

Anti-epileptic drug changes and quality of life in the community

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Objective – Changes in anti-epileptic drug (AED) regimens may indicate unsatisfactory treatment results such as insufficient seizure control or adverse effects. This inference underlies epilepsy management and research, yet current studies often do not account for AED changes. We assessed AED change patterns and their association with quality of life (QoL), as main outcome measure, in a community-based setting. **Methods** – We assessed a cohort of 248 people with epilepsy identified from community pharmacy records from whom we retrieved AED dispensing history. We assessed all changes in AED use during the 2 years prior to the index date and current QoL using the validated Dutch QOLIE-31 questionnaire.

Results – Thirty-one per cent had at least one AED change during the study period, either in drug type or dose. People who changed showed significantly lower QoL (QOLIE score 73 vs 79), especially those who intensified their treatment. Each additional change was associated with a further reduction of 4.9 points in QoL score. **Conclusions** – AED changes are common practice, even in people with long-standing epilepsy. Frequent changes, as objective measure of epilepsy severity, are associated with a progressively lower QoL. Changes, even in dose, should be monitored in daily clinical practice and used as a red flag that may require adjustments in epilepsy management. This may include earlier referral to a specialized centre for a more thorough evaluation or counselling. AED changes can also be used as an outcome marker in epilepsy research as a proxy of QoL for better translation of drug-efficacy results to general practice.

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Introduction

Most people with epilepsy achieve complete seizure control with anti-epileptic drugs (AEDs). Initial monotherapy is efficacious in about 50% (1–3). AED changes, such as dose adjustments, substitution or addition of an AED, result in seizure control in another 20–30%. AEDs are not always well tolerated; adverse effects (AEs) occur in 40–80% of people (4). AED treatment aims at achieving the best balance between seizure control and tolerability (4), leading to long-term AED retention (5). A suboptimal balance frequently triggers the physician to make changes in AED regimes. Changes are thus considered an indicator of unfavourable treatment results. We

assume that this will translate into a lower health-related quality of life (QoL) which is the most comprehensive measure of treatment outcome (2, 4). This inference is generally accepted and underlies clinical epilepsy management and drug-effectiveness research, but it has never been properly documented. Current studies (6–8) often do not take into account the total number of AEDs people have taken, which could indicate disease severity (9). The impact of changes themselves on treatment outcomes has only been assessed in a few studies. A recent prospective observational study assessed treatment outcomes before and after AED change in people who failed their first drug trial, but did not compare outcomes to those without treatment change (7).

Another study of people in remission described the impact on QoL of changes due to (concerns about) AEs (10). We assessed AED change patterns in a Dutch community-based setting and investigated the association between such changes and QoL.

Methods

As part of a community-based retrospective cohort study on epilepsy treatment outcomes (2010), people with epilepsy over 11 years of age who had had two or more AED prescriptions dispensed in the previous 2 years were selected from community pharmacy records in the 'Het Gooi-Utrecht' region. Eligible individuals were invited to participate by sending them an information letter including an informed consent form (including permission for retrieving their medical records from their GP or neurologist) and a short questionnaire to confirm AED use for epilepsy. We excluded people using AEDs for reasons other than epilepsy. The study was approved by Utrecht University Medical Center Ethics Committee. As part of our ethical approval, we were only able to invite people once and so no further attempts were made to contact them after the initial approach.

After informed consent, participants were sent detailed questionnaires about their seizures and treatment-related characteristics [age at onset, seizure type, frequency, seizure control (seizure freedom in the last 2 years before the index date, i.e. the date medication history was acquired from participants), level of epilepsy care (type and frequency of visits), adverse effects (using the SIDAED-list)] (11), and QoL, using the validated Dutch version of the QOLIE-31. Four neurologists with a special interest in epilepsy extensively evaluated questionnaires and medical records to confirm a diagnosis of epilepsy and its subtypes. Participants in whom a definite diagnosis of epilepsy could not be established, based on available data, were excluded.

Demographic data (age, sex) and medication history, (i.e. individual prescriptions of all dispensed medicines including dates, amount, prescriber and dosage regimen) covering at least the last 2.5 years before the index date, were acquired from pharmacy records. AED treatment changes during the last 2 years before the index date were identified from these pharmacy dispensing data.

