of scores between baseline and LEV-add-on divided by SD of difference; pairwise comparisons (Bonferroni-adjusted): *$p < .05$. **$p < .01$.
[d] Mean difference of scores between baseline and LEV monotherapy divided by SD of difference; pairwise comparisons (Bonferroni-adjusted): *$p < .05$. **$p < .01$.
[e] Number of seizures per 4 weeks.

other $p < .05$) (Table 3). However, the effects were smaller for all scales except Energy/Fatigue and Cognitive Functioning (Table 3).

The number of patients with clinically important changes in the QOLIE-31 total score according to the MIC criterion (see Methods) is shown in Table 4.

Mean levels of anxiety and depression as measured with the HADS changed significantly during the study (both $p < .001$) (Table 3, Fig. 3). Pairwise comparisons showed that this was due to a decrease in both anxiety and depression after the add-on of LEV (both $p < .001$) whereas the conversion to LEV mono did not lead to further change (both $p > .10$). However, the improvements remained significant for LEV mono compared to baseline (anxiety $p < .001$; depression $p = .009$). Effect sizes for the adjunctive LEV phase were moderate (anxiety $d = -0.63$; depression $d = -0.55$) (Table 3). Again, effects were lower when comparing LEV mono with an AED

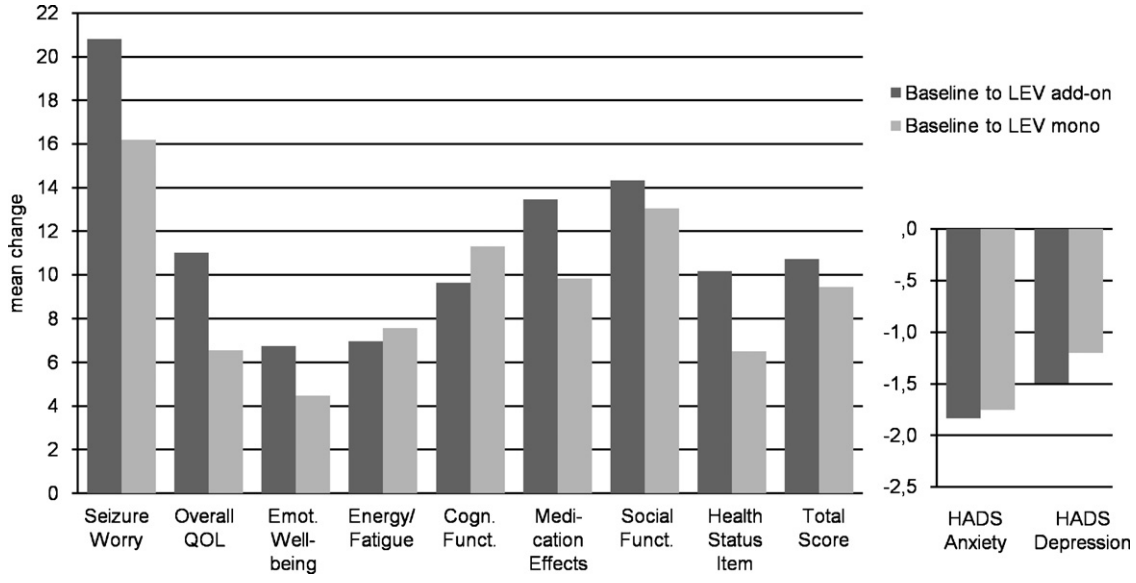

Figure 3 Mean QOLIE-31 and HADS score change from baseline to LEV add-on and from baseline to LEV monotherapy.

Table 4 Clinically important change of the QOLIE-31 total score for both study periods (monotherapy group).[a]

	Worse	No change	Better
Baseline to LEV add-on	4 (7.0%)	29 (50.9%)	24 (42.1%)
LEV add-on to LEV mono	11 (19.3%)	43 (75.4%)	3 (5.3%)

[a] $N = 57$. Clinically important change according MIC criterion: see Methods.

treatment without LEV (anxiety $d = -0.54$; depression $d = -0.40$).

Effects of conversion to LEV monotherapy on HRQoL, depression and anxiety (PP population)

The results of the PP population were very similar to those of the ITT population (data not shown). Exceptions are significant changes from baseline to LEV mono for Emotional Well-Being and Medication Effects which were not found for the ITT population, whereas the significant change for Energy/Fatigue from baseline to LEV add-on could not be confirmed. Effect sizes of the PP population were generally higher.

