



Quality of life after switching to generic levetiracetam – A prospective comparative study

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ABSTRACT

Background: Improved quality of life (QoL) is one of the most important objectives in the treatment of epilepsy. Recent prospective, clinical studies proved no significant differences between brand antiepileptic drugs (AEDs) and their generic equivalents in terms of seizure control, pharmacokinetics, or safety. In this study, we focused on possible changes in QoL and adverse events in connection with generic substitution of levetiracetam (LEV). **Methods:** This was a prospective, naturalistic, two-cohort, twin-center study. After a baseline period of 10 weeks, outpatients with epilepsy on stable treatment with Keppra® either continued on this brand (reference group, $n = 16$) or switched to generic LEV (1A Pharma®) (study group, $n = 16$) for an eight-week study period. The Quality of Life in Epilepsy Inventory-31 (QOLIE-31) and an adverse events' questionnaire were administered at inclusion, after baseline, and at the end of the study period. The study protocol included a close clinical follow-up with repeated LEV serum concentration measurements and nurse-led outpatient visits.

Results: Clinically relevant improvements in overall QOLIE-31 scores according to minimally important change (MIC) estimates were seen in both groups. QOLIE-31 subscales in both groups showed significantly less worry about seizures at the end of the study compared to scores at inclusion (study group: $p = 0.01$; reference group: $p = 0.02$). No significant deterioration in QoL or adverse events were observed following generic substitution. No switchbacks occurred.

Conclusions: We found reduced seizure worries over time among people with epilepsy allocated to either generic switch or continued treatment with brand LEV. We hypothesize that the nurse-led structured follow-up had an impact on seizure worries and switchback rates because of reduced nocebo effects. Further studies on generic AED substitution, focusing on psychological outcome measures, are warranted to test this supposition.

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1. Introduction

Possible pharmacokinetic differences, seizure control, and adverse effects have been the main scope of research in the ongoing debate about whether generic antiepileptic drugs (AEDs) are equally safe and effective as brand name AEDs. To the best of our knowledge, no prospective study has found any significant pharmacokinetic differences between brand and generic AEDs, except for the older narrow therapeutic index drugs phenytoin and carbamazepine [1,2]. Since most studies used relatively small numbers of subjects, it cannot be ruled out that clinically relevant pharmacokinetic alterations may occur in certain subsets of patients following generic substitution. However, even if

such subgroups exist, this would not be sufficient to explain the high switchback rates observed in retrospective studies on generic substitution of AEDs [3–5]. Instead, the observed negative clinical outcomes are most likely caused by factors independent of pharmacokinetics, such as the nocebo effect and other psychological factors [6].

The Swedish Medical Products Agency has decided that generic substitution of AEDs must be evaluated and prescribed by the treating physician; no automatic switch to generic AEDs may be carried out at the pharmacy. The rationale behind this decision is that seizure aggravation cannot be ruled out at individual level. The upcoming Swedish national guidelines on generic substitution of AEDs recommend cautiousness handling seizure-free individuals, but provide no further details on which patients should switch to generics. This decision is left to the physician, with sparse conclusive support in the literature.

Internationally, most epilepsy societies recommend caution and to avoid substitution in those patients that are seizure-free [7]. This is

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contrasted by the term “generic brittle”, as defined by Ting and colleagues, suggesting that people with drug-resistant epilepsy are more susceptible to negative outcomes after generic substitution [8]. In summary, no consensus exists on which patients, if any, should avoid generic substitution of AEDs because of a risk of negative outcome. Potential ways to counteract the supposed psychological causes of negative outcomes following generic substitution of AEDs have not yet been studied.

People with epilepsy have lower quality of life (QoL) than both healthy individuals and individuals with other chronic diseases [9]. Improving the QoL for people with epilepsy is therefore a clinical top priority. Our aim in a recent prospective study was to assess pharmacokinetic and clinical outcomes in connection with generic substitution of levetiracetam (LEV) in a naturalistic clinical outpatient setting [10]. This paper focuses on the secondary aim of that study and is the first to highlight possible changes in QoL related to generic substitution of LEV.

2. Material and methods

2.1. Study design

This was a prospective, open, nonrandomized, naturalistic cohort study of generic substitution from brand name LEV (Keppra®) to a generic LEV product (Levetiracetam 1A Pharma®). The study was carried out at two outpatient clinics in the south of Sweden, with patient inclusion taking place between May 2014 and April 2016. Ethical approval was granted by the Regional Ethical Review Board at Lund University, Lund, Sweden.