Changes were defined and categorized as: (i) substitution: start of an AED with discontinuation of another within 90 days before or after this start, (ii) add-on; start of an AED with continu-

ous use (more than 90 days) of one already in use, (iii) discontinuation; no follow-up dispensing of a specific or all AEDs for at least 6 months following the last prescription that was >6 months prior to the index date, (iv) dose increase and (v) dose decrease. Changes were further classified as treatment intensification (substitution, add-on or dose increase) or reduction (discontinuation or dose decrease). In case of multiple change patterns (substitution, add-on or discontinuation), the last change was used for the classification into intensification or reduction. In the case of an intensification and a reduction change at the same date (e.g. add-on combined with a dose reduction), changes were categorized after consensus discussion. People with new-onset epilepsy, who started treatment in the 2 years before inclusion, were not deemed to have changed their medication.

Differences in characteristics between changers and non-changers were assessed using one-way ANOVA, Mann-Whitney *U*-test or chi-squared tests. Statistical significance was defined as a *p*-value ≤ 0.05 . Linear regression modelling was used to assess the association between (the number of) AED changes and QoL. We assessed potential confounding factors including sex, age, age at onset, seizure frequency (number of weekly seizures), type of epilepsy (localization related, generalized or unclassifiable), new-onset epilepsy or not, number of current AEDs and co-medication (SPSS statistics for windows, version 20.0 (IBM Corp: Armonk, NY, USA)). We presented the crude (unadjusted) model as well as the final model, that is the model adjusted for only those factors that were found to confound the association between AED change and QoL. Multiple imputation techniques were used in our analysis to correct for missing values. Crude and adjusted results with corresponding 95% confidence intervals are presented.

Results

About a third (575) of the 1894 originally selected individuals responded to our single mail request for participation and indicated to use AEDs for epilepsy. Of these, 327 were excluded as a definite diagnosis of epilepsy could not be confirmed on review (Fig. 1).

Table 1 presents the baseline characteristics of the 248 people with epilepsy included. A total of 77 participants (31%) changed their AED treatment at least once during the study period of 2 years with a median of 1 change (range 1–4). Forty-three people (56%) intensified their treatment (14%