Change in efficacy and tolerability after conversion to LEV monotherapy and effects on HRQoL, depression and anxiety

Comparing the LEV add-on treatment with LEV mono, an increase of two or more categories on the 4-point rating scale indicates a better patient-rated efficacy or tolerability, respectively, whereas a decrease of two or more categories is a sign of a worse efficacy or tolerability rating (no change = ±1 category).

Multivariate analysis revealed a significant effect of patient-rated efficacy on HRQoL (MANOVA, Pillai's trace, $F(20,80) = 1.8$, $p = .040$), especially with regard to the QOLIE-31 total score (ANOVA, $p = .003$) and the subscales Seizure Worry, Overall QoL and Social Functioning (all $p < .05$) (Table 5, Fig. 4). For those patients who rated efficacy worse after the conversion, a decrease in QOLIE-31 scale scores was observed, especially for Seizure Worry, Overall QoL and Social Functioning, whereas the group with better self-rated efficacy at the end of the study showed an increase, particularly for the Social Functioning scale, but also for Seizure Worry, Cognitive Functioning and the total score (Table 5, Fig. 4). PP analyses led to comparable results, however, the effect for the HADS depression scale was more pronounced ($p = .036$, data not shown).

Additional analyses were performed to investigate the effect of change in seizure frequency after conversion to monotherapy on HRQoL, anxiety and depression. The patients were divided into those with a noticeable increase in seizure frequency of at least 25% compared to LEV add-on ($n = 17$) and those without such an increase ($n = 48$). In accordance with the patient-rated efficacy, significant differences between the two groups were found for the QOLIE-31 scales mentioned above; moreover a change in seizure frequency was significantly related with depression (HADS, data not shown).

In contrast to patient-rated efficacy, the effect of patient-rated tolerability on QOLIE-31 or HADS scales was not significant (MANOVA, Pillai's trace, $F(20,80) = 1.4$, $p = .148$) (Table 5, Fig. 5). PP analyses confirmed these results. Additional analyses showed as well that a change in clinician-rated occurrence or absence of side effects had no significant effect on HRQoL or depression and anxiety in patients converted to LEV mono (data not shown).

Discussion

The primary aim of this study was to examine whether the conversion to a LEV monotherapy is beneficial with respect to HRQoL, anxiety and depression. Data had been collected from patients in whom the add-on therapy of LEV was efficacious and in whom LEV add-on should subsequently be converted to LEV mono in the course of a prospective, investor-initiated study.

HRQoL (QOLIE-31)

After LEV add-on, those patients with a reduction in seizure frequency (≥50%) perceived considerable improvements in HRQoL and its domains. This is in agreement with other studies (Cramer et al., 2000; Cramer and Van Hammee, 2003; Steinhoff et al., 2007; Lopez-Gongora et al., 2008). It probably reflects the impact of seizures on patients' HRQoL as LEV add-on has led to a significant seizure reduction in the present study as well as in the studies mentioned above. This conclusion is supported by particularly large improvements on the Seizure Worry and Social Functioning subscales, which have been shown to be responsive to changes in seizure frequency (May et al., 2001).

More interesting are the findings regarding the conversion to LEV mono since previous studies investigating the effects of an AED monotherapy on HRQoL have come to mixed results. In a multicenter double-blind randomized study comparing carbamazepine (CBZ) monotherapy with a combination of carbamazepine and valproic acid (VPA) no differences in HRQoL between the two treatment groups were found (Deckers et al., 2001). In accordance with this, our study did not confirm an (overall) improvement of HRQoL after the conversion to LEV mono. However, HRQoL remained significantly higher after reduction to LEV mono compared to an antiepileptic treatment without LEV (baseline). Similar to that, an analysis of patients taking lamotrigine (LTG) in combination with an enzyme-inducing AED who were converted to LTG monotherapy (Cramer et al., 2004) revealed a large increase in HRQoL from baseline (before the add-on of LTG) to follow-up assessments at the end of the monotherapy phase. On the other hand, a retrospective chart review of patients with medically refractory

Table 5 Mean QOLIE-31 and HADS score change by change in patient-rated efficacy and tolerability from LEV-add-on to the end of the study (LEV monotherapy).