Inclusion criteria were age ≥ 18 years, confirmed diagnosis of epilepsy, and stable treatment with Keppra® for at least four weeks prior to inclusion. Exclusion criteria were pregnancy and/or risk of seizure aggravation during study participation because of progressive structural etiology of epilepsy. The prescribing physicians first decided whether or not patients were suitable for a generic switch at routinely scheduled visits and informed the patients accordingly. Criteria for switching to generic LEV were not included in the naturalistic study protocol. Since no national guidelines on generic substitution of AEDs existed when the study was conducted, decisions were mainly based on the prescribing physician's clinical evaluation and the patients' expectations. The exact reasons for each decision at the individual level were not documented. The study personnel only were notified of patients who were interested in participating in the study. Thus, all patients knew whether they were to switch to generic LEV prior to being asked to participate in the study. Written informed consent was obtained from all study participants before inclusion.

All participants stayed on Keppra® treatment during the initial 10 weeks of the study (baseline period). Subjects who switched to generic LEV for the eight-week study period (T0 to T8) formed the KEP-LEV group (study group), while the KEP-KEP group (reference group) continued with Keppra® throughout the study.

The study subjects had three scheduled epilepsy nurse visits (T-10/inclusion, T0/end of baseline period, T8/end of study) during which questionnaires were administered (QOLIE-31 and adverse events). Generic substitution for the KEP-LEV group was performed after the visit at T0. A study nurse was available for questions when filling out the questionnaires, in order to minimize misunderstandings and ensure the quality of questionnaire responses. Study participants were also monitored with biweekly serum concentration measurements of LEV, yielding a total of 10 measurements per subject during the study. For a more detailed explanation of the study design, we refer to our previous article [10].

2.2. QOLIE-31

We used the Swedish version of the Quality of Life in Epilepsy Inventory-31 (QOLIE-31) version 1.1 to assess QoL [11]. QOLIE-31 is a

validated and frequently used epilepsy-specific instrument, designed for health-related QoL assessments in people with epilepsy. It contains 31 items, grouped into the seven following subscales: *seizure worry*, *overall QoL*, *emotional well-being*, *energy/fatigue*, *cognitive functioning*, *medication effects*, and *social functioning*. Additionally, an overall score is retrieved by calculating a weighted mean of the subscales in accordance with the scoring manual. Scores can range from 0 to 100, with higher scores indicating better QoL.

2.3. Minimally important change (MIC)

Minimally important change (MIC) is a population-specific threshold value, an estimate of how much scores need to change to be of clinical relevance [12]. Minimally important change values for QOLIE-31 have been established in several studies with varying subject characteristics and epilepsy severity [12–14]. Changes in QOLIE-31 score in this study were evaluated considering both statistical significance and whether the change exceeded the lowest of the calculated MIC values in the above cited studies.

2.4. Adverse events' questionnaire

The adverse events' questionnaire was designed with one initial open question followed by five questions with a yes-or-no design. The open question was added in order to avoid suggestive effects. The dichotomized questions asked about 1) drug-specific symptoms reported in connection with LEV treatment: aggressiveness, irritability, and weight changes, and 2) general symptoms associated with central nerve system toxicity (somnolence and dizziness) [15].

2.5. Statistics

Subscale scores of QOLIE-31 showed large interindividual differences with nonnormal distribution of data in some subscales in both groups. Log transformation was not sufficient to correct the skewness. Consequently, the Wilcoxon signed rank test was used for within-group comparisons (e.g., score T8 vs. score T-10), and the Mann-Whitney *U* test was used for between-group comparisons (e.g., score T-10; KEP-LEV vs. score T-10; KEP-KEP) of QOLIE-31 scores.

As described above (Section 2.3), absolute changes in QOLIE-31 score were also compared to established MIC values. To account for the skewed nature of the data in some subscales, we report median changes (Δ median = median T8 – median T-10) per group for each subscale and the overall score. The number of patients in each group with Δ median exceeding MIC was calculated and compared descriptively.

Statistical analyses were performed using SPSS 23.0 (Windows version, IBM Corp., Armonk, NY, USA) and Excel 2016 (Microsoft Corp., Redmond, WA, USA). The significance level was set at $\alpha = 0.05$.

