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Non-interventional surveillance study of adverse events in patients with epilepsy

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Objectives – Compare adverse events (AEs) in patients with epilepsy taking different antiepileptic drugs (AEDs) using standardized physician-completed questionnaires. *Materials and methods* – Multicenter, observational, cross-sectional study in epilepsy patients aged ≥4 , stable on 1–2 AED(s) for ≥3 months. *Results* – One thousand and nineteen patients were evaluated: 28.7% took newer, 71.3% older (or older + newer) AED(s); 56.9% monotherapy; 43.1% polytherapy. Overall, 68.3% reported ≥1 AE (61.3% newer; 71.1% older AEDs), most commonly: cognitive function disturbances, sedation, psychological problems. Patients taking newer AEDs were significantly less likely to report ≥1 AE (OR [95% CI]: 0.64 [0.46–0.89], $P = 0.008$). Treatment/dose changed at study visit: 22.8% (17.5% newer; 24.9% older AEDs) because of (newer/older); lack of efficacy (6.2%/7.8%); AEs (4.1/8.4%); absence of seizures (3.8/4.0%). Patients receiving levetiracetam or lamotrigine were significantly less likely to report AEs/modify treatment. *Conclusion* – Patients taking newer AEDs were significantly less likely to report AEs, although the non-randomized study design does not allow the lower rate of AEs to be attributed with certainty to the use of newer AEDs. A standardized AE questionnaire appeared useful for monitoring AEs/optimizing AED therapy.

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Key words: antiepileptic drugs; lamotrigine; levetiracetam; monotherapy; polytherapy; tolerability

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Introduction

Epilepsy is one of the most common serious neurological disorders, affecting approximately 50 million people worldwide (1). For patients with epilepsy, the goal of treatment is to achieve seizure freedom with minimal adverse events (AEs) (2–4), as both of these factors can contribute to treatment failure, and adversely affect quality of life (5–8).

Antiepileptic drugs (AEDs) may cause AEs, and many of these are easily overlooked in everyday clinical practice (9). Mattson et al. (2, 10) have used structured questionnaires to elicit patient concerns about systemic and neurological effects of AEDs throughout 1–3 years of follow-up. They and others have found that systematic assessment using standardized instruments may be helpful in identifying AEs, understanding patient needs, and guiding medication changes (2, 8–12).

Since the introduction of various new AEDs in the early 1990s, treatment options for epilepsy have increased dramatically (13, 14), and newer AEDs appear to be better tolerated than older AEDs (15–18). However, further research is needed to confirm the apparent improvement in tolerability offered by some of the newer AEDs (19). Overall, the AE profiles of AEDs are often determining factors in drug selection (19, 20). Also, monotherapy has been associated with fewer AEs than polytherapy (9, 11, 12).

The adverse Event SCAle in Patients with Epilepsy (aESCAPE) study explored the incidence and type of AEs experienced by patients with epilepsy treated with AEDs (grouped into older + newer AEDs, and monotherapy and polytherapy) in a systematic and standardized way and assessed the reasons for modifying AED therapy at the study visit.

Materials and methods

This was an observational, cross-sectional, multicenter, surveillance study (NCT00394927). All subjects (or their legal representatives) provided written informed consent before the study. If required by local regulations concerning non-interventional studies, written approval was obtained from a duly constituted Independent Ethics Committee and/or the relevant Regulatory Authorities.

Patients (aged ≥4) with a confirmed diagnosis of epilepsy and no other severe and/or uncontrolled symptomatic chronic illness, on stable AED treatment for ≥3 months with 1 or 2 AED(s) within the terms of marketing authorization, were eligible. Choice of medication was not influenced by the study protocol; patients taking the following AEDs were enrolled:

- Newer AEDs: gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), pregabalin (PGB), tiagabine (TGB), topiramate (TPM), zonisamide (ZNS) or any combination of these;
- Older AEDs: carbamazepine (CBZ), clobazam (CLB), clonazepam (CZP), phenobarbital (PB), phenytoin (PHT), valproate (VPA), a combination of two older AEDs or a combination of one older and one newer AED.

