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Seizure Reduction and Quality of Life Improvements in People with Epilepsy

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Summary: *Purpose:* Previous research suggests that seizure freedom may be necessary to improve health-related quality of life (HRQOL) for epilepsy surgery patients, but little is known regarding the seizure-frequency reduction needed to improve HRQOL among medically treated individuals.

Methods: With data from 134 adults with refractory complex partial seizures participating in a randomized controlled antiepileptic drug (AED) trial, we compared the change in HRQOL across groups having different levels of change in seizure frequency: 100%, 75–99%, 50–74% reduction, and 0–50% increase or decrease. Changes over time within each seizure-reduction group also were assessed. HRQOL was measured by the QOLIE-31, QOLIE-89, and SF-36.

Results: Subjects who became seizure free reported significantly more positive change than those who did not on the QOLIE-31 and QOLIE-89 overall scores, the QOLIE-89 mental health, physical health, and epilepsy-targeted composites, as well as the SF-36 mental health summary score. Changes over time in overall QOLIE-31 and QOLIE-89 scores were significantly more positive for subjects who achieved seizure freedom (i.e., 100% reduction in seizure frequency) than for those who did not. No significant change in QOLIE-31 and QOLIE-89 overall scores was observed for subjects who did not achieve seizure freedom.

Conclusions: In this study, HRQOL improvement occurred primarily among patients who achieved complete seizure freedom. Many AED trials use a 50% seizure-frequency reduction criterion as a trial end point, but measurable impacts of this degree of reduction in seizure frequency on HRQOL in this sample were not observed. These results further support striving for seizure freedom as an epilepsy care goal. **Key Words:** Epilepsy—Health-related quality of life—Quality of life—Seizure freedom—AED trials

Health-related quality of life (HRQOL) measures, which assess daily functioning and well-being, can complement traditional outcomes and help to capture the full range of relevant clinical end points. The QOLIE-89 is an HRQOL measure for people with epilepsy that includes the SF-36 as the generic core and plus disease-targeted items. The QOLIE-31 is a subset of items from the QOLIE-89.

Clinicians have long recognized the impact of seizure frequency on the well-being of their patients with epilepsy. Seizure frequency has been found to be negatively associated with all SF-36 scales, and those who are seizure free have HRQOLs similar to those of the general population (1). In antiepileptic drug (AED) trials, a ≥50% reduction in seizure frequency rather than seizure freedom has been the dominant end point used to assess efficacy (2–5). There is a growing debate about the impact partial reduction in seizure frequency may have on HRQOL, especially if the baseline seizure occurrence is relatively high. Some speculate that a 50% reduction in seizure frequency may not reflect a clinically meaningful improvement, at least in certain contexts (6). Others have suggested that those having a ≥75% reduction in seizures as well as the percentage of subjects attaining seizure freedom be reported in all AED therapeutic trials (7). Although seizure frequency is the end point used to assess efficacy of AEDs, no consensus exists as to what magnitude of seizure reduction is required to result in a clinically meaningful change or to produce an improvement in HRQOL.

To explore this issue, we analyzed data collected for a randomized trial of an AED. Patients were grouped into four categories according to the change in their seizure frequency during the course of the trial. Changes in the SF-36, QOLIE-31, and the QOLIE-89 were compared with change in seizure frequency.

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METHODS

Analytic sample

Data were gathered from a national, multicenter randomized controlled trial of vigabatrin (VGB) add-on therapy (8). Among the 142 subjects who completed the trial and composed the sample used in these analyses, the mean age was 38.2 years, 48% were men, and 85% were white. Prominent seizure types included complex partial seizures (51.6%), tonic–clonic seizures (26.2%), or both (21.7%). Subject characteristics are summarized in Table 1. All enrollees were taking phenytoin (PHT) or carbamazepine (CBZ) monotherapy at study entry. Mean seizure frequency at baseline was 3.6 seizures per month.

Data collection and measures

Seizure diaries were used to assess seizure frequency. Auras were not counted as seizures. Baseline monthly seizure frequency was seizure frequency during the 12-week interval *after* enrollment but *before* randomization. Follow-up seizure frequency was seizure frequency during the final 12 weeks of the 28-week follow-up period. HRQOL was measured at baseline and at a 28-week follow-up by using the QOLIE-31 overall score, the QOLIE-89 overall score, the four QOLIE-89 composite scores, and the SF-36 physical and mental health summary scores (9,10). All HRQOL measures were scored on a T-score metric (mean, 50; SD, 10). Participating institutional review boards approved all procedures for recruitment and interaction with subjects.

