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# Long-Term Seizure, Quality of Life, Depression, and Verbal Memory Outcomes in a Controlled Mesial Temporal Lobe Epilepsy Surgical Series Using Portuguese-Validated Instruments

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■ OBJECTIVE: We aimed to evaluate long-term surgical outcomes in patients treated for mesial temporal lobe epilepsy compared with a similar group of patients who underwent a preoperative evaluation.

■ METHODS: Patient interviews were conducted by an independent neuropsychologist and included a sociodemographic questionnaire and validated versions of the Beck Depression Inventory-II, Adverse Events Profile, Quality of Life in Epilepsy-31, and Rey Auditory Verbal Learning Test.

■ RESULTS: Seventy-one patients who underwent surgery and 20 who underwent mesial temporal lobe epilepsy preoperative evaluations were interviewed. After an 81-month mean postoperative follow-up, 44% of the surgical patients achieved complete seizure relief according to the Engel classification and 68% according to the International League Against Epilepsy classification. The surgical group had a significantly lower prevalence of depression ($P = 0.002$) and drug-related adverse effects ($P = 0.002$). Improvement on unemployment ($P = 0.02$) was achieved but not on driving or education. Delayed verbal memory recall was impaired in 76% of the surgical and 65% of the control cases ($P = 0.32$). Regarding the Quality of Life in Epilepsy-31, the operated patients scored higher in their total score (mean, 75.44 vs. mean, 60.08; $P < 0.001$) and in all but the cognitive functioning domain irrespective of the follow-up length. Seizure control, Beck Depression Score, and Adverse Events Profile severity explained 73% of the variance in the surgical group quality of life.

■ CONCLUSIONS: Our study found that, although surgical treatment was effective, its impact on social indicators was modest. Moreover, the self-reported quality of life relied not only on seizure control but also on depressive symptoms and antiepileptic drug burden.

## INTRODUCTION

Surgical intervention as a treatment option for epilepsy remains largely underused[1,2] despite robust, positive evidence from randomized clinical trials of mesial temporal sclerosis.[3,4] However, improvements in health-related quality of life (QOL) are substantially difficult to assess in limited, short-term studies.[5] Nonetheless, such assessments are important regarding patient aims.[6] In a multicenter trial of resective epilepsy surgery, Spencer et al.[7] reported that the QOL in epilepsy (QOLIE) improves early regardless of the seizure outcome; however, sustained and further developments are related to seizure relief, for which the rate decreases beyond 2 years after mesial temporal sclerosis surgery.[8,9] Moreover, seizure freedom-related

gains that are of paramount importance[10] may be hampered by social-related (e.g., the burden of normality)[11] and treatment-related drawbacks (e.g., new memory deficits and mood disorders).[12] It has been reported that drug toxicity and depression are the highest QOLIE predictors in drug-resistant,[13] well-controlled,[14] and surgical patients.[15] Furthermore, there are notable regional differences worldwide in access to care, socioeconomic disparities, comorbid conditions, treatment choices,[16] and rehabilitation,[17] which should also be considered.

Since the beginning of our surgical program in 2000 in Brasilia, Brazil, we have preoperatively administered freely translated QOL questionnaires and psychometric instruments; however, the reliability and reproducibility of these tools are not sufficient and are a widely encountered problem in the field. The existence of discrepancies in the application of nonvalidated tests to different populations has long been noted.[10] Therefore, lengthy efforts (from 2000 to 2012) have been made by different research groups to overcome the translation, synthesis, back translation, expert committee review, and pretesting processes[18] involved in the full cross-cultural adaptation of the commonly used questionnaires and tests. To date, only short-term studies have been reported that concern the Brazilian population.[19,20]

Thus, in 2012, an investigation of patients who underwent surgical intervention for anterior mesial temporal epilepsy was initiated by using a structured demographic interview, a verbal memory test, and previously validated Brazilian Portuguese versions of widely used patient-based tools. This study was aimed at verifying the effects of surgery and clinical treatment on long-term QOL and its associations with seizure outcome, social relations, depression, and medication side effects, as well as their impact on existing verbal memory deficits.

## METHODS

### Patient Selection
Adult patients underwent an operation at Hospital de Base do Distrito Federal, Brasília-DF, Brazil, for drug-resistant mesial temporal lobe epilepsy (MTLE), as defined by the International League Against Epilepsy (ILAE).[21] Patients met the inclusion criteria of the electroclinical (video-electroencephalography) presentation of MTLE onset, had solely unilateral disease, showed structural magnetic resonance imaging evidence of hippocampal atrophy, or showed hippocampal sclerosis disease if they were magnetic resonance imaging—negative. Patient ages were encompassed by the QOLIE-31 survey[22] (i.e., 18—60 years old), and there was a minimum follow-up of 3 years.