The division into older and newer AED groups for the purpose of data analysis was prospectively defined in the study protocol, and patients were allocated *a posteriori* to one of the two groups. An AE questionnaire developed for the longitudinal Veterans Administration Cooperative Studies (2, 10, 21, 22) was used in this study, and collected information includes baseline demographics; epilepsy characteristics; frequency of visits and type of physician consulted in the past year; treatment; AEs listed in the Neurological and Systemic Adverse Event Rating Scales (N&SAERS) [adapted from Cramer et al. (21)] considered by the treating physician as being associated with the current AED therapy; decision on the treatment strategy of the treating physician during the study visit, including reason(s) for any modification of treatment. Data were entered into the standardized questionnaire, completed by a treating physician (certified neurologist) based on the medical history, a regular physical and neurological examination, and a structured interview. Data from a single consultation were collected upon completion of the informed consent procedure with no further follow-up. The standardized questionnaire data were entered into an electronic database using a clinical data management system.

Outcomes

The primary outcome variable was the percentage of patients reporting ≥1 AE and the prevalence of each type of AE based on the N&SAERS. Other variables assessed were reasons for AED therapy modification at the study visit; baseline demographics and epilepsy characteristics; AED treatment; pattern of healthcare.

Statistical methods

The sample size was not determined via statistical considerations because of the exploratory nature of this cross-sectional surveillance study. All analyses were performed on the eligible population, defined as all patients included in this surveillance study who took 1 or 2 AEDs: AEDs were grouped by patients who received only newer AED(s) vs those receiving older AED(s) (including a combination of an older + newer AED); and by patients receiving monotherapy vs those receiving polytherapy.

The primary outcome analysis consists of descriptive presentations of the percentage of patients who reported ≥1 AE as described in the N&SAERS. The percentage of patients who reported ≥1 AE as described in the N&SAERS by type of physician and frequency of visits was also assessed. Logistic regression models on the presence of ≥1 AE were performed, including a number of explanatory variables: type of treatment (polytherapy vs monotherapy, newer vs older AEDs), frequency of visits (considered as a continuous variable), type of physician (neurologist/psychiatrist/epileptologist vs not, internal medicine physician vs not, general practitioner vs not, geriatrician/pediatrician vs not, other practitioner vs not), and individual selected AEDs (CBZ vs not, VPA vs not, OXC vs not, LTG vs not, LEV vs not).

Summary statistics for the decision to modify treatment at the study visit (no change, change of AED, change of dose, change [AED or dose]) are presented. Logistic regression models on the proportion of patients modifying treatment were performed, including a number of explanatory variables: type of treatment (polytherapy vs monotherapy, newer vs older AEDs), presence vs absence of AEs, generalized vs not generalized seizures, time since last seizure (≥1 vs < 1 year ago), presence vs absence of various AEs, and individual AEDs.

Results

Patients

One thousand and nineteen patients were recruited between 18 April and 8 August 2007 by 62 physicians in the Czech Republic (31.4%), Poland (30.3%), Romania (17.2%), Germany (16.2%), Italy (4.2%), and Spain (0.7%). Demographics and clinical characteristics were largely similar across groups, although AED polytherapy patients tended to have had their last seizure more recently (Table 1). The majority of patients were taking older AED(s) (or a combination: older + newer) (71.3% vs 28.7% on newer AED[s]). A total of 56.9% patients were on monotherapy and 43.1% on polytherapy; 47.7% patients were taking VPA. The most common treatments were VPA (24.0%), CBZ (12.1%), and LTG (8.2%) monotherapy, then combinations of LTG + VPA (8.1%) and LEV + VPA (6.0%), then OXC monotherapy (5.0%).

AEs

AED-related factors – Overall, 68.3% of patients reported ≥1 AE, 58.1% ≥1 neurological AE, and 39.6% ≥1 systemic AE (Fig. 1). Patients on newer