	Change in patient-rated efficacy[a]			p[d]	η^2
	Worse[b]	No change	Better		
Seizure worry	−28.3 ± 19.8	3.0 ± 18.2	8.2 ± 18.5	**<.001**	.403
Overall QoL	−13.7 ± 21.4	−0.6 ± 11.5	3.8 ± 13.0	**.010**	.165
Emotional well-being	−6.5 ± 11.7	−1.3 ± 15.6	2.5 ± 10.5	.272	.050
Energy/fatigue	−0.6 ± 14.1	2.4 ± 15.3	2.5 ± 11.3	.782	.010
Cognitive functioning	0.3 ± 13.7	2.1 ± 14.7	9.9 ± 13.0	.279	.049
Medication effects	−11.7 ± 22.9	1.3 ± 20.2	−5.2 ± 36.2	.203	.062
Social functioning	−13.1 ± 21.4	0.9 ± 21.9	14.6 ± 16.7	**.015**	.159
Health status item	−9.1 ± 18.2	0.2 ± 13.2	−1.9 ± 18.7	.166	.069
QOLIE-31 total score	−8.3 ± 13.4	1.0 ± 9.9	8.0 ± 7.6	**.003**	.209
HADS anxiety	1.1 ± 2.5	−0.3 ± 3.4	−0.9 ± 1.6	.197	.062
HADS depression	1.6 ± 3.3	−0.1 ± 2.7	−0.9 ± 1.4	.062	.103
MANOVA (Pillai's trace)				**.040**	.306
	Change in patient-rated tolerability			p[d]	η^2
	Worse[c]	No change	Better		
Seizure worry	−12.1 ± 32.5	−4.0 ± 24.1	−5.2 ± 16.2	.675	.016
Overall QoL	−11.1 ± 25.2	−3.8 ± 15.7	0.0 ± 10.3	.305	.045
Emotional well-being	−6.9 ± 10.8	−1.4 ± 11.7	−1.8 ± 20.3	.579	.021
Energy/fatigue	−5.0 ± 10.0	3.4 ± 14.6	1.2 ± 15.3	.300	.046
Cognitive functioning	−3.6 ± 15.2	1.4 ± 13.1	10.3 ± 14.1	.054	.108
Medication effects	−13.9 ± 30.4	−4.2 ± 21.6	4.4 ± 23.0	.209	.061
Social functioning	−8.3 ± 30.1	−2.1 ± 19.5	4.4 ± 24.3	.431	.034
Health status item	−1.7 ± 20.0	−3.4 ± 15.3	−3.3 ± 16.4	.958	.002
QOLIE-31 total score	−7.3 ± 14.7	−0.8 ± 10.9	3.3 ± 11.5	.126	.081
HADS anxiety	−0.1 ± 3.4	0.2 ± 3.0	−0.4 ± 2.7	.822	.008
HADS depression	2.3 ± 3.9	−0.1 ± 2.4	−0.2 ± 2.7	.062	.104
MANOVA (Pillai's trace)				.148	.259

[a] Patient-rated tolerability and efficacy not available $N = 11$.
[b] Change in patient-rated efficacy: worse $N = 16$—17, no change $N = 28$—29, better $N = 7$—8.
[c] Change in patient-rated tolerability: worse $N = 9$, no change $N = 30$—32, better $N = 12$—13.
[d] ANOVA.

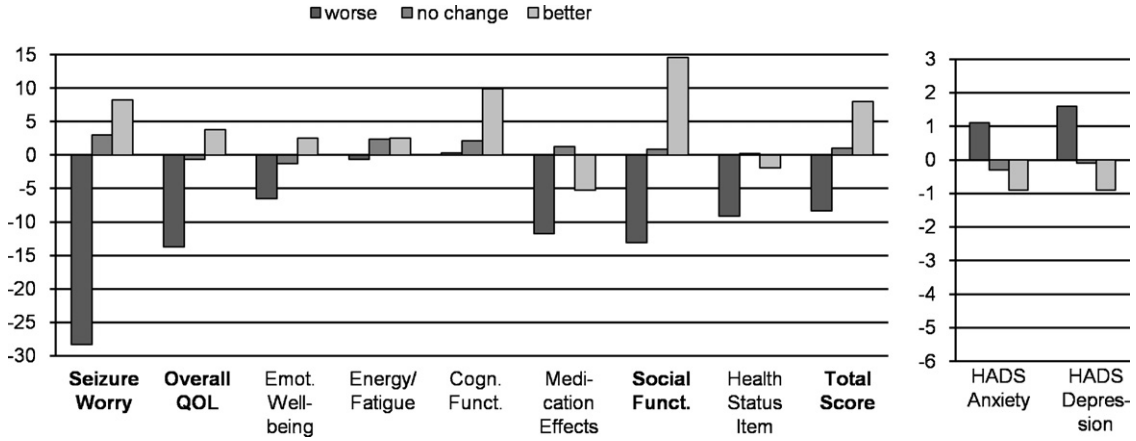

Figure 4 Mean QOLIE-31 and HADS score change in the monotherapy group by change in patient-rated efficacy from LEV add-on to LEV mono. QOLIE-31: positive scores indicate an increase in HRQOL; HADS: positive scores indicate an increase in anxiety/depression. Scales with significant ANOVA ($p < .05$) are shown in boldface type.

