ARTICLE CLASS OF EVIDENCE

Does screening for adverse effects improve health outcomes in epilepsy?

A randomized trial

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Abstract

Objective
To determine whether systematic screening for adverse effects of antiepileptic drugs (AEDs) reduces toxicity burden and improves health-related quality of life in patients with epilepsy.

Methods
Consecutive patients with uncontrolled seizures aged ≥16 years and a high Adverse Event Profile (AEP) score were randomized to 2 groups and followed up for 18 months at 11 referral centers. AEP scores were made available to treating physicians at all visits in the intervention group, but not in the control group. Co–primary endpoints were changes in AEP scores and Quality of Life Inventory for Epilepsy-31 (QOLIE–31) scores.

Results
Of 809 enrolled patients able to complete the AEP questionnaire, 222 had AEP scores ≥45 and were randomized to the intervention (n = 111) or control group (n = 111). A total of 206 patients completed the 18-month follow-up. Compared with baseline, AEP scores decreased on average by 7.2% at 6 months, 12.1% at 12 months, and 13.8% at 18 months in the intervention group ($p < 0.0001$), and by 7.7% at 6 months, 9.2% at 12 months, and 12.0% at 18 months in controls ($p < 0.0001$). QOLIE-31 scores also improved from baseline to final visit, with a mean 20.7% increase in the intervention group and a mean 24.9% increase in the control group ($p < 0.0001$). However, there were no statistically significant differences in outcomes between groups for the 2 co–primary variables.

Conclusions
Contrary to findings from a previous study, systematic screening for adverse effects of AEDs using AEP scores did not lead to a reduced burden of toxicity over usual physician treatment.

Italian Medicines Agency (AIFA) identifier
FARM52K2WM_003.

Clinicaltrials.gov identifier
NCT03939507 (registered retrospectively in 2019; the study was conducted during the 2006–2009 period and registration of clinical trials was not a widely established practice when this study was initiated).

Classification of evidence
This study provides Class II evidence that the additional collection of formal questionnaires regarding adverse effects of AEDs does not reduce toxicity burden over usual physician treatment.

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Coinvestigators are listed at links.lww.com/WNL/B167

Glossary

AE = adverse effect; **AED** = antiepileptic drug; **AEP** = Adverse Event Profile; **BDI** = Beck Depression Inventory II; **CGI** = Clinical Global Impression; **DDD** = defined daily dose; **HRQoL** = health-related quality of life; **QOLIE-31** = Quality of Life Inventory for Epilepsy–31.

Pharmacoresistant epilepsy is characterized by poor health-related quality of life (HRQoL) due to the consequences of seizures, adverse effects (AEs) of antiepileptic drugs (AEDs), and associated comorbidities such as depression.[1–3] Observational studies have demonstrated that in patients with pharmacoresistant epilepsy reducing seizure frequency without achieving complete seizure control has little impact on quality of life, and that addressing the burden of AED toxicity should be a major component of clinical management.[4,5] A 4-month randomized study from North America suggested that systematic screening for AEs of AEDs by means of a self-administered standardized instrument is effective in guiding physicians to reduce overtreatment and associated toxicity scores compared with conventional clinical management.[6] The generalizability of these findings to the longer term and to other populations and clinical settings, however, is unclear. Large prospective studies are needed to assess the impact of systematic screening for AEs on the burden of toxicity and HRQoL in patients with epilepsy. Hence, we applied a validated self-administered questionnaire for AEs to a cohort of over 800 consecutively enrolled patients with uncontrolled seizures and followed them up prospectively for 18 months. By using a nested-in randomized controlled design, the influence of systematic screening for AEs on HRQoL, burden of AEs, seizure frequency, mood status, and AED load was evaluated for those patients who had high AED toxicity scores at enrollment.

