Original article

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Addressing overtreatment in patients with refractory epilepsy at a tertiary referral centre in Brazil

Veriano Alexandre Jr [1], Edna Almeida Monteiro [1], Priscila Freitas-Lima [1], Kylvia Dantas Pinto [1], Tonicarlo Rodrigues Velasco [1], Vera Cristina Terra [1], Ana Paula Pinheiro-Martins [1], Roberto Molina Souza [2], Emilio Perucca [3], Americo Ceiki Sakamoto [1]

[1] Ribeirão Preto Medical School University Hospital, University of São Paulo
[2] Federal Technological University of Paraná, Cornélio Procópio, Brazil
[3] Clinical Pharmacology Unit, University of Pavia and National Neurological Institute IRCCS C. Mondino Foundation, Pavia, Italy

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ABSTRACT – *Background*. Patients with refractory epilepsy often have impaired quality of life (QOL) as a consequence of seizures and adverse effects of antiepileptic drugs. We assessed the impact of adverse effects on QOL and the utility of a structured instrument to help the physician manage adverse effects in patients with refractory epilepsy. *Methods*. Clinical characteristics, drug treatment and adverse effects were evaluated in 102 patients with refractory epilepsy at a single tertiary referral centre. The Adverse Events Profile (AEP) and Quality of Life in Epilepsy-31 (QOLIE-31) questionnaires were completed at baseline and after six months. At baseline, patients with a high burden of adverse effects (AEP scores $\geq$45) were randomized to an intervention or control group. AEP scores in the intervention group were available to the physician as an instrument to help to reduce adverse effects. *Results*. Ninety-five patients (93.1%) were on polytherapy. Sixty-six completed the questionnaires and, of these, 43 (65.1%) had a high AE burden and were randomized to the intervention and control group. QOLIE-31 scores were inversely correlated with AEP scores at both visits. Among randomized patients, AEP scores tended to decrease between the baseline and the final visit without significant differences between groups (intervention group: 54.1 ± 6.1 *vs* 51.1 ± 9.1; control group: 55.8 ± 5.8 *vs* 50.5 ± 12.2). QOLIE-31 scores did not change substantially between visits (intervention group: 45.9 ± 17.4 *vs* 48.4 ± 14; control group: 47.5 ± 15.7 *vs* 45.2 ± 18.9). *Conclusion*. A significant proportion of patients had a high toxicity burden which had an impact on their QOL. Reduction of overtreatment is a difficult challenge which cannot be addressed solely by providing a structured assessment of adverse effects, but requires a more comprehensive approach aimed at optimizing the many components of the management strategy.

Key words: epilepsy, drug resistance, antiepileptic drugs, overtreatment, adverse effects

Correspondence:
V. Alexandre Jr
Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo,
Departamento de Neurociências e Ciências do Comportamento-CIREP,
Av. Bandeirantes 3900,
Ribeirão Preto, SP,
Brasil, 14048-900
<verialex@rnp.fmrp.usp.br>

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About one third of people with epilepsy fail to achieve seizure freedom with available antiepileptic drugs (AEDs) (Kwan and Brodie, 2000), which may result in the use of unnecessarily high drug loads or overtreatment (Perucca and Kwan, 2005). Patients on polytherapy or excessive drug dosages have a high probability of developing adverse effects, with a consequent negative impact on quality of life (QOL) (Bourgeois, 2002; Cramer *et al*., 2007). Therefore, treatment strategies in refractory epilepsy should be aimed at reaching an optimal balance between seizure control and adverse effects, by reducing overtreatment and its associated negative consequences on QOL.

In this study, we investigated the characteristics of AED treatment and its impact on adverse effects and QOL in patients with refractory epilepsy. In addition, we assessed the usefulness of a structured instrument aimed at reducing adverse effects in this population.

Methods

This was a prospective, mostly observational, investigation which replicated the design of the recently reported SOPHIE study (Study of Outcome of PHarmacoresistance In Epilepsy) (Alexandre *et al*., 2010). The protocol was approved by the institutional review board and all patients signed an informed consent form.