Table 1 Demographics and epilepsy characteristics

	Overall (*N* = 1019)	Newer AEDs (*N* = 292)	Older AEDs[a] (*N* = 727)	Monotherapy (*N* = 580)	Polytherapy (*N* = 439)
Age,[b] mean ± SD (years)	31.5 ± 19.2	31.7 ± 19.0	31.4 ± 19.3	30.3 ± 20.0	33.1 ± 18.1
Age class,[b] *n* (%)					
4–<16 years	255 (25.2)	65 (22.4)	190 (26.3)	166 (28.9)	89 (20.3)
≥16–<55 years	616 (60.8)	183 (63.1)	433 (59.9)	324 (56.3)	292 (66.7)
≥55 years	142 (14.0)	42 (14.5)	100 (13.8)	85 (14.8)	57 (13.0)
Male,[c] *n* (%)	485 (47.6)	117 (40.1)	368 (50.6)	276 (47.6)	209 (47.6)
Age at epilepsy onset,[d] median (Q1–Q3) (years)	13 (7–23)	14 (8–24)	12 (7–22)	14 (7–24)	12 (6–22)
Duration since last seizure, median (Q1–Q3) (months)	7.7 (1.4–23.0)	7.0 (1.5–19.5)	8.0 (1.3–24.0)	12.5 (4.0–29.1)	4.0 (0.7–11.0)
Time since last treatment modification,[e] median (Q1–Q3) (months)	13 (6–27)	12 (6–21)	14 (6–30)	14 (6–32)	12 (6–24)
Type of Seizure, *n* (%)					
None reported	6 (0.6)	2 (0.7)	4 (0.6)	4 (0.7)	2 (0.5)
Partial	690 (67.7)	218 (74.7)	472 (64.9)	361 (62.2)	329 (74.9)
Simple partial	127 (12.5)	47 (16.1)	80 (11.0)	59 (10.2)	68 (15.5)
Complex partial	307 (30.1)	94 (32.2)	213 (29.3)	138 (23.8)	169 (38.5)
Partial onset with secondary generalization	468 (45.9)	138 (47.3)	330 (45.4)	242 (41.7)	226 (51.5)
Primary generalized	352 (34.5)	81 (27.7)	271 (37.3)	224 (38.6)	128 (29.2)
Absence	68 (6.7)	12 (4.1)	56 (7.7)	39 (6.7)	29 (6.6)
Myoclonic	61 (6.0)	15 (5.1)	46 (6.3)	28 (4.8)	33 (7.5)
Clonic	3 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Tonic	19 (1.9)	5 (1.7)	14 (1.9)	11 (1.9)	8 (1.8)
Tonic–clonic	247 (24.2)	55 (18.8)	192 (26.4)	152 (26.2)	95 (21.6)
Atonic	26 (2.6)	5 (1.7)	21 (2.9)	19 (3.3)	7 (1.6)
AED medication, *n* (%)					
VPA	486 (47.7)	NA	486 (66.9)	245 (42.2)	241 (54.9)
CBZ	241 (23.7)	NA	241 (33.1)	123 (21.2)	118 (26.9)
LTG	223 (21.9)	123 (42.1)	100 (13.8)	84 (14.5)	139 (31.7)
LEV	182 (17.9)	91 (31.2)	91 (12.5)	31 (5.3)	151 (34.4)
OXC	114 (11.2)	89 (30.5)	25 (3.4)	51 (8.8)	63 (14.4)
TPM	94 (9.2)	57 (19.5)	37 (5.1)	28 (4.8)	66 (15.0)
PB	41 (4.0)	NA	41 (5.6)	4 (0.7)	37 (8.4)
Other[f]	77 (7.6)	21 (7.2)	56 (7.7)	14 (2.4)	63 (14.4)
AEDs, *n* (%)					
1 older	377 (37.0)	–	377 (51.9)	377 (65.0)	–
1 newer	203 (19.9)	203 (69.5)	–	203 (35.0)	–
2 older	77 (7.6)	–	77 (10.6)	–	77 (17.5)
2 newer	89 (8.7)	89 (30.5)	–	–	89 (20.3)
1 older + 1 newer	273 (26.8)	–	273 (37.6)	–	273 (62.2)

[a]Included one older and one newer AED.

[b]Age data were missing for six patients.

[c]Gender data were missing for three patients.

[d]Age at onset data was missing for nine patients.

[e]Time since last treatment modification data was missing for five patients.

[f]CLB, CZP, GBP, PGB, PHT, TGB, ZNS.

AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; GBP, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PB, phenobarbital; PGB, pregabalin; PHT, phenytoin; Q1 (25th percentile); Q3 (75th percentile); SD, standard deviation; TGB, tiagabine; TPM, topiramate; VPA, valproate; ZNS, zonisamide.