Methods

Standard protocol approvals, registrations, and patient consents

The protocol of this study was approved by ethics committees of all participating centers. Written informed consent was obtained from all participants or their parents or tutors. The study was conducted during the 2006 to 2009 period and was not initially registered in clinicaltrials.gov because trial registration was not a widely established practice then, and the International Council of Medical Journal Editors clarified its definition of what constitutes a clinical trial only in 2008. Registration at clinicaltrials.gov (identifier code NCT03939507) was made in 2019, when we became aware that the site allows studies to be registered retrospectively.

Study design and patients

SOPHIE (Study of Outcome of Pharmacoresistance in Epilepsy) was primarily a prospective observational study aimed at assessing AEs, HRQoL, mood status, seizure outcome, and AED treatment in patients with uncontrolled epilepsy enrolled consecutively at 11 tertiary referral epilepsy centers in Italy and followed up for 18 months.[7,8] Adult patients with high toxicity scores at baseline participated in a nested-in randomized interventional study, described in the present article, to determine the impact of systematic screening for AEs on health outcomes.

Eligibility criteria

Detailed eligibility criteria for participation in the core (observational) study have been described elsewhere.[7,8] In brief, the study enrolled consecutive patients with epilepsy whose seizures were not controlled despite treatment with one or more AEDs at maximally tolerated doses. Patients with progressive disorders were excluded. For enrollment in the nested-in randomized study, patients had to be 16 years or older, be able to complete the Adverse Event Profile (AEP) questionnaire,[9] and have a total AEP score ≥45, indicative of a high toxicity burden.

Randomization method and study procedures

Eligible patients were randomized 1:1 to 2 groups. In the intervention group, the results of the AEP questionnaires were made available to the treating physician at each assessment visit, while in the control group the questionnaire results were made available only at the end of follow-up. Patients were not informed of their group allocation. The randomization list was generated by a computer program (SAS version 9.1) with stratification for center using blocks of 4. Enrolling physicians accessed the randomization program online by using investigator-specific username/passwords. After registering the patient's initials and year of birth in the central database, the physician received a patient number and group allocation for that patient.