3. Results

3.1. Demographics

A total of 32 study subjects with completed QoL and adverse events' questionnaires were included in the analysis. One subject belonging to the KEP-KEP group did not want to continue the study and dropped out of the study four weeks into the study period (T4) for unknown reasons.

Table 1 shows baseline characteristics per treatment group at study inclusion. Levetiracetam dose was kept constant during the study for all but two participants. Both belonged to the KEP-LEV group and increased their dose during the baseline period (while still on Keppra®) [10]. The switchback rate was 0% (no patient switched back from generic to branded LEV).

Table 1
Demographics and clinical characteristics at study inclusion.

	KEP-LEV n = 16	KEP-KEP n = 16
Gender, n		
Men	7	5
Women	9	11
Age, years		
Mean	52.0	55.4
Median (range)	55.5 (20–84)	62.0 (21–81)
LEV daily dose, mg		
Mean ± SD	1438 ± 710	1594 ± 741
Median (range)	1375 (500–3000)	1625 (500–2500)
Polypharmacy, n		
Yes	7	10
No	9	6
Seizure type ^a , n		
Focal onset – LOC	6	2
Focal onset + LOC	5	6
Generalized ± focal onset	6	11
Seizure frequency, n		
Seizure-free	7	7
1–2 per year	3	2
3–11 per year	3	3
1–3 per month	1	2
≥1 per week	2	2

KEP-LEV = Patients on branded LEV for the initial 10 weeks of the study (baseline period) and generic LEV for the last eight weeks (study period).
 KEP-KEP = Patients on branded LEV throughout the study.
 LOC = Loss of consciousness.

^a Some patients had more than one type of seizure.

3.2. QOLIE-31

Table 2 shows MIC thresholds for each subscale, the QOLIE-31 overall score and subscale scores, and Δmedian (change in median QOLIE-31 points over time).

Between-group comparison showed no significant difference in QOLIE-31 overall score at T-10. In two subscales, a significant difference was seen between the study and the reference groups at inclusion. Higher scores were seen in cognitive functioning (p = 0.02) and seizure worry (p = 0.05) in the KEP-LEV group, compared to KEP-KEP. This difference between groups persisted throughout the study. There were fewer subjects on polytherapy of AEDs and with focal to generalized seizures in the KEP-LEV group, but the difference was not statistically significant.

Intragroup comparison of the Δmedian overall QOLIE-31 score increased in both groups between T-10 and T8. The median overall score increased by 6.5 points in KEP-LEV and 8.0 points in KEP-KEP.

Both changes were above the MIC threshold for clinically relevant change, but did not reach statistical significance.

Fig. 1 shows subscales with statistically significant intragroup improvement and Δmedian exceeding MIC. Seizure worry improved significantly in both groups between T-10 and T8 (KEP-LEV: p = 0.01 and KEP-KEP: p = 0.02). At the individual level, eight subjects in KEP-LEV (50%) and seven subjects in KEP-KEP (44%) showed a clinically relevant Δmedian improvement exceeding MIC. No subject in either group showed decrements exceeding MIC. Men improved more than women (p = 0.05). In addition, the KEP-LEV group improved in social functioning (p = 0.02) while KEP-KEP improved in cognitive functioning (p = 0.02). The between-group comparison of Δmedian between T-10 and T8 was not statistically significant for any subscale.

Intragroup increases of the Δmedian seizure worry score for separate periods, between T-10 - T0 and between T0 - T8, respectively, were not statistically significant. Note that an increase in seizure worry score implies less worry for seizures.

Two subscales decreased between T-10 and T8. At the group level, medication effects dropped from a median score of 79.5 to 70.5 for KEP-LEV, and overall QoL dropped from a median score of 83.0 to 75.5 in KEP-KEP. Neither of these changes reached statistical significance.

3.3. Adverse events

At inclusion, a total of 15 patients (KEP-LEV: n = 9; KEP-KEP: n = 6) were experiencing one or more adverse symptoms. The most commonly reported was somnolence, reported by nine (56%) of the participants in KEP-LEV and five (31.3%) in KEP-KEP. The frequencies of the other symptoms in the questionnaire with dichotomized questions were as follows (KEP-LEV; KEP-KEP): dizziness (2; 2), irritability (3; 1), weight changes (1; 2), and aggressiveness (2; 0). The following disparate symptoms were reported in the open question part by a total of five (31%) subjects in KEP-LEV and 6 (37.5%) in KEP-KEP (all: n ≤ 2): diminished appetite, mood swings, paresthesia, memory impairment, hallucinations, nightmares, sexual dysfunction, easy bruising, headache, disturbance in attention, dry mouth, and dry mucous membranes.