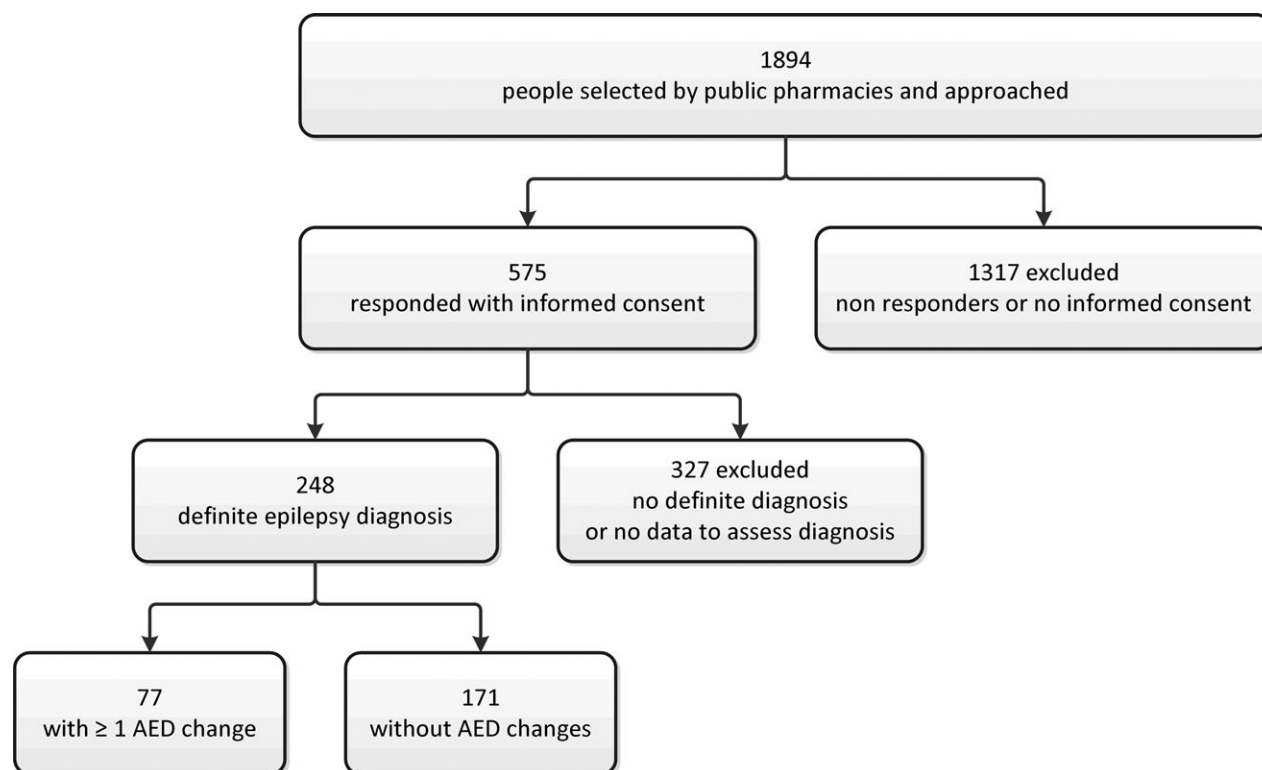


Figure 1. Flowchart of the selection and inclusion procedure.

Table 1 Baseline characteristics and differences between people with and without AED changes in the last 2 years

	Total population (n = 248)	AED change (n = 77)	No AED change (n = 171)	P value
Age (years), median (IQR)	53 (39–65)	51 (30–63)	54 (42–66)	0.024
Age at onset (years), median (IQR)	27 (15–50)	21 (9–52)	30 (17–47)	0.086
Epilepsy duration (years) median (IQR)	17 (7–31)	14 (6–27)	19 (8–33)	0.192
Male sex (%)	54	48	57	0.176
Epilepsy type				0.524
Focal (symptomatic/cryptogenic) epilepsy %	47	52	44	–
Generalized (idiopathic) epilepsy %	13	10	14	–
Unclassified epilepsy %	41	37	42	–
Number of current AEDs, median (IQR)	1 (1–1)	1 (0–2)	1 (1–1)	0.833
Current monotherapy %	76	49	85	<0.001
Co-medication %	77	82	75	0.268
Seizure control (no seizures in last 2 years prior to the index date) %	54	35	63	<0.001
>1 seizure per week (last year) %	5	6	4	0.635
Acceptability of uncontrolled seizures %	54	56	53	0.676
Adverse effects %	83	91	79	0.025

(n = 6) substitution, 9% (n = 4) add-on, 47% (n = 20) dose increase and 30% (n = 13) a combination of these) and 34 (44%) had a treatment reduction (59% (n = 20) discontinuation, 35% (n = 12) dose decrease and 6% (n = 2) a combination of these). Reasons for changes were lack of efficacy (23%), AEs (29%), both lack of efficacy and AEs (18%), concerns of teratogenicity (1%) or unknown (29%). Of the people who changed to a different AED type, 8 (40%) changed from an

older (valproate, carbamazepine, phenytoin, phenobarbital) to a newer AED (levetiracetam, lamotrigine, oxcarbazepine, topiramate, lacosamide, vigabatrin, felbamate).

Changers were younger (median 51 vs 54 years) and more frequently on polytherapy (51 vs 15%). Those who changed had less seizure control in the previous 2 years (35% vs 63%) and had more AEs (91% vs 79%) (Table 1). There were no significant differences in epilepsy type, epilepsy

duration, sex or use of co-medication between those who changed and those who did not.

The average QoL score, adjusted for number of AEDs used at index date, was 77.6 (SD 16.3). People who changed treatment had a 6.2 points (95% CI: -10.4 to -1.9) lower QoL score (average 73.2) compared with those who did not change (average 79.4). The effect was most pronounced in people with a treatment intensification in whom the adjusted QoL score was 6.9 points (95% CI: -12.6 to -1.2) lower compared with the QoL of those without changes. Treatment reduction was also associated with a reduced quality of life (-5.3 points; 95% CI -11.6 to 1.0), although not statistically significant (Table 2 showing crude and adjusted results).