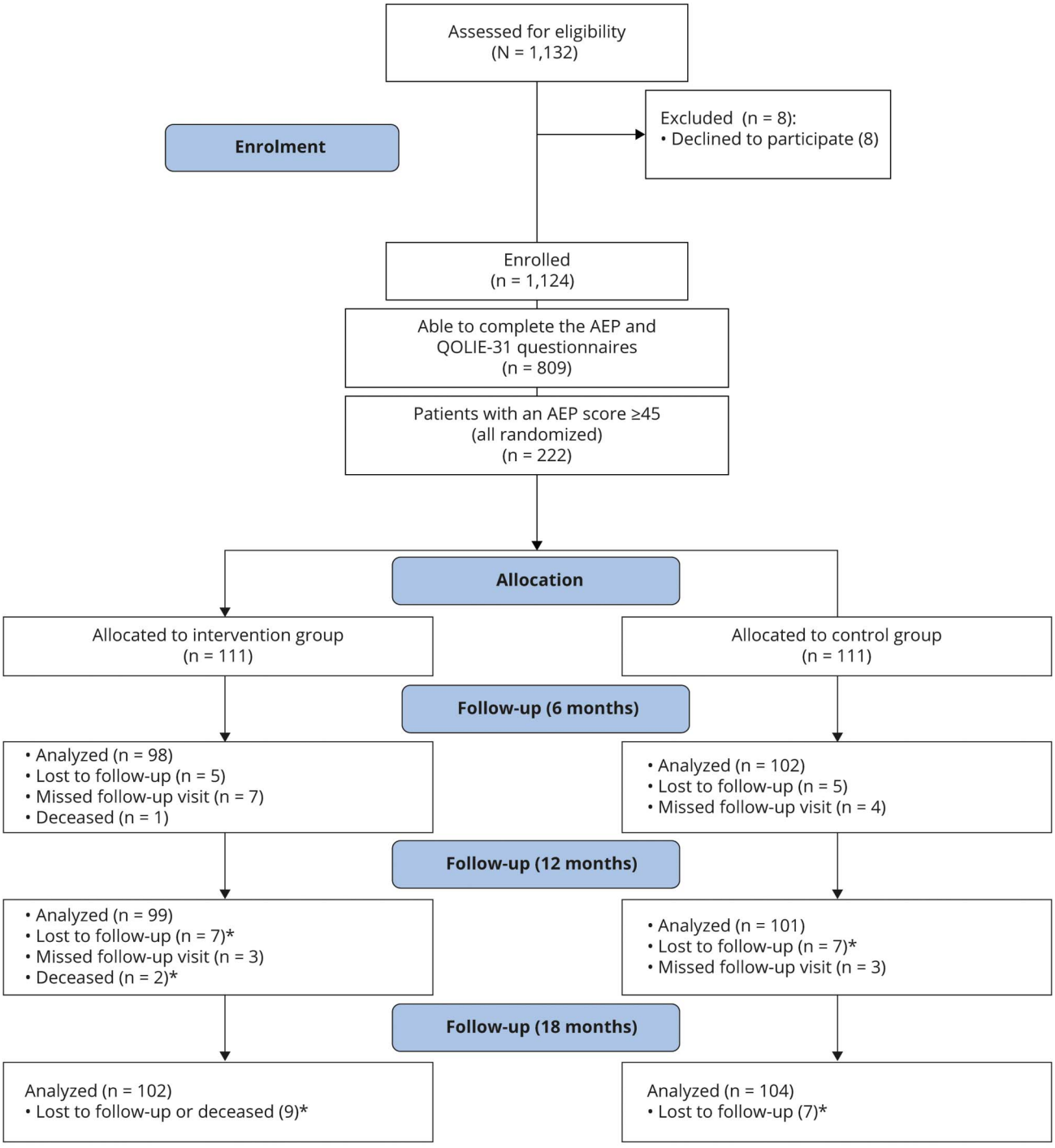
Patients were seen in the clinic at times 0 (enrollment), 6, 12, and 18 months. At the first visit, detailed information was collected on demographics, medical and drug history, current clinical status, and current therapies. At all visits, health status was assessed by means of the 31-item epilepsy-specific Quality of Life Inventory for Epilepsy–31 (QOLIE-31) questionnaire[10]; the 19-item AEP questionnaire[9]; and the Beck Depression Inventory II (BDI), all of which were compiled before seeing the physician.[11] In addition, a 5-digit Clinical Global Impression (CGI) scale was compiled separately by the physician and patient or caregiver. All instruments were administered by using validated Italian language versions.[12] Seizure frequency was recorded by using seizure diaries compiled by patients or caregivers. AEs were also recorded at each visit based on general and neurologic examination and nonstructured interview. Drug loads were estimated as the sum of the prescribed daily dose/defined daily dose (DDD) ratios for each AED included in the treatment schedule, where DDD is the average

maintenance drug daily dose based on WHO records.[13] All data were entered on electronic Case Report Forms.

Primary endpoints and statistical analysis

The protocol-defined co–primary endpoints were changes in total AEP and QOLIE-31 scores (final visit vs initial visit). These endpoints were handled by a hierarchical approach by ranking AEP scores as first co–primary endpoint and QOLIE-31 scores as second co–primary endpoint. To accomplish this, AEP scores (dependent variable) were fitted to a longitudinal linear model using the randomization group (intervention and control) as dummy covariate. Analyses on secondary

Figure 1 Flow diagram of patient disposition (CONSORT 2010)



AEP = Adverse Event Profile; QOLIE-31 = Quality of Life Inventory for Epilepsy–31.

endpoints were performed in the same fashion using a longitudinal generalized linear model with continuous, ordinal, and dichotomous outcomes. p Values <0.05 were considered statistically significant. All analyses were performed using SAS release 9.4.