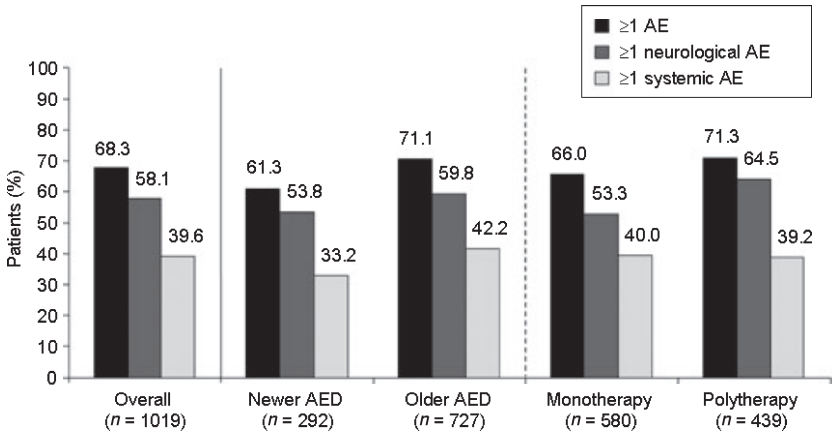

Figure 1. Percentages of patients reporting ≥1 AE, ≥1 neurological AE and ≥1 systemic AE. AE, adverse event; AED, antiepileptic drug.

AED(s) were less likely to report ≥1 AE than those on older AED(s) (61.3% vs 71.1%) and were also less likely to report ≥1 neurological or ≥1 systemic AE. Patients on monotherapy were less likely to report ≥1 AE than those on polytherapy (66.0% vs 71.3%) and were also less likely to report ≥1 neurological AE (Fig. 1). Of the patients on monotherapy, fewer patients on newer AEDs reported ≥1 AE (125/203; 61.6%) than those on older AEDs (258/377; 68.4%). The percentage of patients reporting ≥1 AE, ≥1 neurological AE, or ≥1 systemic AE on monotherapy or polytherapy is shown in Table 2 for AEDs that were taken as monotherapy by >30 patients (CBZ, LEV, LTG, OXC and VPA). The numbers (percentages) of patients with ≥1 AE in descending order were OXC 35/51 (68.6%), VPA 162/245 (66.1%), CBZ 89/123 (72.4%), LTG 49/84 (58.3%), and LEV 16/31 (51.6%). Among patients on monotherapy, the highest incidence of neurological AEs was reported in patients on OXC (34/51; 66.7%) and CBZ (79/123; 64.2%), while systemic AEs were more frequently reported in VPA-treated (119/245; 48.6%) and LTG-treated (29/84; 34.5%) patients.

Logistic regression analysis found that patients were significantly less likely to report ≥1 AE if they were on newer AED(s) compared to older AED(s) (OR [95% CI]: 0.64 [0.46–0.89], $P = 0.008$; Fig. 2), and there was a trend toward patients being more likely to report ≥1 AE if they were on polytherapy compared with monotherapy (OR [95% CI]: 1.23 [0.89–1.68], $P = 0.207$; Fig. 2). Patients on LTG or LEV, whether as monotherapy or part of polytherapy, were significantly less likely to report ≥1 AE than those not on LTG or LEV, respectively (LTG: OR [95% CI]: 0.51 [0.31–0.84], $P = 0.008$; LEV: OR [95% CI]: 0.33 [0.19–0.56], $P < 0.001$; Fig. 3).

Overall, the most commonly reported AEs were disturbances in cognitive function (28.0%), sedation (27.9%), psychological problems (26.1%), weight changes (19.3%), tremor (15.4%), and headache (11.0%) (Table 3). Of the AEs that could be rated in terms of severity, most were mild-to-moderate. Compared to patients on newer AEDs, those on older AEDs reported significantly more disturbances in cognitive function, sedation, tremor, and hair changes. Compared with monotherapy, polytherapy was associated with significantly more disturbances in cognitive function, psychological problems, tremor, gait problems, and drug-related gastrointestinal problems. Although

Table 2 Percentages of patients on CBZ, LTG, LEV, OXC or VPA monotherapy or polytherapy reporting ≥1 AE, ≥1 neurological AE and ≥1 systemic AE