The QOLIE-89 was developed by supplementing the SF-36 with additional items (solicited from an expert panel) and subsequent psychometric analyses (9). The QOLIE-31 was developed by selecting items from the QOLIE-89 considered most important by expert opinion (10). The QOLIE-31 includes primarily epilepsy-targeted items (10). Field tests of the QOLIE-89 and the QOLIE-31 provide support for the reliability of their scales for group comparisons (9,10).

Categories of seizure reduction

We classified all clinical trial subjects completing both baseline and follow-up measures into one of four mutually exclusive categories of change in seizure frequency: 100% decrease, 75–99% decrease, 50–74% decrease, and 0–50% increase or decrease. Eight subjects having a >50% increase in seizure frequency during the trial were excluded from the analysis, yielding an analytic sample of 134.

TABLE 1. *Characteristics of the 142 subjects completing the trial*

Subject characteristics	
Age (mean)	38.2 years (range, 18.8–66.8)
Gender	48% Men
Race	85% white
	12.2% black
	1.4% Asian-American
Seizure subtype	51.6% Complex partial
	26.2% Tonic–clonic
	21.7% Both

Analysis

Analyses of variance (ANOVAs) comparing the change in HRQOL across groups having different changes in seizure frequency were completed for the QOLIE-31 overall score, the QOLIE-89 overall score and four composite scores, and the SF-36 physical and mental health summary scores. Duncan's multiple-range test was used to evaluate the significance of differences in HRQOL-change scores across categories of change in seizure frequency. Within-group paired *t* tests were calculated for the same HRQOL measures to determine whether significant changes over time in HRQOL were experienced within each category of seizure reduction during the clinical trial.

RESULTS

Of the 134 subjects who experienced a reduction in seizure frequency, 22 (16%) became seizure free, 18 (13%) had a 75–94% reduction in seizure frequency, and 33 (25%) experienced a 50–74% reduction. Less than a 50% increase or decrease in seizure frequency was observed in 61 (46%) of the subjects.

Table 2 shows the mean changes in HRQOL scores for each of these four categories. The ANOVA indicated a significant difference in HRQOL-change scores across groups, as measured by the overall QOLIE-31 ($F = 8.59$; $p < 0.0001$). Similar results were obtained for the overall QOLIE-89 ($F = 6.45$; $p < 0.0004$) and SF-36 mental health summary score ($F = 5.97$; $p = 0.0008$). All four composite scores for the QOLIE-89, except the cognitive function composite, indicated similar relations (all p values <0.008). Changes in the SF-36 physical health summary score and QOLIE-89 cognitive function composite across categories of seizure reduction were not significant ($F = 1.73$, $p = 0.16$; and $F = 1.91$, $p = 0.13$, respectively). Duncan's multiple-range test comparing the mean changes in the overall QOLIE-31 and QOLIE-89 scores, the QOLIE-89 physical health composite, QOLIE-89 mental health composite, QOLIE-89 epilepsy-targeted composite and SF-36 mental health summary scores revealed that those subjects who achieved seizure freedom experienced significant improvements in HRQOL relative to subjects in all the remaining seizure-reduction categories.

The paired *t* test comparisons for HRQOL change within each seizure-reduction category from baseline to trial completion demonstrated significant improvement for those patients achieving seizure freedom as measured by the overall QOLIE-31 ($p = 0.0006$), overall QOLIE-89 ($p = 0.0035$), QOLIE-89 mental health composite

TABLE 2. *Mean T-score changes in HRQOL over 28 weeks for 134 subjects across varying levels of change in seizure frequency*

HRQOL measure	100% reduction (n = 22)	75–99% reduction (n = 18)	50–74% reduction (n = 33)	0–50% change (n = 61)	*F* value (p value)
Overall QOLIE-31	6.96 (a)[a]	1.76 (b)	−0.80 (b)	−0.17 (b)	8.59 (0.0001)
Overall QOLIE-89	7.32 (a)	0.96 (b)	−0.20 (b)	−0.62 (b)	6.45 (0.0004)
QOLIE-89 mental health composite	6.41 (a)	1.71 (b)	−2.09 (b)	−0.52 (b)	6.65 (0.0003)
QOLIE-89 physical health composite	7.11 (a)	−0.67 (b)	−0.37 (b)	−1.07 (b)	5.12 (0.0023)
QOLIE-89 epilepsy-targeted composite	7.26 (a)	3.04 (b)	1.86 (b)	0.57 (b)	4.13 (0.0079)
QOLIE-89 cognitive function composite	4.29 (a)	−0.16 (a)	−0.37 (a)	−0.12 (a)	1.91 (0.1313)
SF-36 Mental health summary score	7.11 (a)	1.92 (b)	−3.53 (c)	−0.98 (b,c)	5.97 (0.0008)
SF-36 Physical health summary score	3.66 (a)	−1.14 (a)	1.79 (a)	−0.98 (a)	1.73 (0.1642)

HRQOL, health-related quality of life.