Sample size

Sample size was determined by considering 2 primary endpoints (AEP global score and QOLIE-31 total score) based on data published by Gilliam et al.[6] Because both co–primary endpoints were expected to change in parallel, no correction for multiplicity was applied. A sample size of 105 patients per group ensures 90% power to detect a between-group difference of 5 points for change from baseline in 18-month AEP global score (first co–primary endpoint), assuming an SD of 11.0 and a 2-tailed type error of 0.05. For the second co–primary endpoint (QOLIE-31 total score), 85 patients per group are required to detect, with 90% power and a p value set at 0.05, a between-group 6-point difference in 18-month change from baseline assuming an SD of 12.0 points. A total of 222 patients (111 patients in each group) were actually enrolled.

Classification of evidence

The primary research question was the following: Does the systematic screening for AEs of AEDs reduce toxicity burden in patients with epilepsy?

This study provides Class II evidence that the additional collection of formal questionnaires regarding AEs of AEDs does not reduce toxicity burden over usual physician treatment.

Data availability

Datasets generated or analyzed during the present study are available on reasonable request in an anonymized form from the corresponding author.

Results

Characteristics of the population and patients' disposition

Out of 1,132 patients meeting eligibility criteria, 1,124 (99.3%) agreed to participate in the study (figure 1). Of those, 933 were 16 years or older and 809 (86.7%) were able to complete the questionnaires. Among the latter, 222 (27%) had an AEP score ≥45 and were randomized, with 206 (93%) completing the 18-month follow-up.

The 2 randomization groups were comparable in demographic, disease-related, and treatment-related characteristics, and questionnaire scores at baseline (table 1). More than 90% of randomized patients had failed to respond to ≥2 AEDs, either alone or in combination. The majority of patients (75% in the control arm and 81% in the intervention arm) were on polytherapy. The most commonly prescribed

Table 1 Demographic, disease-related, and treatment-related characteristics of the 222 randomized patients at baseline

	Intervention group (n = 111)	Control group (n = 111)
Sex		
Male	38 (34.2)	31 (27.9)
Female	73 (65.8)	80 (72.1)
Age, y		
Mean (SD)	42.4 (13.8)	41.4 (14.2)
Median (range)	40.4 (17.5–80.5)	39.1 (16.2–78.3)
Age at seizure onset, y		
Mean (SD)	22.5 (17.1)	20.2 (14.7)
Median (range)	19.4 (0–68.7)	18.2 (0–61.6)
Disease duration, y		
Mean (SD)	21.2 (13.6)	19.8 (13.8)
Median (range)	18.6 (0.4–58.7)	18.6 (0.4–58.7)
No. of previously failed AEDs[a]		
1	9 (8.1)	11 (9.9)
2	12 (10.8)	10 (9.0)
3	90 (81.1)	90 (81.1)
No. of AEDs per patient, mean (SD)	2.2 (0.9)	2.2 (1.0)
Type of epilepsy		
Idiopathic generalized	17 (15.3)	4 (3.6)
Nonidiopathic generalized	4 (3.6)	6 (5.4)
Focal	90 (81.1)	99 (89.2)
Unknown or undefined	0	2 (1.8)
No. of seizures during previous 6 months, median (IQR)	15.5 (3.0; 47.0)	18 (6.0; 35.0)
Neurologic examination		
Normal	85 (76.6)	85 (76.6)
Abnormal	26 (23.4)	26 (23.4)
QOLIE-31 (total score), mean (SD)	43.7 (13.5)	44.7 (13.2)
BDI-II (total score), mean (SD)	21.5 (11.4)	19.2 (10.4)
AEP (total score), mean (SD)	57.3 (6.8)	56.7 (6.1)

Abbreviations: AED = antiepileptic drug; AEP = Adverse Event Profile; BDI = Beck Depression Inventory II; IQR = interquartile range; QOLIE-31 = Quality of Life Inventory for Epilepsy–31.
Unless indicated otherwise, values are number of participants with percentages of the relevant sample shown in parentheses.
[a] Includes AEDs taken at enrollment. AEDs tried at insufficient doses or discontinued prematurely due to idiosyncratic reactions are excluded from the count.