Patients were excluded from this study if they had associated disease (e.g., hemiconvulsion-hemiplegia-epilepsy syndrome, type II cortical dysplasia) or cognitive or psychiatric impairment that precluded an adequate evaluation or if their residence at the time of the study was in another state.

A similar group of patients with MTLE who were waiting for surgery or video-electroencephalography and who were evaluated before June 2012 were enrolled as the control group.

All patients provided written informed consent for study participation, which was approved by our institution's ethics committee and registered to the Brazilian federal clinical trials registry (Plataforma Brasil) under no. 06623212.1.0000.5553.

### Surgical Procedure
All operations were executed by the same surgeon (L.A.D.). A 3.5-cm to 4-cm anterior temporal corticectomy was performed, which spared the superior temporal gyrus (disregarding the side of the disease), combined with an amygdalohippocampectomy, which extended to at least the superior colliculus, as described by Spencer et al.[23]

### Interview
From June 2012 to July 2013, all patients underwent a complete, in-person interview (of approximately 1.5 hours duration) by an independent neuropsychologist who had not been involved in the patients' previous investigations or treatments.

The demographic and clinical data questionnaire was adapted, and all neuropsychometric evaluation instruments were selected from the National Institute of Neurological Disorders and Stroke 2011 Common Data Elements Project recommendations.[24] The psychosocial profiling focused on employment, education, driving record, and family bonds (partnership and children). Seizure outcome was based on both Engels classification,[25] which considered groups Ia, I (Ia, Ib, Ic, Id), II, III, and IV, and the 1—6 group ILAE classification,[26] which considered only the most recent year of follow-up. The control group was also classified according to their seizure frequency for comparison.

Each patient's QOLIE, mood, antiepileptic drug (AED) burden, and verbal memory were evaluated by Brazilian Portuguese-validated versions of the following self-report instruments:

**Table 1.** Patients Who Were Excluded or Refused to Participate

| Original Sample | Surgery Group (n = 156) | Medically Treated (n = 34) |
|---|---|---|
| Age <18 or >60 years | 5 | 1 |
| Bilateral temporal | 1 | |
| Nonlesional* | 7 | 1 |
| Tumoral pathology | 11 | |
| Dual pathology† | 6 | |
| Selective amygdalohippocampectomy‡ | 2 | |
| Another surgeon | 3 | |
| Cognitive impairment | 5 | 1 |
| Psychiatric disorder | 5 | 2 |
| Living elsewhere | 13 | 2 |
| Total noneligible | 58 | 7 |
| Eligible refused | 8 | 2 |
| Eligible not found | 19 | 5 |
| Total eligible | 27 | 7 |

*Magnetic resonance imaging and pathology negative.
†Hippocampal atrophy plus another magnetic resonance imaging lesion.
‡Niemeyer technique.

**Table 2.** Summary of Clinical Characteristics of Patients Who Underwent Surgery for Mesial Temporal Lobe Epilepsy and the Control Group

| Demographic and Clinical Data | Surgical (n = 71) | Control (n = 20) | P |
|---|---|---|---|
| Sex (male) | 33 (46.5) | 6 (30) | 0.19 |
| Having a partner (yes) | 28 (39.4) | 6 (30) | 0.44 |
| Children (yes) | 36 (52.2) | 11 (64.7) | 0.35 |
| Religion (yes) | 64 (90.1) | 20 (100) | 0.34 |
| >9 years of education | 50 (70.4) | 11 (55) | 0.20 |
| Employed (yes) | 38 (53.5) | 5 (25) | 0.02 |
| Driving (yes) | 22 (31) | 2 (10) | 0.06 |
| Age at first seizure (years), mean ± SD | 12.99 ± 8.9 | 8.75 ± 6.41 | 0.09 |
| Onset of epilepsy (years), mean ± SD | 13.58 ± 10.85 | 12.85 ± 6.79 | 0.78 |
| Duration of epilepsy (months), mean ± SD | 370.56 ± 131.01 | 310.70 ± 99.35 | 0.06 |
| Age at surgery (years), mean ± SD | 38 (9) | | |
| Duration of epilepsy until surgery (months), mean ± SD | 289.32 ± 130.44 | | |
| Age at interview (years), mean ± SD | 43.90 ± 9.03 | 39.40 ± 6.61 | 0.04 |
| Side of pathology (left) | 38 (53.5) | 14 (70) | 0.19 |
| Presence of aura (yes) | 55 (78.6) | 18 (90) | 0.47 |
| Taking AEDs (yes) | 50 (70.4) | 20 (100) | 0.005 |
| Number of preoperative AEDs, mean ± SD | 1.94 ± 0.65 | 2.00 ± 0.65 | |
| Number of postoperative AEDs, mean ± SD | 1.13 ± 0.88 | 2.00 ± 0.65 (not operated) | 0.009 |