	Monotherapy				Polytherapy			
AED medication	*N*	≥1 AE (%)	≥1 neurological AE (%)	≥1 systemic AE (%)	*N*	≥1 AE (%)	≥1 neurological AE (%)	≥1 systemic AE (%)
CBZ	123	72.4	64.2	32.5	118	76.3	71.2	38.1
VPA	245	66.1	49.8	48.6	241	73.4	64.3	39.8
OXC	51	68.6	66.7	27.5	63	71.4	71.4	46.0
LTG	84	58.3	45.2	34.5	139	66.9	59.0	36.7
LEV	31	51.6	45.2	25.8	151	60.3	53.0	25.8

AE, adverse event; AED, antiepileptic drug; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; VPA, valproate.

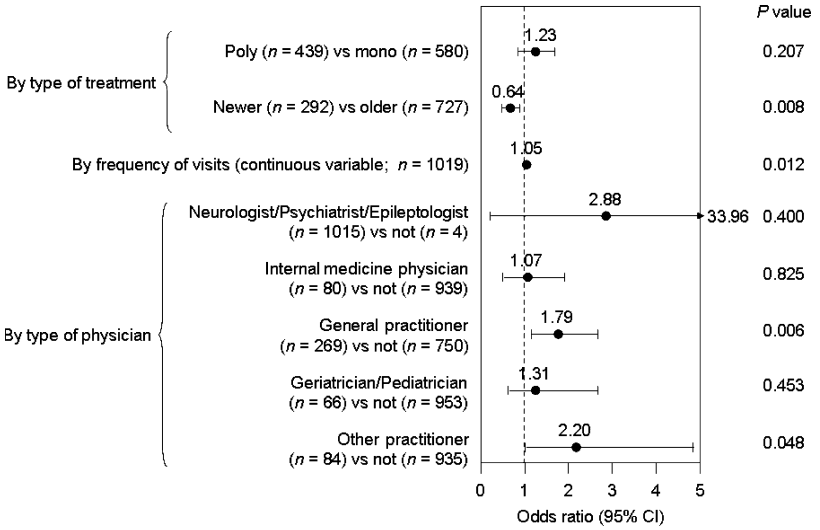

Figure 2. Logistic regression on the proportion of patients with ≥1 AE by type of treatment, frequency of visits (as a continuous variable), and type of physician (visited during the last year). AE, adverse event; CI, confidence interval.

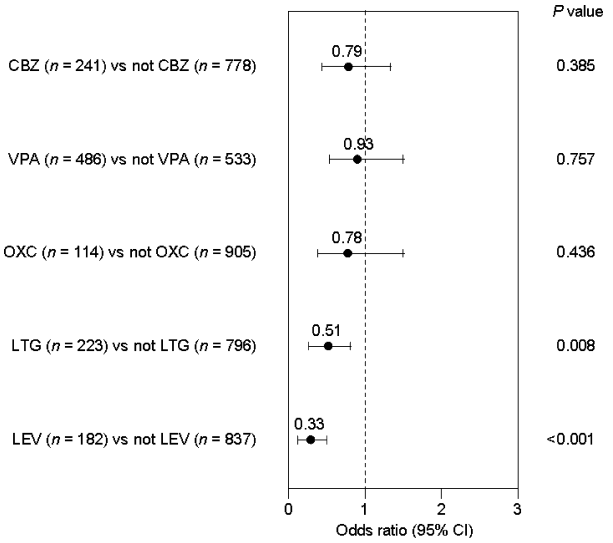

Figure 3. Logistic regression on the proportion of patients with ≥1 AE, by individual AED. AE, adverse event; CBZ, carbamazepine; CI, confidence interval; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; VPA, valproate.

weight changes were comparable among groups, older AEDs resulted in more weight gain (18.0% vs 8.6% newer AEDs), while newer AEDs resulted in more weight loss (7.9% vs 2.5% older AEDs).