Table 2 Total Beck Depression Inventory II (BDI) scores, Clinical Global Impression (CGI) scores, drug loads, and number of seizures in the 2 study groups at baseline and at the end of follow-up (18 months)

	Intervention group	Control group
BDI-II scores		
Baseline, median (IQR) (n = 111)	21 (13–30)[a]	17 (12–24)[a]
18-month change vs baseline, median (IQR)	−9 (−17 to −1) (n = 102)[b]	−6 (−13 to −1) (n = 100)[b]
CGI self-assessment, 18-month change vs baseline, % of patients (n)		
1. Worse	14.7 (15/102)	14.4 (15/104)
2. Unchanged	41.2 (42/102)	44.2 (46/104)
3. Slightly better	17.6 (18/102)	17.3 (18/104)
4. Moderately better	15.7 (16/102)	16.3 (17/104)
5. Much better	10.8 (11/102)	7.7 (8/104)
CGI assessment (physician), 18-month change vs baseline, % of patients (n)		
1. Worse	9.8 (10/102)	10.6 (11/104)
2. Unchanged	45.1 (46/102)	51.9 (54/104)
3. Slightly better	18.6 (19/102)	21.2 (22/104)
4. Moderately better	14.7 (15/102)	11.5 (12/104)
5. Much better	11.8 (12/102)	4.8 (5/104)
Drug load		
Baseline, median (range)	2.3 (0.3–6.7) (n = 111)	2.4 (0.2–7.3) (n = 111)
18-month change, median (range)	2.7 (0.3–8.0) (n = 102)	2.6 (0.3–8.5) (n = 104)
No. of seizures, median (range)		
Months 1–6	10 (0–924) (n = 102)	11 (0–513) (n = 104)
Months 7–12	10 (0–924) (n = 102)	12 (0–943) (n = 104)
Months 13–18	10 (0–375) (n = 102)	12 (0–943) (n = 104)

Abbreviation: IQR = interquartile range.
[a] $p < 0.01$ (between groups, median test).
[b] $p < 0.0001$ (between and within groups, Wilcoxon test).

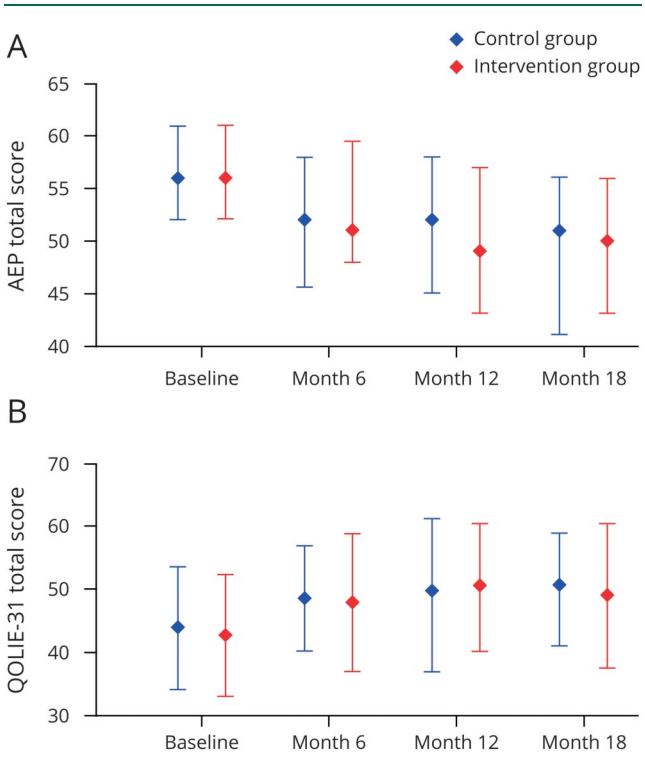
AEDs were levetiracetam (16.7%), oxcarbazepine (12.6%), and lamotrigine (12.4%). During the study, dosage of at least 1 AED was increased, or another AED was added, in 84 out of the 102 patients who completed 18-month follow-up in the intervention group (82.4%) and in 74 of 104 patients in the control group (71.2%). Dosage reduction or discontinuation of at least 1 AED was recorded in 73 of 102 (71.6%) patients in the intervention group and in 70 of 104 (67.3%) patients in the control group. Median AED load in the intervention group increased from 2.3 at baseline to 2.7 at 18-month follow-up. In the control group, median AED load increased from 2.4 at baseline to 2.6 at 18-month follow-up (table 2).