[a] T-score changes are significantly different across values in a row that do not share at least one letter in common. HRQOL measures are scored on a T-score metric (mean, 50; SD, 10).

(p = 0.0039), QOLIE-89 physical health composite (p = 0.0069), QOLIE-89 epilepsy-targeted composite (p = 0.0021), and SF-36 mental health summary scores (p = 0.0054). No improvement was detected in the seizure-free group by the SF-36 physical health summary score (p = 0.11) or the QOLIE-89 cognitive function composite (p = 0.067). Evidence for HRQOL improvement among the remaining groups, who did not achieve seizure freedom, was limited to the 75–99% reduction category for the overall QOLIE-89 epilepsy-targeted composite (p = 0.022) and the 50–75% reduction group by the QOLIE-89 mental health composite (p = 0.047) and SF-36 mental health summary score (p = 0.019).

DISCUSSION

In this study, HRQOL improvement was consistently evident only among those patients achieving seizure freedom. HRQOL changes across other seizure-reduction categories were less positive. The small number of subjects in the 75–99% reduction category (n = 18) limited the power to detect a difference for this group. HRQOL improvement within seizure-reduction groups for two disease-targeted measures was entirely limited to those patients achieving seizure freedom.

The QOLIE-89 Physical Health Composite, but not the SF-36 Physical Component Score, was responsive to change across varying levels of seizure frequency. This difference could be because the QOLIE-89 Physical Health Composite includes additional items addressing health issues most applicable to people with epilepsy (e.g., epilepsy-targeted Health Perceptions).

Previous work demonstrated that the QOLIE-89 epilepsy-targeted composite is more sensitive to seizure frequency and type than are the physical health, mental health, and cognitive function composites (1). The QOLIE-31 includes primarily epilepsy-targeted items from the QOLIE-89, so it is not surprising that this study found the QOLIE-31 to be the most responsive measure in detecting improvement in seizure frequency. Comparisons in other populations are warranted to determine if using the shorter QOLIE-31 is an acceptable trade-off to the QOLIE-89 for studies in which respondent burden is of primary concern and comparison with nonepilepsy samples is unimportant.

These findings suggest that for a significant improvement in HRQOL to occur, at least in some patient populations, seizure freedom is imperative. Studies have suggested that HRQOL may worsen over time among epilepsy surgery patients who have a <90% reduction in seizure frequency after surgery (11). We also found a significant decrease in the SF-36 mental health summary score, comparing the 50–74% reduction group with the 0–50% change in seizure frequency group during the course of this AED trial.

Although a 50% reduction in seizure frequency has become a traditional end point for add-on AED therapy, this is a somewhat arbitrary goal. Our findings provide further evidence to support the importance of striving for seizure freedom when caring for patients with epilepsy.

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REFERENCES

1. Leidy NK et al. Seizure frequency and the health-related quality of life of adults with epilepsy. *Neurology* 1999;53(1):162–6.
2. Ben-Menachem E, et al. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 1996;37(6):539–43.
3. Gabapentin as add-on therapy in refractory partial epilepsy: a

double-blind, placebo-controlled, parallel-group study. The US Gabapentin Study Group No. 5. *Neurology* 1993;43(11):2292–8.
4. Beran RG et al. Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalized epilepsy. *Epilepsia* 1998;39(12):1329–33.
5. Loiseau P et al. Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. *Epilepsia* 1986;27(2):115–20.
6. Chadwick D. Better comparisons of antiepileptic drugs: what measures of efficacy? *Pharm World Sci* 1997;19(5):214–6.
7. Perucca E. Evaluation of drug treatment outcome in epilepsy: a clinical perspective. *Pharm World Sci* 1997;19(5):217–22.
8. Edwards K et al. Rational polytherapy with Sabril (Vigabatrin) versus carbamazepine or phenytoin monotherapy in the management of patients with complex partial seizures. *Epilepsia* 1998; 39(Suppl 6):190.
9. Devinsky O et al. Development of the quality of life in epilepsy inventory. *Epilepsia* 1995;36(11):1089–104.
10. Cramer JA et al. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. *Epilepsia* 1998;39(1): 81–8.
11. McLachlan RS et al. Health-related quality of life and seizure control in temporal lobe epilepsy. *Ann Neurol* 1997;41(4):482–9.