Treatment modifications

A treatment modification was decided during the study visit for 22.8% patients (13.4% dose change; 9.3% AED change) (Fig. 4). Fewer patients on newer AEDs and monotherapy changed treatment than those on older AEDs and polytherapy. Of those that changed AED, the main reasons were AEs (51.6%) and lack of efficacy (27.4%). Of those that changed dose, the main reasons were lack of efficacy (35.8%), absence of seizures (25.5%), AEs (17.5%) or fear of breakthrough seizures (16.8%).

Logistic regression analysis found that patients were significantly less likely to modify treatment if they had their last seizure ≥1 vs < 1 year ago (OR [95% CI]: 0.39 [0.27–0.57], $P < 0.001$), and there was a trend toward fewer treatment modifications if they were treated with newer AED(s) vs older AED(s) (OR [95% CI]: 0.81 [0.55–1.18], $P = 0.265$). There was a trend for patients to be more likely to modify treatment if they were presented with ≥1 vs no AE(s) (OR [95% CI]: 1.48 [0.99–2.22], $P = 0.055$); or they were on polytherapy vs monotherapy (OR [95% CI]: 1.29 [0.93–1.81], $P = 0.132$). Type of seizure did not affect the likelihood of treatment modification (partial vs generalized: OR [95% CI]: 1.03 [0.73–1.47], $P = 0.860$; partial vs partial + generalized: OR [95% CI]: 1.07 [0.45–2.53], $P = 0.884$).

Tremor was the only individual AE that significantly increased the chance of treatment modification (OR [95% CI]: 1.74 [1.17–2.58], $P = 0.006$). Other AEs showed a trend toward increased chance of treatment modification (OR [95% CI]): sedation (1.32 [0.93–1.89], $P = 0.124$); psychological disturbances (1.28 [0.87–1.87], $P = 0.204$); and disturbance in cognitive function (1.22 [0.84–1.79], $P = 0.297$).

Patients taking LTG or LEV (as monotherapy or part of polytherapy) were significantly less likely to change treatment than patients not taking LTG

Table 3 Incidence of AEs reported by >5% of patients in any group

	Overall (*N* = 1019)	Newer AED (*N* = 292)	Older AED (*N* = 727)	Mono-therapy (*N* = 580)	Polytherapy (*N* = 439)
Neurological AEs (%)					
Disturbance in cognitive function	28.0	21.9	30.4**	21.9	36.0***
Sedation	27.9	22.6	30.0*	25.5	31.0
Psychological problems[a]	26.1	25.0	26.5	22.1	31.4***
Tremor	15.4	9.9	17.6**	11.2	21.0***
Drug-related headache	11.0	12.0	10.6	10.7	11.4
Gait problems, abnormal walking	9.2	8.6	9.5	7.2	11.8*
Drug-related dizziness/lightheadedness	8.6	9.9	8.1	7.4	10.3
Dysarthria	4.8	4.5	5.0	3.3	6.8
Diplopia	4.6	5.5	4.3	3.1	6.6
Systemic AEs (%)					
Gain or loss of weight because of increase or decrease in appetite related to AED	19.3	16.4	20.5	20.7	17.5
Changes in hair quantity/texture since starting drug	9.0	5.5	10.5*	7.8	10.7
Drug-related GI problems	8.6	6.5	9.5	6.7	11.2*
Arthralgia	5.4	4.8	5.6	6.6	3.9
Dental	5.2	2.1	6.5	4.8	5.7
Skin reaction to drug	4.2	6.2	3.4	3.6	5.0

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

[a]Depression, tension/agitation, anger/hostility, vigor/excitability, fatigue/apathy, confusion/thought disorder.

AE, adverse event; AED, antiepileptic drug; GI, gastrointestinal.