Primary outcome variables

Compared with baseline, AEP scores decreased on average by 7.2% at 6 months, 12.1% at 12 months, and 13.8% at 18 months in the intervention group ($p < 0.0001$), and by 7.7% at 6 months, 9.2% at 12 months, and 12.0% at 18 months in controls ($p < 0.0001$). There were no statistically significant differences in AEP score changes between groups (figure 2A). A marked (≥15-point) improvement in AEP scores was recorded in 25 patients in the intervention group compared with 26 patients in the control group. Similarly to AEP scores, QOLIE-31 scores improved from baseline to final visit, with a mean 20.7% increase in score in the intervention group compared with a mean 24.9% increase in controls ($p < 0.0001$). There was no statistically significant difference in the improvement in QOLIE-31 scores between groups (figure 2B).

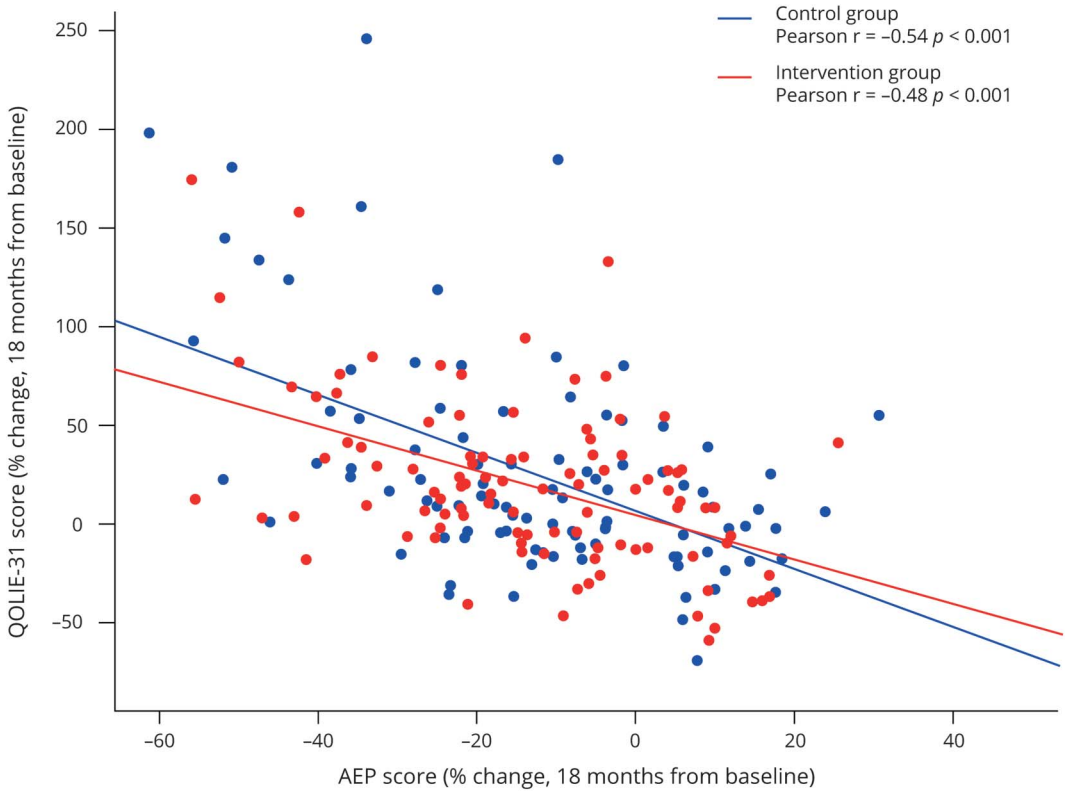
In the overall cohort, baseline AEP scores and QOLIE-31 scores were inversely correlated ($r = -0.51$, $p < 0.001$). Within

Figure 2 Adverse Event Profile (AEP) scores and Quality of Life Inventory for Epilepsy–31 (QOLIE-31) scores at each time point



AEP scores (A, repeated-measures analysis of variance [ANOVA], $p = 0.78$ between groups and <0.0001 within groups) and QOLIE-31 scores (B, repeated-measures ANOVA, $p = 0.59$ between groups and <0.0001 within groups) in the study groups at baseline and during follow-up. Values at each time point are medians and interquartile range.