Adults with drug-resistant epilepsy attending the epilepsy outpatient clinic of the Ribeirão Preto Medical School University Hospital were enrolled between November 2007 and April 2008. Eligibility criteria included: age $\geq$16 years, at least one seizure in the previous six months, and a diagnosis of pharmacoresistant epilepsy defined as persistent seizures after adequate treatment with one or more appropriate AEDs at maximal tolerated doses, excluding treatments in which idiosyncratic reactions prevented titration to usually effective doses (Perucca, 1998). Because the number of eligible patients on each clinic day exceeded the maximum number that could undergo the study evaluations, a randomly selected subgroup was enrolled on consecutive clinic days. Assessments at baseline included collection of data based on demographics, medical history, seizure rate, syndromic classification, treatment characteristics, AED load, presence of adverse effects using an unstructured interview as well as the standardized 19-item AEP (Adverse Events Profile) questionnaire (Baker *et al*., 1997), and QOL as determined using the Brazilian version of the QOLIE-31 scale (da Silva *et al*., 2007). The AEP and the QOLIE-31 were completed only by those patients who were able to read and understand the questions. AED load was defined as the sum of the prescribed daily dose/defined daily dose ratio (PDD/DDD) (Lammers *et al*., 1995) for each AED in the treatment regimen, DDD values being derived from the WHO database (WHO Collaborating Centre for Drug Statistics Methodology, 2009). All assessments were repeated at a follow-up visit six months later but patients generally underwent one additional visit during this period, as clinically indicated. At all visits, patients were seen by the same neurologist, jointly with a postgraduate trainee. Physicians were instructed to manage all patients to the best of their knowledge, according to routine medical care, using all the information available to them.

Patients with an AEP score $\geq$45 at baseline, which is indicative of a major AE burden (Gilliam *et al*., 2004), were included in a nested-in randomized study aimed at reducing the toxicity burden. The 1:1 randomization list was generated by a computer program (SAS PLAN Procedure version 9.1) and the attending physicians were blind with regards to the randomization of participants. For the intervention group, AEP scores were made available to the attending physicians at each visit, but not for the control group. Evaluations in the randomized study were identical to those in the observational study, and the physicians were left to manage patients at their discretion in order to achieve an optimal clinical response.

Data frequencies were analysed by descriptive statistics. For continuous variables, means and standard deviations, medians and ranges were calculated, as appropriate. For categorical variables, the relative number of patients was calculated. Differences in AEP and QOLIE-31 scores between baseline and final visit were tested by using the Wilcoxon's rank test. Correlations were assessed by using the Spearman's correlation test. The level of significance was set at $p < 0.05$, two-tailed.

Results

Demographic and epilepsy-related data

A total of 102 patients (57 females, 45 males) were enrolled, with a mean age of 36.8 ± 11.3 years (range 16 to 60 years), and a mean age at epilepsy onset of 10 ± 9.8 years (range: 1 to 41 years). Ninety-seven (95.1%) patients had focal epilepsy. Median number of seizures in the six months prior to the baseline assessment was 18 (mean: 62.8; SD: 143.5; range: 1 to 1080). The vast majority of patients (89.2%) had on average one or more seizures per month. Seventy seven (75.4%) failed to respond to at least three AEDs used sequentially or in combination. All patients completed the follow-up assessment as scheduled.

Treatment characteristics

Ninety-five (93.1%) patients were on polytherapy (39 with two, 46 with three, and 10 with four AEDs. The mean PDD/DDD ratio was 3.3 (range: 0.6 to 7.7). AED load increased with increasing number of AEDs co-prescribed ($r = 0.73$; $p < 0.01$). The most commonly prescribed AEDs were carbamazepine (70.5%), clobazam (64.7%), lamotrigine (34.3%), and topiramate (34.3%). Treatment remained unchanged between baseline and the final visit in 38 (37.6%) cases. In 31 (30.6%) patients, dosage was increased or another AED was added. Dosage reduction or discontinuation of at least one AED was recorded in 14 (13.8%) patients.

Adverse effects, adverse events profile (AEP) and QOLIE-31 data

Adverse effects were reported spontaneously by 39 (38.2%) patients at baseline and by 47 (46%) at the final visit. Those most commonly recorded were dizziness and somnolence, which were reported by 21% and 36% of patients at baseline and 18.8% and 16.8% at final visit, respectively *(table 1)*.

The AEP and QOLIE-31 questionnaires were completed by 66 (64.7%) patients. The mean AEP score was 48.9 ± 10.3 at baseline and 46.2 ± 11.2 at the final (six-month) visit, a non-significant difference. The most frequently reported adverse effects (defined as those occurring always/frequently or sometimes in the previous four weeks) based on the AEP questionnaire were "nervousness and/or agitation" (54 patients at baseline) and "somnolence" (47 patients at the final visit). The mean QOLIE-31 score remained substantially unchanged between baseline (52.5 ± 18) and final visit (52.7 ± 18.7).