The QoL declined with the number of changes (independent of type of change, that is intensification or reduction). Each additional change was associated with a further reduction in QoL (QOLIE-31). The corresponding effects on QoL compared to not changing were 3.1 points lower for one change (not significant), 8.4 points lower for two changes (95%CI: -15.8 to -1.1) and 18.8 points lower for 3 or more changes (95%CI: -29.4 to -8.1) (Table 2 and Figure S1). This corresponds with an average reduction in QoL of 4.9 points per additional change (95% CI: -7.4 to -2.4, P -value <0.001).

Discussion

Principal findings

A third of our cohort (31%) had at least one treatment change in the previous 2 years, whether in drug type or dose. Previous reports provided an estimation that AED changes occur in between 23% and 67% of all cases (4, 12, 13). Direct comparisons are, however, difficult due to the lack of consistency in methodology, settings and study populations. The number of changes in

our study seems rather high in a population with relative long-standing epilepsy (median epilepsy duration of 17 years) and only few with new-onset epilepsies (9%), who are most likely to change treatment (13). Changes may suggest relapses after long-term remission, occurring in about 15% of people with epilepsy (2). In our population, only 8% had a renewed treatment start-up in the last 2.5 years. These data, thus, more likely suggest that people have experienced many years of ineffective AED treatment.

Our results suggest that AED changes, as an objective marker of epilepsy severity, indicate unfavourable outcomes of epilepsy treatment with respect to QoL. AED changes may be a surrogate outcome parameter in treatment efficacy studies. To date, most studies did not include AED changes to assess outcome (9), which may be due to their design (placebo-controlled trials) or selection of (drug-naïve) individuals. Previous AED exposure is associated with both a low placebo-response and a decreased likelihood of remission; neglecting this knowledge in research limits generalizability of the results to clinical practice (9). The number of changes is thus important for interpretation and translation of treatment outcomes from research into clinical practice in which switches occur frequently.

Treatment should be aimed at improving an individual's QoL, as this is the most important outcome measure in epilepsy from a person's perspective. Our data show that people with AED changes had a significantly lower QoL than people who did not, with each additional change associated with a further reduction in QoL. Within subjects, a change of 10 points on the QOLIE-31 scale can be considered clinically meaningful (14). If we would apply this criterion to compare groups, people with two or more changes would be considered to have a clinically significant reduced QoL compared to people without changes. Changes, although sometimes

Table 2 Association of treatment changes and QoL (QOLIE-31)

	Crude analysis			Adjusted analysis corrected for potential confounders ^a		
	Mean (SD)	Difference in QoL (β) with 95% CI	P value	Mean (SD)	Difference in QoL (β) with 95% CI	P value
No AED change in last 2 years ($n = 171$)	74.0 (15.8)	Ref		79.4 (29.5)	Ref	
AED changes in last 2 years ($n = 77$)	67.7 (16.5)	-6.3 (-10.6 to -2.0)	0.004	73.2 (19.1)	-6.2 (-10.4 to -1.9)	0.005
Intensification	64.7 (16.9)	-9.3 (-14.6 to -3.9)	0.001	72.1 (19.1)	-6.9 (-12.6 to -1.2)	0.018
Reduction	71.4 (15.4)	-2.5 (-8.4 to 3.4)	0.398	73.7 (18.8)	-5.3 (-11.6 to 1.1)	0.111
1 change	70.9 (15.5)	-3.1 (-8.9 to 2.0)	0.233			na ^b
2 changes	65.6 (16.5)	-8.4 (-15.8 to -1.1)	0.025			na ^b
3 or more changes	55.2 (15.8)	-18.8 (-29.4 to -8.1)	0.001			na ^b

^aAdjusted for number of AEDs used at index date.