Figure 3 Relationship between percent change in Quality of Life Inventory for Epilepsy–31 (QOLIE-31) scores and percent change in Adverse Event Profile (AEP) score (18-month assessment vs baseline) during follow-up in the 2 groups



groups, percent change in AEP scores during follow-up (last observation vs baseline) correlated inversely with changes in QOLIE-31 scores ($r = -0.48$, $p < 0.001$ for the intervention group, and $r = -0.54$, $p < 0.001$ for the control group; figure 3).

Secondary outcome variables

Changes in secondary variables (18 months vs baseline) are summarized in table 2. No statistically significant differences between groups were identified for changes in BDI scores, self-rated CGI scores, physician-rated CGI scores, and median seizure frequency. Median AED load increased slightly from baseline to final visit, from 2.3 to 2.7 in the intervention group and from 2.4 to 2.6 in the control group (table 2).

Discussion

The design of the present study was inspired by an earlier single-center investigation conducted in the United States by Gilliam et al.,[6] who applied a similar protocol and found that patients whose AEP scores were made available to physicians experienced a greater reduction in burden of toxicity after 4 months (mean 25% reduction in AEP scores) than patients whose AEP scores were not made available (mean 4% reduction in AEP scores).[6] In our study, the improvement in AEP score in the intervention group at a similar time point was much more modest (mean 7.2% reduction at the 6-month assessment) and did not differ from that recorded in the control group (mean 7.7% reduction at 6 months). Failure of the present study to confirm a greater improvement in the intervention group may have several explanations. Although the present study had a larger sample size than the US study (222 vs 62 patients randomized), enrollment took place at 11 different centers, which may have resulted in greater variability in clinical management among participating physicians. While in the US study participating neurologists were instructed to make any medication changes that were necessary to minimize identified toxicity without causing a significantly increased risk of worsening seizures,[6] physicians in the present study were simply instructed to manage their patients according to best clinical practice. This still requires achieving the best compromise between AEs and seizure control, but physicians may have underestimated the need to reduce the burden of toxicity. Unlike the earlier study, which included a mixed group of individuals with uncontrolled seizures and individuals in remission, all our patients had uncontrolled seizures, which could have made physicians more cautious in reducing AED load. For patients in the control group, it is also possible that completing the questionnaires prior to each visit could have made them more aware of specific AEs, and influenced how they reported AEs to their physician. Gilliam et al.[6] expressed the same concern, but noted that in their study any bias in AE reporting due lack of complete masking of the use of questionnaires did not prevent identification of

a major difference in outcome between the intervention group and controls. Duration of follow-up, on the other hand, is unlikely to have contributed to differences in outcome between the 2 studies, because intermediate assessments at 6 and 12 months in our patients also failed to identify any between-group difference in AEP and QOLIE-31 scores. Interestingly, a recent underpowered study conducted in Brazil that applied a similar design but limited follow-up to 6 months also failed to demonstrate any impact of systematic screening for AEs over usual physician visit in reducing the burden of AED toxicity.[14]