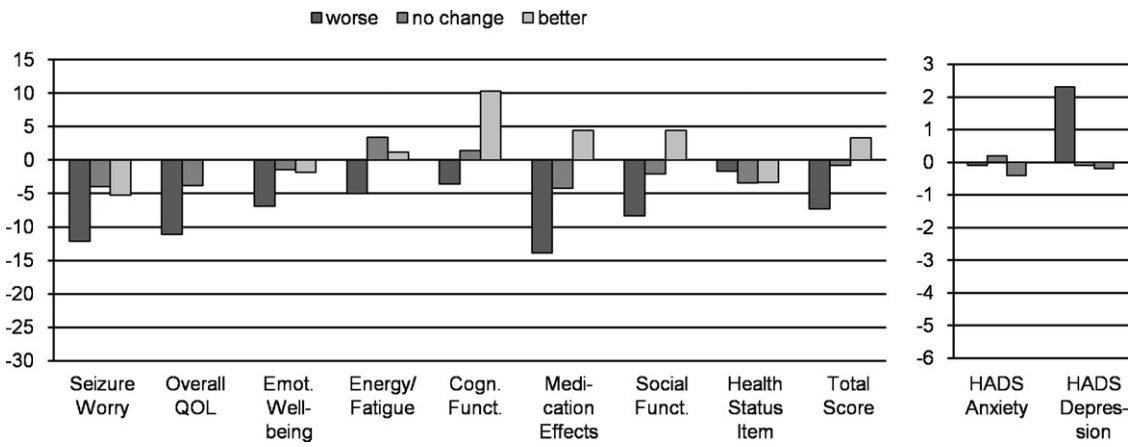

Figure 5 Mean QOLIE-31 and HADS score change in the monotherapy group by change in patient-rated tolerability from LEV add-on to LEV mono. QOLIE-31: positive scores indicate an increase in HRQOL; HADS: positive scores indicate an increase in anxiety/depression.

epilepsy who were converted from polytherapy to monotherapy and stayed on monotherapy for at least 12 months showed improvements in HRQoL (Pirio Richardson et al., 2004). However, it is important to note that in the latter study, the proportion of patients with seizure reduction ≥50% was much higher than in our study and HRQoL under polytherapy was assessed retrospectively.

The significant improvements found after LEV add-on were preserved with the exception of Emotional Well-Being and Medication Effects. Compared to baseline, the largest improvement was observed for Seizure Worry, Cognitive Functioning, Social Functioning and Energy/Fatigue. The findings once more suggest that HRQoL was considerably influenced by the seizure reduction after LEV add-on, which was maintained after the conversion to LEV mono. Nevertheless, the improvements in both Cognitive Functioning and Energy/Fatigue (Table 3) can at least partly be attributed to better tolerability of LEV monotherapy compared to baseline treatment without LEV.

In line with the positive effects of LEV add-on on seizure frequency, a considerable number of patients (24 out of 57, 42.1%) perceived a substantial improvement in HRQoL (according to Wiebe et al., 2002) after add-on of LEV, whereas only a few patients' HRQoL decreased (7.0%). After conversion to LEV mono, the majority of patients did not perceive a marked change in HRQoL (75.4%) and only three patients' ratings improved. However, about a fifth of the patients perceived a substantial deterioration in HRQoL, which emphasizes that some patients did not benefit from the conversion to LEV monotherapy. For some patients, a combination of LEV with other AED may be preferable to LEV monotherapy.

Anxiety and depression (HADS)

LEV add-on has led to significant improvements in anxiety and depression in patients with reduced seizure frequency compared to a treatment without LEV. These improvements were maintained after conversion to LEV mono and emphasize the close relationship between mood and HRQoL found in other studies (e.g. Cramer et al., 2005). The positive effect of LEV on anxiety and depression reported in previous studies (with a smaller number of patients) (Mazza et al., 2008; Ciesielski et al., 2006) was confirmed by the present results. Since both anxiety and depression have been shown to be related to (perceived) seizure control as well as to AED side effects (Mensah et al., 2006, 2007; Souza and Salgado, 2006), efficacy and tolerability of LEV has probably contributed to the improvements.