Values are number (%) except where indicated otherwise.
SD, standard deviation; AED, antiepileptic drug.

1) QOLIE-31,[27] the most widely used epilepsy specific measure.[28] This instrument comprises 31 questions and assesses 7 domains (seizure worry, overall QOL, emotional well-being, energy-fatigue, cognitive functioning, medication effects, social functioning, and an overall score). Scoring occurs on a scale of 0–100, in which a higher value indicates a better life.

2) Beck Depression Inventory—II (BDI-II),[29] a 20-item depression screening tool. Scoring takes place on a scale of 0–63, which is categorized as 0–13 for minimum depression, 14–19 for mild depression, 20–28 for moderate depression, and 29–63 for potentially severe depression.

3) Liverpool Adverse Events Profile (AEP scale),[30] a measure of burden from AEDs. Scoring occurs on a scale of 19–76, in which a higher value indicates worse toxicity; a cutoff point of 45 was used.[31]

4) Rey Auditory Verbal Learning Test.[32,33] Patients are administered a 15-word list (A) over trials I–V, which is followed by an interference list (B), immediate recall (VI), a free recall trial (VII) 30 minutes later, and a recognition task at the end of the test. Learning over trials is also evaluated. Scoring occurs on a scale of 0–15, in which a higher value indicates better performance. A cutoff score of 1.5 standard deviations (SDs) below age-matched and sex-matched peers indicates memory

impairment,[34] whereas a score lower than 2 SDs indicates a profound deficit. In the current study, visual memory was not addressed because no test has been Common Data Elements recommended because of an overall lack of clear results.[35]

## Statistical Analysis

Data analysis was conducted with SPSS for Windows (SPSS Inc., Chicago, Illinois, USA) and graphs were derived from Minitab Statistical Software (MinitAB Inc., State College, Pennsylvania, USA). Percentage distributions for categorical variables and means with SDs for continuous variables were applied in the descriptive statistics. For exploratory univariate analyses, after Kolmogorov-Smirnov testing, a $\chi^2$ and t tests were administered for normal variables and the Mann-Whitney U test was used for nonnormal variables. Correlation analyses (r, Pearson correlation coefficient) were performed to investigate the effects of continuous variables on seizure and QOL outcomes. A list of significant demographic, clinical, disease, and treatment-related factors was subsequently identified and submitted to stepwise linear regression multivariate analyses, which examined for multicollinearity problems (variance inflation factor <5) to serve as predictors of a better QOL. A 95% confidence interval that yielded a P value <0.05 was considered significant. For the sequential long-term follow-up groupings,

after testing for normality, an analysis of variance was conducted followed by a Bonferroni post hoc test or a Kruskal-Wallis test was conducted followed by a Dunn post hoc test.

## RESULTS

From an original cohort of 156 patients who underwent surgery from June 2000 to June 2009, 98 patients met the inclusion criteria. From the list of 34 patients who were clinically treated, 27 were eligible. Additional patients refused to participate or could not be found, despite several attempts (Table 1). Thus, we pursued a full evaluation in 71 surgical patients (72.4%) (mean follow-up, 81 months; range, 34−152 months) and 20 clinically treated patients.

### Demographic and Social Outcomes

Demographic data were not significantly different between groups, with the exception of age at the time of interview; operated patients were significantly older (P = 0.04) because of the prolonged follow-up period (Table 2). Otherwise, no disease-specific variables, such as age of onset or epilepsy duration, were implicated in seizure or QOL outcomes between the groups. There was also no difference in family bonds (partnership and children), and although driving ability indicated a positive nonsignificant trend for the surgical group (31% vs. 10%), only 4 of 53 surgical patients who were not previously driving were able to do so. Nevertheless, patients who had been operated on were more frequently employed (odds ratio [OR], 3.46; 1.13−10.53) and often needed less medication, whereas 30% of the patients withdrew from medications.