During the baseline period (between T-10 and T0), three patients in KEP-LEV reported a change in adverse events: 1) increased somnolence; 2) disappearance of hallucinations, aggressiveness, and dizziness; and 3) disappearance of irritability and mood swings. During the study period (between T0 and T8), two patients in KEP-LEV experienced a decrease in adverse events: 1) disappearance of somnolence and 2) increased appetite, whereas one patient in KEP-KEP reported memory decline and pruritus. No patient reported an increase in adverse events following generic substitution.

Table 2
QOLIE-31 scores per group at inclusion and at the end of the study (eight weeks after generic substitution for the KEP-LEV group).

Subscale	MIC	KEP-LEV			KEP-KEP		
		T-10	T8	ΔMedian	T-10	T8	ΔMedian
		Median (range)	Median (range)		Median (range)	Median (range)	
Seizure worry	7.4	73 (38–100)	93 (39–100)	20.0*	47 (12–100)	64.5 (23–100)	17.5*
Overall quality of life	6.4	78 (18–100)	78 (0–100)	0.0	83 (20–100)	75.5 (20–100)	– 7.5
Emotional well-being	4.8	76 (36–100)	82 (28–100)	6.0	72 (24–96)	74 (24–100)	2.0
Energy/fatigue	5.3	65 (5–100)	65 (0–90)	0.0	65 (5–90)	65 (0–100)	0.0
Cognitive functioning	5.3	84 (37–100)	89 (46–100)	5.0	64.5 (20–80)	71 (24–100)	6.5*
Medication effects	5.0	79.5 (0–100)	70.5 (28–100)	– 9.0	79 (0–100)	83 (42–100)	4.0
Social functioning	4.0	77.5 (9–100)	83 (40–100)	5.5*	78 (28–100)	88.5 (32–100)	10.5
Overall score	5.2	72.5 (32–98)	79 (43–98)	6.5	67.5 (34–98)	75.5 (32–100)	8.0

T-10 = Inclusion. T8 = End of study. MIC = Minimally important change.

ΔMedian = difference in median score, median_{T8} – median_{T-10}.

Bold text = ΔMedian > MIC.

* = p < 0.05.