In eight of the 140 patients, LEV was withdrawn in the add-on period due to psychiatric adverse effects including aggression, mood disorders, depression, anxiety and one case of suicidal ideation. These numbers are in line with previous studies investigating psychiatric adverse events during LEV therapy (Mula and Sander, 2007; Weintraub et al., 2007; White et al., 2003). A history of psychiatric diseases which has been found to be a risk factor for psychiatric adverse events (Lee et al., 2011; Mula et al., 2003) was recorded only for one of the eight patients discontinuing LEV because of adverse effects.

The findings in these eight patients are — at least on first sight — contradictory to the significant improvements in anxiety and depression scores after LEV add-on. However, it has to be kept in mind that these improvements were significantly only in the patient group of responders (≥50% seizure reduction). So, improvements in anxiety and depression were probably caused by the reduction of seizure frequency and not by a 'psychotropic' effect of LEV. With regard to the eight patients in whom LEV had to be withdrawn due to psychiatric adverse events, four patients were responders. Two possible explanations have to be discussed: First, the known psychiatric adverse effects of LEV (see previous paragraph) appear to occur in a relatively small number of patients independent of changes in seizure frequency. Alternatively, the occurrence of the adverse psychiatric events may be independent from the drug and for instance be caused by life events.

Efficacy and tolerability of levetiracetam and effects on HRQoL, depression and anxiety

Patients' ratings of efficacy were significantly related to change in HRQoL, especially Seizure Worry, Overall QoL and

Social Functioning. The deteriorations found in patients who rated efficacy of LEV mono worse than that of LEV add-on suggest that in these patients the withdrawn AED had substantially contributed to seizure reduction. On the other hand, patients who did not indicate change in efficacy from LEV add-on to monotherapy — a group that comprised about half of the patients — did not show a considerable change in any HRQoL domain while patients who perceived an increase in efficacy improved, especially with respect to Social Functioning.

A change in perceived tolerability did not necessarily correspond to change in HRQoL or in any of its domains. Although the mean change in some scales is relatively large, especially for patients who rated tolerability of monotherapy worse, none of the comparisons reached significance and standard deviations are large. Altogether, the results indicate that HRQoL after the conversion from LEV add-on to LEV mono is substantially influenced by patients' rating of efficacy of LEV, whereas the impact of tolerability was not statistically significant in this patient group.

This seems to be in contrast to other studies which demonstrate a highly significant impact of patient-rated adverse effects of AED on HRQoL. However, this effect appears to be especially pronounced in patients with pharmacoresistant epilepsies as shown for example in the study by Elsharkawy et al. (2012). In our study, a considerable portion of patients was seizure free (for at least 4 weeks) after conversion from LEV add-on to LEV monotherapy (60%). Furthermore, it has to be kept in mind that most patients reported no changes of tolerability after conversion to LEV monotherapy.

The impact of patient-rated efficacy rating was confirmed by the analysis of seizure frequencies and the impact of side effects corresponded to that of patient-rated tolerability. Thus, patients' subjective ratings proved to be useful and easily applicable measures of efficacy and tolerability and important predictors of HRQoL.

Limitations

There are some limitations to this study, the most important being the lack of a control group. Furthermore, some patients did not completely answer the QOLIE-31 and HADS at all study visits so that the sample size per analysis was less than 65 (patients who started the conversion to LEV mono). Eight patients were withdrawn from the study before the end of the monotherapy period for different reasons (e.g. increase in seizure frequency). Most of them were included in the analysis because QOLIE-31 and HADS scores were assessed at the final study visit. Thus, also patients for whom the conversion was not beneficial were included in the analysis. Another point to consider is that the number of protocol deviations was relatively high. This was taken into account by analyzing both ITT and PP population, which led to comparable results.

Conclusion

In patients, in whom an add-on therapy of LEV is efficacious, a conversion to LEV monotherapy does not lead to further improvement. However, the positive impact of LEV add-on is maintained in the majority of the patients. This may be an important argument in the ongoing debate whether mono- or combination therapy is preferable. Nevertheless, the findings may be specific for LEV, and no conclusions concerning other AEDs can be drawn. Maintenance or loss of positive effects is closely linked to the effect on seizure frequency. Conversion to LEV monotherapy did not necessarily improve tolerability.

Disclosure

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This study has been approved by the appropriate ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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