### Seizure Outcomes

In the surgical group, 43.7% of the patients remained seizure-free (Engel Ia) after surgery, whereas 67.6% of the patients achieved complete remission during the last year of follow-up (ILAE I) because some patients did relapse and remit. In the clinically treated set, all but 1 patient (5%) showed frequent seizures. Thus, the surgically treated patients had a substantially better chance of achieving remission (Engel I; OR, 48.45; 6.08−386.39; Table 3).

### Beck BDI-II and AEP Scales

There was a high prevalence of depression in the preoperative group, which was found to have significantly decreased after surgery, because the BDI-II >13 decreased from 50% to 16.9% (P = 0.002); as a result, there was an approximately 5-fold chance that nonoperated patients had mild, moderate, or severe depression (OR, 4.92; 1.68−14.39), with no difference between right and left temporal epilepsies.

Regarding the drug-related burden, AEP means indicated a significant improvement in the surgical group (P = 0.002) and a decrease from 35% to 8.7% in their self-report of high toxicity (AEP ≥45).

### Rey Auditory Verbal Learning Test

The patients included in this study commonly presented with verbal memory deficits that were independent of surgery (Table 4). Regarding patients with left MTLEs, the immediate recall (A1) deficit was more frequent in operated patients (22.3% vs. 0% of

**Table 3.** Summary of Seizure Outcome by Engel[27] (left) and International League Against Epilepsy's[23] (right) Classifications of Patients Who Underwent Surgery for Mesial Temporal Epilepsy and the Control Group

| Surgical | Clinical | | Surgical | Clinical | |
| --- | --- | --- | --- | --- | --- |
| n (%) | n (%) | P | n (%) | n (%) | P |
| | Ia | | | 1 | |
| 31 (43.70) | 0 (0) | <0.001 | 48 (67.6) | 0 (0) | <0.001 |
| | I | | | 2 | |
| 51 (71.8) | 1 (5) | <0.001 | 6 (8.5) | 0 (0) | |
| | II | | | 3 | |
| 15 (21.1) | 2 (10) | | 10 (14.1) | 3 (15) | |
| | III | | | 4 | |
| 4 (5.6) | 0 (0) | | 6 (8.5) | 0 (0) | |
| | IV | | | 5 and 6 | |
| 1 (1.4) | 17 (85) | <0.001 | 1 (1.4) | 17 (85) | <0.001 |

the controls; P = 0.05), but only when profoundly impaired patients were considered (more than 2 SDs below the mean). There were no differences between the right temporal lobe epilepsy groups.

### QOLIE-31

Regarding the self-reported QOL, results of the surgical group were clearly superior for the total score and in all but the cognitive function domain (Table 5). Moreover, the mean QOL of the seizure-free patients (Engel Ia mean, 80.64; SD, 14.71) was approximately the same (P = 0.79) as the Engel I controlled patients (seizure-free for at least 2 years, persisting auras, or withdrawn from AED seizures), which had a mean of 79.30 (SD, 11.64); thus, both groups were highly correlated with a better QOL (P < 0.001). This goal was not achieved by the Engel II rare seizures surgical group (mean, 66.71; SD, 15.01; P = 0.15). Considering the ILAE classification, QOLIE-31 outcomes did not significantly differ among ILAE 1 (mean, 78.88), ILAE 2 (mean, 75.55), and ILAE 3 (mean, 74.53) means (Kruskal-Wallis, P = 0.31).

**Table 4.** Rey Auditory Verbal Learning Test: Patients with a Performance of >1.5 Standard Deviations Lower than the Age-Adjusted and Sex-Adjusted Mean

| | A1 | A7 | Learning Over Trials | Recognition A |
| --- | --- | --- | --- | --- |
| Surgical | 15 (21.1) | 54 (76.1) | 20 (28.2) | 23 (32.4) |
| Controls | 2 (10.0) | 13 (65.0) | 8 (40) | 5 (25) |
| P | 0.34 | 0.32 | 0.53 | 0.31 |

Values are number (%) except where indicated otherwise.

**Table 5.** Quality of Life in Epilepsy-31 Inventory: Domain and Total Quality of Life Scores

|  | Total Score | Seizure Worry | Overall Quality of Life | Emotional Well-Being | Energy Fatigue | Cognitive Functioning | Medication Effects | Social Functioning |
|---|---|---|---|---|---|---|---|---|
| Surgical | 75.44 | 80.23 | 75.11 | 75.89 | 74.94 | 66.22 | 80.75 | 84.90 |
| Clinical | 60.08 | 46.25 | 63.13 | 62.86 | 61.75 | 57.02 | 63.33 | 63.83 |
| P | <0.001 | <0.001 | 0.01 | 0.03 | 0.006 | 0.176 | 0.006 | <0.001 |

This result was in contrast to the group mean, which experiences frequent seizures ILAE 4+5+6 (53.08; $z = -2.635$; $P = 0.008$).