The reason for the improvement in AEP and QOLIE-31 scores over time in both groups in our study is unclear. Seizure frequency could not be a factor because it did not change over time in either group. In both groups, discontinuation of at least 1 AED or a reduction in dose occurred less frequently than addition of another AED or an increase in dose, and therefore it is unlikely to have led to improved AEP scores. In fact, drug load at the final visit was actually slightly higher in both groups compared with baseline. It is possible that awareness of participating in a study intended to reduce the burden toxicity influenced patient expectations, leading per se to improvement in perceived AEs and QOLIE-31 scores. As an additional potential source of bias, we cannot exclude that the study itself may have sensitized physicians to assess all their patients more scrupulously for potential manifestations of toxicity. While these hypotheses may contribute to explain the improvement in health status scores and the similarity in outcomes between the 2 groups, it remains a fact that the reduction in toxicity burden over time in the intervention group was modest, and much smaller compared with that reported in the earlier US study.[6]

Although we could not confirm the results of Gilliam et al.[6] in terms of influencing health outcomes, other findings were in good agreement between the 2 studies. Importantly, we confirmed that a large proportion of AED-treated patients with epilepsy (27% in our study, compared with 31% in the US study) exhibit a severe burden of toxicity as defined by high AEP scores. Moreover, we confirmed that high AEP scores correlate inversely with HRQoL, and that patients whose AEP scores improved during follow-up also showed a parallel improvement in HRQoL.

Overall, these data reinforce existing evidence that AEs of AEDs more than seizures themselves are a major determinant of quality of life in patients with drug-resistant epilepsy, and that greater efforts to reduce drug toxicity should be made in the management of these individuals.[4,6,8,12,14] Based on the results of our study, we can conclude that systematic screening for AEs can be useful in identifying manifestations of drug toxicity, but is not sufficient to guide medication changes and cause a major improvement in AEP scores. We suggest that any intervention to reduce overtreatment should also include educational initiatives to improve awareness of the impact of AEs on quality of life, and to highlight the benefits of reducing excessive AED dosages and unnecessary polypharmacy.[15,16]

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Disclosure

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Publication history

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Appendix 1 Authors

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Valentina Franco, PhD	Clinical Pharmacology Unit, University of Pavia; IRCCS Mondino Foundation, Pavia, Italy	Assistance with study coordination, analysis of the data, production of first draft of the manuscript
Maria Paola Canevini, MD	Department of Health Sciences, University of Milan; Epilepsy Center, San Paolo Hospital, Milan, Italy	Enrollment of patients, data collection, reviewing the manuscript for intellectual content
Giovambattista De Sarro, MD	Magna Graecia University, Catanzaro, Italy	Enrollment of patients, data collection, reviewing the manuscript for intellectual content

Continued

Appendix 1 *(continued)*

Name	Location	Contribution
Cinzia Fattore, MD	IRCCS Mondino Foundation, Pavia, Italy	Assistance with study coordination and analysis of the data, reviewing the manuscript for intellectual content
Guido Fedele, BsC	School of Hospital Pharmacy, University of Milan, Italy	Analysis of the data, reviewing the manuscript for intellectual content
Carlo Andrea Galimberti, MD	IRCCS Mondino Foundation, Pavia, Italy	Enrollment of patients, data collection, reviewing the manuscript for intellectual content
Giuliana Gatti, PhD	Clinical Pharmacology Unit, University of Pavia, Italy	Assistance with study coordination and analysis of the data, reviewing the manuscript for intellectual content
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Eleonora Rosati, MD	Unit of Neurology, Usl Centro Toscana Health Authority, Prato, Italy	Enrollment of patients, data collection, reviewing the manuscript for intellectual content
Luigi Maria Specchio, MD	University of Foggia, Italy	Enrollment of patients, data collection, reviewing the manuscript for intellectual content

Appendix 1 *(continued)*

Name	Location	Contribution
Salvatore Striano, MD	Epilepsy Center, Federico II University, Naples, Italy	Enrollment of patients, data collection, reviewing the manuscript for intellectual content
Paolo Tinuper, MD	IRCCS, Institute of Neurologic Sciences of Bologna and Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy	Enrollment of patients, data collection, reviewing the manuscript for intellectual content
Emilio Perucca, MD	Clinical Pharmacology Unit, University of Pavia; IRCCS Mondino Foundation, Pavia, Italy	Conceptualization of the study, coordination of the study, analysis of the data, reviewing the manuscript for intellectual content

Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B167

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