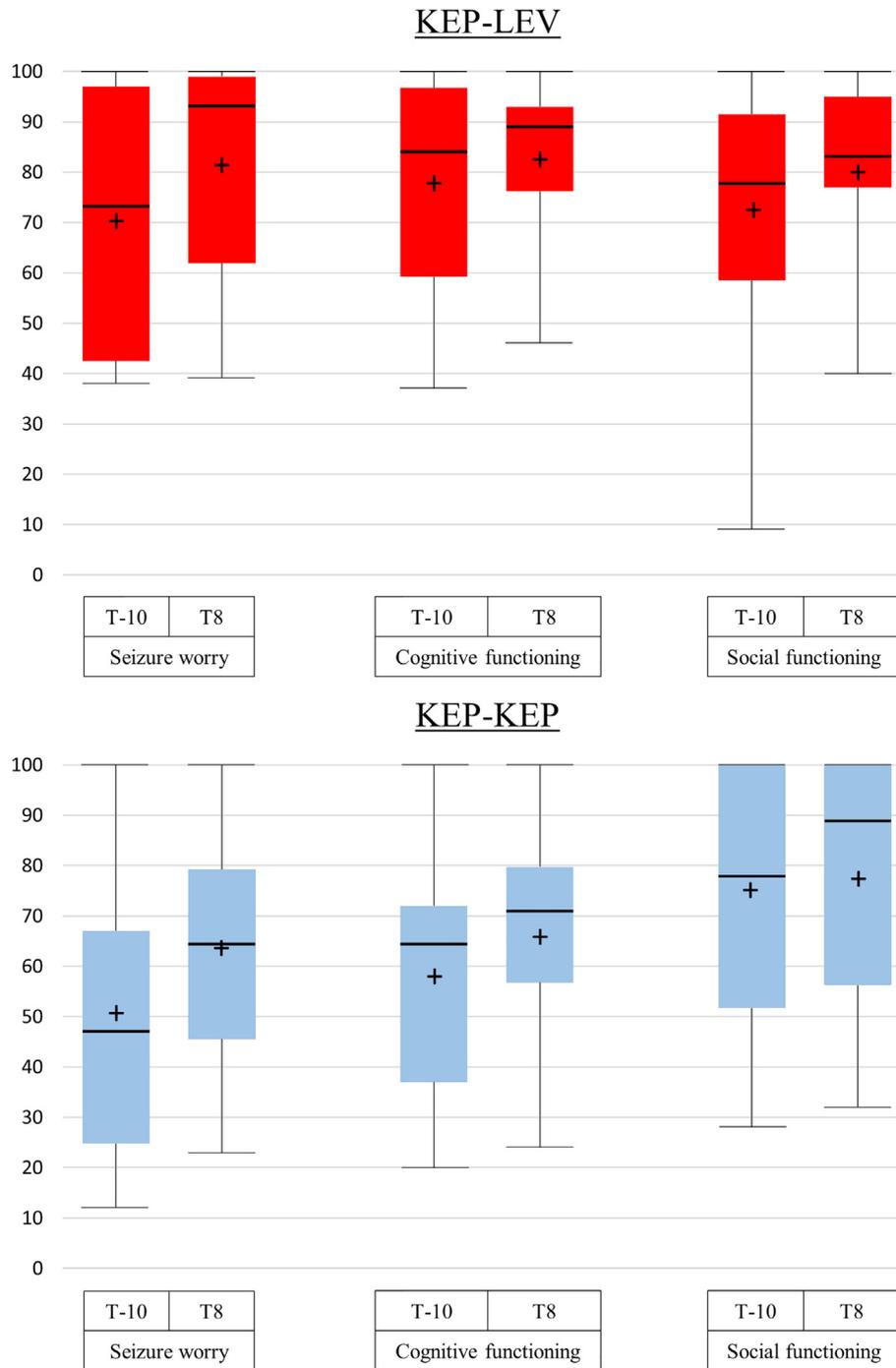


Fig. 1. QOLIE-31 scores per group for subscales with significant changes (seizure worry, cognitive functioning, and social functioning) from inclusion (T-10) to the end of the study (T8). A higher value implies less worry about seizures and better cognitive/social functioning (maximum score: 100). Boxplots showing median (bold), upper and lower quartiles, and total range. + denotes the mean value. KEP-LEV = Changed to generic LEV at T0. KEP-KEP = On branded LEV throughout the study.

4. Discussion

This prospective, naturalistic study showed neither a negative impact on patient QoL, nor an increase in adverse events, after switching from brand Kepra® to generic Levetiracetam 1A Pharma®. By contrast, our results showed an improvement in the overall QOLIE-31 score, reaching clinical relevance according to MIC estimates. This was found for both the switch group and the reference group on continuous treatment with brand LEV. Our most prominent QoL finding was that participants in both groups were less worried about seizures at the end of the study compared to at inclusion.

Retrospective studies have taught us that mandatory overnight generic substitution because of regulative demands results in a high rate of switchback to brand name AEDs [3–5]. Various explanations for this have been proposed, including pharmacokinetic differences between brand and generic AEDs [3,7], psychological factors such as the nocebo effect [16], and variations in pill appearance resulting in nonadherence [17,18]. We have not been able to confirm these assumptions. Our previously published pharmacokinetic data showed no significant differences in fluctuations of serum concentrations between groups [10]. Furthermore, similar adherence issues were observed in the group that continued on brand LEV and the group that switched to generic LEV.

Pharmacokinetic properties of brand and generic AEDs have been rigorously studied, including three double-blinded, prospective, randomized trials of brand-generic and generic-generic switching of lamotrigine [8,16,19]. It seems unlikely that significant differences in pharmacokinetic properties between brand and generic AEDs can explain the high switchback rates seen in retrospective studies based on healthcare and pharmacy registries. Given what we know from more recent prospective studies, the placebo effect and/or other nonpharmacological reasons are more probable explanations [6]. Open-label prospective studies on generic AED substitution have reported switchback rates from 0% to 8% [10,20–23]. This is in line with reported switchback rates for several non-AEDs [3,5,24].