There was a significant inverse correlation between the AEP and the QOLIE-31 scores, both at baseline ($r = -0.59$, $p < 0.01$) and follow-up ($r = -0.69$, $p < 0.01$) *(figure 1)*, indicating that QOL decreased with increasing adverse effect burden. Four (3.9%) patients had no recurrence of seizures during the six-month follow-up visit, 19 (18.6%) had a reduction in seizure frequency of at least 50%, and 38 (37%) had a greater than 100% increase in frequency compared with baseline.

Table 1. Adverse effects spontaneously reported at baseline and at the final visit. NR: not reported.

Adverse effects	Baseline n (%)	Final visit n (%)
Somnolence	24 (36)	17 (16.8)
Dizziness	14 (21)	19 (18.8)
Memory impairment	4 (6)	4 (3.9)
Mental slowness	3 (4.5)	4 (3.9)
Anorexia	3 (4.5)	3 (2.9)
Diplopia	3 (4.5)	3 (2.9)
Sexual dysfunction	1 (1.5)	4 (3.9)
Difficulty in concentration	3 (4.5)	1 (0.9)
Headache	2 (3)	2 (1.9)
Upset stomach	1 (1.5)	3 (2.9)
Blurred vision	1 (1.5)	2 (1.9)
Pruritus	1 (1.5)	2 (1.9)
Nausea	1 (1.5)	2 (1.9)
Tremor	1 (1.5)	2 (1.9)
Fatigue	NR	3 (2.9)
Drooling	1 (1.5)	1 (0.9)
Feelings of aggression	NR	2 (1.9)
Trouble with mouth or gums	1 (1.5)	1 (0.9)
Balance disorder	1 (1.5)	1 (0.9)
Weight gain	NR	2 (1.9)
Anxiety	NR	1 (0.9)
Oedema	NR	1 (0.9)
Paresthesias	NR	1 (0.9)
Restlessness	NR	1 (0.9)
Slurred speech	1 (1.5)	NR
Weight loss	NR	1 (0.9)

Randomized nested-in study

Of the 66 patients who completed the AEP questionnaire, 43 (65.2%) had an AEP score ≥ 45 and were randomly assigned to the intervention (21 patients) and control (22 patients) groups. Drug loads were similar between the intervention and the control group both at baseline (3.1 ± 1.1 *vs* 2.9 ± 1.3, respectively) and at final visit (3.2 ± 1.1 *vs* 3.0 ± 1.2, respectively). In both groups, AEP scores tended to decrease between the baseline and the final visit, without any significant difference between groups (intervention group: 54.1 ± 6.1 *vs* 51.1 ± 9.1; control group: 55.8 ± 5.8 *vs* 50.5 ± 12.2). QOLIE-31 scores did not change substantially between visits (intervention group: 45.9 ± 17.4 *vs* 48.4 ± 14; control group: 47.5 ± 15.7 *vs* 45.2 ± 18.9).