The 71 patients who had been operated on were further divided into 3 groups regarding their follow-up period, which included 34–71 (n = 32), 72–107 (n = 24), and 108–152 (n = 15) months. The QOL of the 3 different follow-up periods compared with the control group's QOL was significant only between the control and 34-month to 71-month follow-up groups ($P < 0.001$) (**Figure 1**). This finding was also true for all QOLIE-31 domains, with the exception of the nonsignificant difference in cognitive function perception. Regarding the surgical group, there was no correlation between the QOLIE-31 total score and the postoperative follow-up ($r = 0.10$; $P = 0.40$), as shown in **Figure 2**.
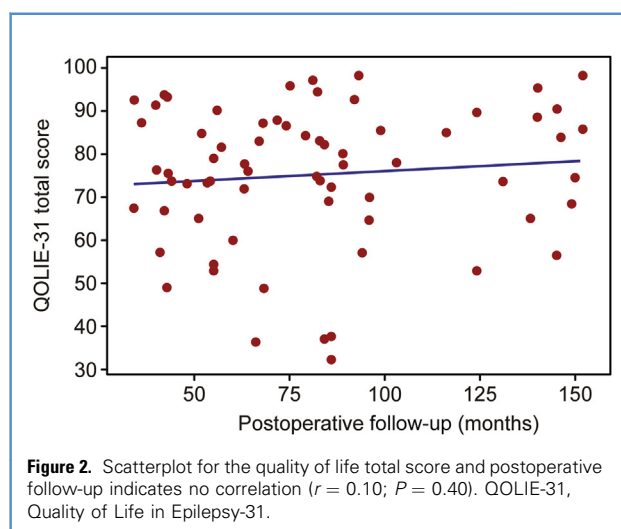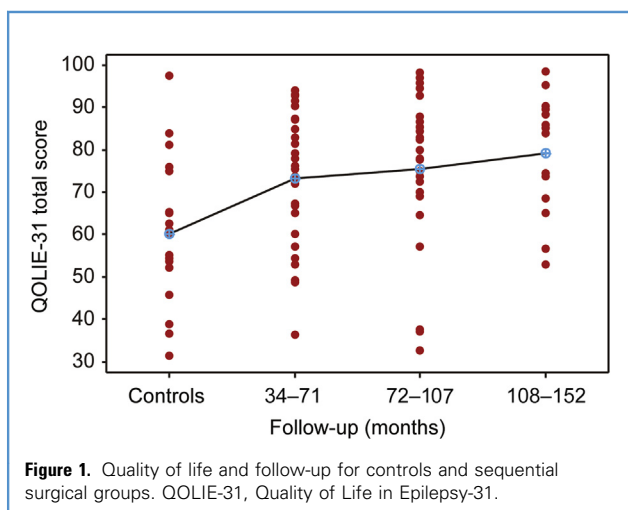
### QOLIE Determinants in Patients with MTLE

Considering the QOLIE-31 total score as the dependent variable and the whole sample regardless of treatment (91 total patients), significant correlations were identified in the univariate analyses as follows: AEP scale ($r = -0.82$; $P < 0.001$), BDI-II ($r = -0.55$; $P < 0.001$), and Engel scale outcome ($r = -0.49$; $P < 0.001$). Furthermore, positive correlations with the categorical variables were identified as follows: surgical group ($P < 0.001$), not taking medications ($P < 0.001$), normal Rey Auditory Verbal Learning Test learning over trials ($P = 0.01$), >9 years of education ($P = 0.02$), and current employment ($P = 0.05$). However, after the multivariate regression analysis, only the AEP, BDI-II, and Engel outcome remained significant in a model that explained 72.4% of

the variability in the QOLIE-31 total score. The same linear regression model was exclusively applied to the surgically treated patients and yielded the same results ($R^2 = 73.1\%$).

### DISCUSSION

Surgical intervention for epilepsy has been traditionally performed to restore function. Thus, although surgery seldom truly reinstates physical function, it aims to improve seizure control as well as to contribute to an individual's health in terms of physical, mental, and social well-being (World Health Organization[36]).