A recent Italian paper studying the switch from brand to generic LEV found a global improvement in QoL for the generic compound [20]. Although this paper only included item 31 of the QOLIE-31 instrument, the reported increase in QoL was similar to the increased overall QOLIE-31 score in our study. Notably, there was one important difference in the study settings. Since drug therapies are publicly subsidized in Sweden, patients do not have the same financial incentive to switch to generics as patients in Italy. However, QoL was improved at the end of our study in both groups. This suggests, although not directly tested, that the increase in QoL in both our study and the Italian study was independent of the type of treatment (brand or generic) and was instead a result of the enhanced medical care imposed by participating in a study. Our finding that participants in both groups were less worried about seizures at each consecutive visit supports this theory. Reduced worry was observed regardless of generic substitution or taking brand LEV during the study period. We believe that including blood sampling and more frequent contact with an epilepsy nurse made our participants feel more secure and comfortable. This is further supported by studies in other areas. Reducing anxiety and increasing the duration of interaction between patients and practitioners have previously been shown to enhance placebo effects and significantly increase QoL in patients with irritable bowel syndrome [25,26]. Extra monitoring is a natural part of most prospective studies and could possibly counteract placebo effects and contribute to lower switchback rates. If confirmed by a larger randomized study, a structured nurse-led follow-up could be a cost-effective way to diminish patients' worries in connection with generic substitution and thereby decrease placebo effects.

Berg and colleagues highlighted the problem that people who have previously experienced problems with generics are less likely to participate in future studies involving generics [19]. This potential selection bias was partially addressed in the study by Ting and colleagues, where nine (26%) out of 34 study subjects had a history of negative consequences following generic substitution [8]. People with epilepsy who are skeptical about medications are more likely to experience increased seizure frequency and adverse effects following generic substitution of AEDs [27]. This probable placebo effect may have contributed to high switchback rates in previous retrospective studies [3–5], while skeptical patients have been able to refuse participation in the previous prospective studies [20–23]. Consequently, a lack of skeptics adds to the problem of selection bias in hitherto performed prospective studies on generic AED substitution.

We used MIC to indicate whether or not changes in QOLIE-31 scores were clinically relevant. We chose to compare differences in QOLIE-31 with the lowest of the previously reported MIC thresholds, with the rationale of not missing any relevant changes. Our study sample, with 44% seizure-free subjects, differs from the populations in which MIC cutoff points were established [12–14]. One could argue that the true cutoff, for subscales such as *seizure worry*, might be set at a lower level among participants with seizure control, as worries for breakthrough seizures constitutes a threat for driving and other daily life activities among people with controlled epilepsy. This further supports our choice to use the lowest of previously reported MIC thresholds.

Besides *seizure worry*, one subscale within each group improved significantly: *social functioning* in the KEP-LEV group and *cognitive functioning* in the KEP-KEP group. *Medication effects* in KEP-LEV and *overall*

QoL in KEP-KEP deteriorated more than MIC. Neither of these decreases were statistically significant, and both subscales showed very large interindividual variations. Given the population specific properties of MIC, and the increased risk of false positives that comes with a lower threshold, we believe that both these deteriorations were due to random variation, even though a type II error cannot be ruled out.

Various adverse symptoms were reported by similar proportions in both groups. The only conclusion that one can draw from the adverse events' data is that symptoms are disparate and scattered. There was no evidence of an increase of adverse events after generic substitution.

4.1. Limitations

This study had several methodological limitations which should be taken into consideration when interpreting our results. First, the nonrandomized and open-label study design may have introduced a selection bias. However, no significant difference between groups was seen regarding factors that may be of high importance for QoL, such as seizure burden and number of AEDs. Our study reflects the real-life clinical situation in Sweden where generic substitution of AEDs is not yet mandatory. All patients knew if they were to switch treatment to generic LEV or not when they were asked to participate in the study. Consequently, generic skeptics may be underrepresented in the study group and overrepresented in the reference group. The significance of such a bias is unclear as changes in QOLIE parameters were seen over time, and the changes did not differ between groups. Second, the study was primarily powered for pharmacokinetic comparisons, not for the detection of changes in QoL and adverse events. This implies that possible differences in QoL between groups may not have been detected because the statistical tests may have been underpowered. Third, participants were followed for only eight weeks after generic substitution, which does not allow for conclusions regarding long-term effects. Fourth, only one specific generic LEV product was used in this study, and any extrapolation of our findings to other generics should be carried out with caution.

5. Conclusions

We found a positive impact on QoL over time among participants in both the study and reference groups. The very similar change in both groups implies the existence of an independent common cause. Our hypothesis is that the nurse-led structured follow-up reduced seizure worries and switchback rates, this was however not tested. Further studies on generic AED substitution focusing on psychological outcomes are warranted.

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Disclosures

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