^bNot confounded by the number of AEDs used at index date or other factors assessed.

inevitable, are frequently driven by an unceasing hope to find an efficacious and well-tolerated therapy, even when prospects are limited (1). This hope may be reflected by a change to newer AEDs, which occurred in 40% of our study population. But simply changing AED regimens does not necessarily lead to better treatment outcomes. It is not clear whether AED changes are cause or consequence of a reduced QoL. The need for AED changes may indicate a more severe epilepsy condition and may thereby be associated with a reduced QoL. AED changes may serve as an objective marker for epilepsy severity, as severity is not always easy to define and may vary over time. Acknowledgement of changes may aid epilepsy management to optimize an individual's QoL. Need for subsequent AED changes may demand referral to a specialized centre for a thorough review of the diagnosis, surgical eligibility or personal counselling and support for coping, compliance issues and guidance of expectations. A recent study in migraine suggested that positive information about drugs contributed to successful management, presumably by influencing expectations (15). This is likely to be true for all types of treatment. Provision of positive information regarding treatment changes may thus also aid epilepsy care.

Strengths and weaknesses

Our analysis includes individual selected from pharmacy records on the use of AEDs. In the Netherlands, individuals are registered with a single community pharmacy where they get their medication independent of prescriber. Pharmacy records, thus, usually cover a person's medication almost completely (16). Our approach included people not under specialized care who are frequently neglected in treatment outcome research (17). The low response rate was partly due to our design, as discussed previously (17). The inability to send reminders is likely to have further reduced the response rate (18). Potential selection bias may exist due to the non-response of people who are well controlled or without adverse effects. This would likely have resulted in an overrepresentation of people with a lower QoL. To get an idea of potential selection bias, we compared demographic and treatment data between responders and non-responders, we found no significant differences indicating such a bias. Our QoL scores are comparable to those reported in other cohorts (19), but QoL is difficult to compare between countries, due to socio-cultural differences. We assume that the low

response rate did not largely influence the association found between AED changes and QoL, and our conclusions remain valid.

People with frequent changes, especially treatment intensification, present with a lower QoL compared to those with stable AED regimens. The numbers in our observational cohort, however, did not allow further investigation into the subtypes of changes and their impact on QoL. We assessed QoL scores at time of inclusion and retrospectively looked at AED changes, which precluded individual comparisons before and after the change. This also impeded direct comparisons with studies showing that changes often do not result in improved treatment outcomes (7, 10).

Lack of seizure control and AEs are known to be major determinants of QoL (19). We chose not to correct for these factors as they were also the main underlying reasons for change. The number of AED changes can thus be seen as a proxy for epilepsy severity, not requiring further corrections for these factors. Changes mainly resulted from lack of seizure control or AEs. We could not ensure that reported AEs are all directly attributable to AED use, and we were not aware of the participant's own perspectives which may underlie AED changes and affect QoL. Coping skills such as the acceptance of AEs and seizures, as well as beliefs in a specific treatment, emotional vulnerability due to failure of previous AED attempts and compliance issues have been found to be related to QoL in epilepsy (20, 21) and may also have influenced decisions to change AED treatment, whether or not justified.

Conclusions

Changes in AED treatment occur frequently, even in people with long-standing epilepsy. Frequent changes, especially treatment intensification, are associated with a progressive decrease in QoL. Even though their contributing mechanisms remain unclear, AED changes can be seen as an objective measure of epilepsy severity and suboptimal treatment outcomes. As QoL is the most important treatment outcome measure, a high frequency of AED changes is important to acknowledge in daily clinical practice. It may imply the need for a review of epilepsy management including referral for specialized care or other interventions to improve the QoL of people with epilepsy. Changes should also be acknowledged in future AED trials and observational studies, as a marker of epilepsy severity, to better interpret treatment outcomes for use in clinical practice.

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Conflicts of interest

All authors declare no conflict of interests. A grant was provided by the NEF for conducting the OPPEC study underlying the submitted work. All authors have no financial relationship with any organization that might have an interest in the submitted work or relationships or activities that could appear to have influenced the submitted work. This work was partly supported by the National Dutch Epilepsy Foundation. JWS has received research grants and honoraria from UCB, Eisai, Teva, Lundbeck and GSK which are involved in the manufacturing of AEDs, and his current position is endowed by the Epilepsy Society. He is a member of the Editorial Board of the *Lancet Neurology*.

Ethical statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study has been approved by the local ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Supporting Information

Additional Supporting Information may be found in the online version of this article.

Figure S1. Association between number of AED changes and QoL.

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