To notice lasting changes in a patient's QOL, a follow-up period of more than 2 years is likely necessary.[37] Moreover, although early positive changes can be observed after surgery, they fade away in noncontrolled patients and, further, may be apparent regardless of seizure status.[38] In the present study, we evaluated long-term outcomes of patients who underwent surgical intervention for epilepsy and determined that after significant QOL improvements were observed in the first few years, no further changes could be identified. This finding may be a result of a ceiling effect because these patients had previously reached the normal population mean.[37,39] In addition, although a few patients may experience very late relapses,[9] they typically reenter remission. Thus, the 76.1% of patients categorized as ILAE I + II (free from disabling seizures), which considered only the most recent year of follow-up, was higher than that of Engel I controlled patients (71.8%), which accounted for at least the 2 most recent years after



**Figure 1.** Quality of life and follow-up for controls and sequential surgical groups. QOLIE-31, Quality of Life in Epilepsy-31.



**Figure 2.** Scatterplot for the quality of life total score and postoperative follow-up indicates no correlation ($r = 0.10$; $P = 0.40$). QOLIE-31, Quality of Life in Epilepsy-31.

surgery and also included patients who experienced seizures caused by drug withdrawal. Furthermore, these patients reported the same overall QOL as did the completely seizure-free patients, suggesting that these escape seizures did not disrupt patient wellness.

However, despite an increase in the number of patients working, approximately half of the patients who underwent surgical intervention were unemployed, only a few began driving, and no gains were detected in their education or family structuring. Thus, in contrast to other investigators,[9,40] we believe that, despite good seizure control, decades of limitations associated with chronic infirmity resulted in surgical patients not requiring long recovery periods; these patients may not ever show drastic improvements unless confronted by early surgical intervention or soon-after surgery. This time frame should be interpreted as a window for vigorous rehabilitation attempts to maximize patient potentialities, as recently proposed.[41] Also of note is that in addition to the large improvement in seizure-induced worry, all other domains, aside from cognitive functioning, also positively changed, which included social functioning. Patients who underwent surgery showed an unaltered, cognitive self-perception and this finding has not previously been reported.[42,43] Despite surgery-associated mood and medication differences, we speculate that the high frequency of verbal memory deficits, especially in delayed recall performance, may account for the lack of change in cognitive self-perception.

We would like to highlight several study limitations and strengths. The design of our study enabled for correlations rather than cause-and-effect associations. Thus, we avoided year-to-year analyses regarding the assessment of patient survival rates and individual changes. However, this approach limited the contact between the patient-research team to a minimum, and no additional intervention other than the regular treatment plan occurred, which minimized potential treatment bias. Furthermore, considering that 1 year of follow-up was too short to overcome possible early transitory postoperative changes, as previously described, we included only patients who had more than 3 years of follow-up.

In contrast to most other long-term studies,[39,40,44,45] we chose to conduct interviews in person rather than mailing out questionnaires. This approach made patients who were living abroad inaccessible; however, we were able to ensure few missing data, and this approach enabled us to administer memory-screening tests to participants during the interview process.

It is inadequate to directly compare BECK, AEP, and Engel/ILAE outcome contributions with patient QOLs because these measures are intrinsically related to the QOLIE-31 questionnaire structure, as well as each other.[46] However, the latter comprises scales that include groups with different outcome weights. Thus, instead of identifying the most important factor, we believe that it is paramount to consider depression and drug-related toxicity as integral components of patient workup and treatment.

We used the Engel and ILAE classifications in a complementary way because the Engel classification tends to describe the entire follow-up history, whereas the ILAE classification focuses on the last year of outcome. Nevertheless, while Engel classification assessed subjective data, such as withdrawal of AEDs or nocturnal-only seizures, ILAE objective seizure counting provided the same overall results in terms of long-term postoperative temporal sclerosis QOL.[47]

Comparisons of outcomes among the surgical patients were statistically cumbersome because of the low treatment failure rate (few Engel III and IV outcomes). The same issue applies to the clinically treated group because of the low seizure-free status rate (few Engel I). Despite these limitations and regardless of whether the surgically treated or entire sample was evaluated, the only factors that were implied in patient QOL were drug toxicity, depression, and seizure control, and none of these factors should be overlooked. Our surgical patients were evaluated after an 81-month mean postoperative follow-up; we thus found many confounding factors regarding QOL issues, because the patients were aging after a 1-point-in-time intervention. Nevertheless, we wanted to highlight the issues related to our Portuguese-speaking population.

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