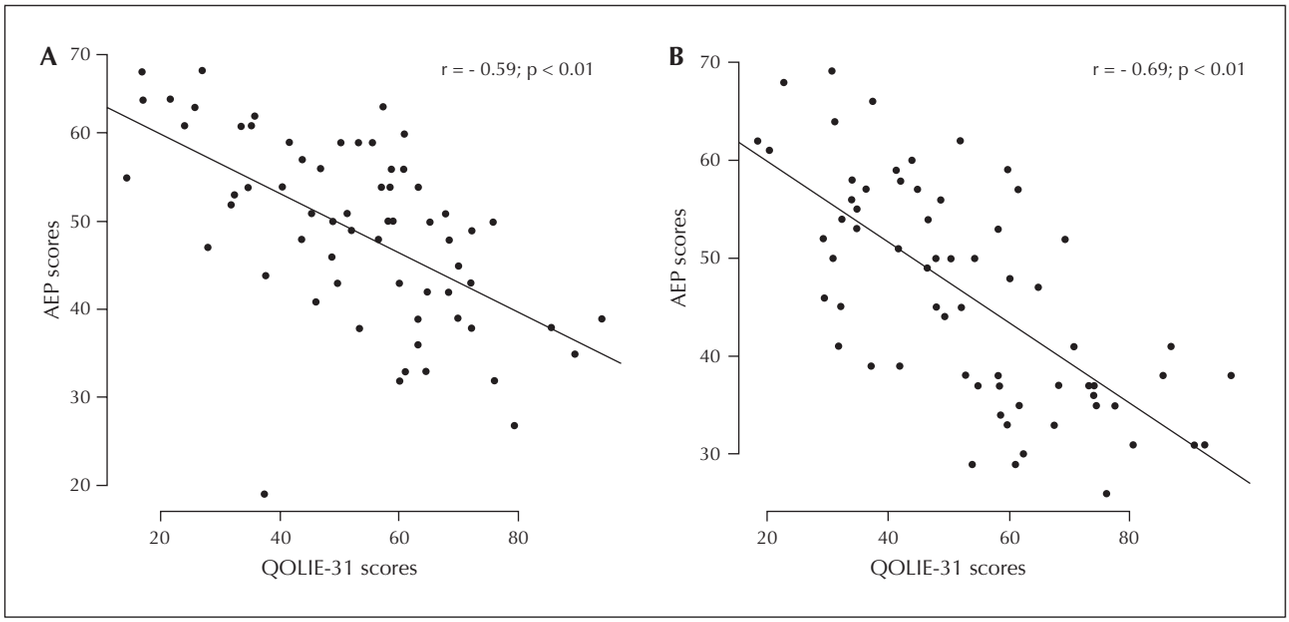

Figure 1. Relationship between AEP and QOLIE-31 scores in individual patients at baseline (**A**) and at the final visit (**B**).

Discussion

Our patients were enrolled at a tertiary level centre, which is likely to have resulted in inclusion of a particularly large proportion of cases with difficult-to-treat epilepsy. This may, in part, explain the high proportion of cases receiving complex polytherapies, with over one half of patients receiving three AEDs or more. Overall, our population shows many similarities to that of a large cohort study recently completed at 11 tertiary referral centres in Italy using the same design (Canevini *et al*., 2010). In the latter study, however, more patients were on monotherapy (22.5% *vs* 6.9% in our study) and fewer received a combination of three AEDs or more (34.6% *vs* 54.9% in our study). AED utilization also differed between these populations, the most remarkable differences being a considerably higher use of clobazam and topiramate in our centre, and the lack of utilization of levetiracetam, which is not yet commercially available in Brazil.

The high proportion of our patients on polytherapy and their high mean drug load are indirect indications that overtreatment was probably prevalent in our population. Although the optimal balance between adverse effects and seizure control in individual cases cannot be inferred from our data, the fact that adverse effects were reported spontaneously in up to 46% of cases, and that AEP scores indicated a high toxicity burden in about 60%, strongly suggests that many patients were exposed to excessive AED loads. In the Italian study, the proportion of cases with high AEP scores (27.7%) was about one half of that observed in our cohort, although, interestingly, in the same study toxicity burden did not differ between patients on monotherapy and those on polytherapy (Canevini *et al*., 2010).

As in previous studies (Cramer *et al*., 2007; Gilliam *et al*., 2004) we found a strong inverse correlation between AEP and QOLIE-31 scores, suggesting that adverse effects had a strong negative impact on QOL in this population. By applying a randomized design similar to that used in our investigation, Gilliam *et al*. (2004) reported in a US multicentre study that making AEP scores available to the treating physician led over four months to a significant reduction in overtreatment and to a reduced burden of adverse effects. In our nested-in randomized study, however, informing physicians about AEP scores did not result in reduced drug load or in greater amelioration of AE burden or QOL. Although this finding should be interpreted cautiously due to the limited statistical power of the study (43 randomized patients, *versus* 62 for the US study), a trend was not even observed for AEP scores to show greater improvement in the intervention group. The apparent discrepancy between our results and those reported by Gilliam *et al*. (2004) cannot be explained by an insufficient duration of follow-up, because the interval between the two structured evaluations was longer in our study than in the US study, and patients were generally seen on an additional occasion during this interval. The most likely explanation for the apparent lack of impact of the AEP information on clinical outcomes in our study may be related to the fact that no specific attempt was made to influence the

physicians' management strategies. In the US study physicians were instructed to attempt to reduce drug load in patients with severe toxicity, whereas, in the present study physicians were simply asked to utilize all available information to optimize clinical response but were not specifically asked to reduce AED loads. The fact that our study, unlike the US study, enrolled exclusively patients with uncontrolled seizures may have also made physicians more reluctant to reduce drug treatment because of concerns about seizure deterioration.

In conclusion, our data indicate that, in a representative population of patients attending a tertiary referral centre in Brazil, the extent of overtreatment may be substantial and results in a toxicity burden higher than that reported in comparable populations from other regions. Our findings also confirm that in refractory epilepsy the adverse effects of treatment are highly prevalent and have a major negative impact on QOL. This evidence should alert physicians about the need to re-assess critically the balance between drug toxicity and seizure control, and to consider the benefits of a reduction in AED load. Interventions to reduce overtreatment should include not only a structured evaluation of adverse effects, but also educational programmes or other measures to ensure that all clinically available information is exploited fully for the patient's benefit. □

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