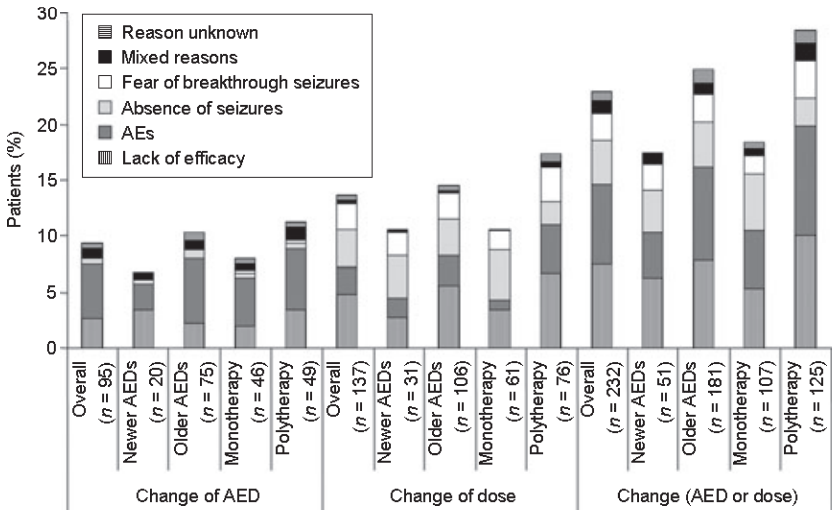

Figure 4. Percentages of patients with treatment modifications decided during the study visit. AE, adverse event; AED, antiepileptic drug.

or LEV, respectively (OR [95%CI]): LTG 0.52 [0.32–0.85], $P = 0.009$; LEV: 0.33 [0.19–0.57], $P < 0.001$). The chance of treatment modification was not significantly affected by the use, or not, of CBZ, VPA, or OXC.

Discussion

This observational, multicenter study of patients who had been on stable regimens for a median of 13 months indicates that AEs are common among patients taking AEDs. The study also demonstrated the utility of the structured questionnaire as a template for physicians to elicit comments about common AEs and optimize treatment.

Studies have shown that more AEs are identified in patients taking AEDs when a questionnaire is used (12) and an AE checklist should be used during routine care of all patients on AEDs (8, 9, 12). Data from this study have demonstrated the usefulness of asking specific questions to elicit patient concerns about AEs. More importantly, the information provided to physicians led to changes in the AED treatment regimen to accommodate

both seizure control and comfort with the AE burden imposed by treatments. We believe that during follow-up of patients with epilepsy, the systematic collection of AE data should become as routine as the collection of information about seizures, to evaluate the full benefit vs burden of the AED regimen in long-term use.

Among patients with epilepsy, seizures and AEs affect quality of life. However, the relative importance of each is poorly defined. Although seizure reduction is assumed to be important to patients (23), it may be only complete seizure freedom that improves quality of life (24). A recent study has reported that patients with more remote seizures are most concerned about seizure control, while patients with more recent seizures are more sensitive to AEs (7).

The questionnaire administered in this study during routine patient consultation, along with neurological and physical examinations, showed that AEs were a common problem of AED therapy, with 68.3% of patients reporting ≥1 AE (mostly mild or moderate). This is in line with results from Carreño et al. (12), where 65% of patients (≥18 years) reported mild-to-moderate AEs when administered a checklist (compared to 34% spontaneously). The most frequently reported AEs in the aESCAPE study were disturbances in cognitive function (28.0% overall; significantly higher in patients on older vs newer AEDs and on polytherapy vs monotherapy), sedation (27.9% overall; significantly higher on older vs newer AEDs), and psychological problems (26.1% overall; significantly higher in patients on polytherapy vs monotherapy). Similar results were found by Carreño et al. (12), who reported that the most frequently reported AEs with the aid of a checklist were cognitive problems and tiredness. Interestingly, without the use of the checklist, the most frequently reported AEs were tremor, fatigue, and dizziness (12). In a study by Carpay et al. (11), 60% of patients reported AEs in at least three domains (most frequently: general central nervous system-related complaints [68%] and cognitive complaints [62%]). A recent study by Hessen et al. (25) involving 139 patients with epilepsy demonstrated significant impairment in neuropsychological functions such as verbal fluency and response inhibition as a consequence of AED monotherapy.

In the current study, patients taking newer AEDs were significantly less likely to report ≥1 AE than those taking older AEDs (OR 0.64, $P = 0.008$). This is consistent with the generally accepted idea that the newer AEDs appear to be better tolerated than older AEDs (15–19). Indeed, switching from older AEDs to newer AEDs because of insufficient efficacy or AEs has been reported to improve seizure control and quality of life in patients with epilepsy (26). In our study, patients treated with LEV or LTG were significantly less likely to report ≥1 AE and to change treatment at the study visit than those not treated with LEV or LTG, respectively. A review of long-term open-label studies has shown LEV and LTG to be significantly better tolerated than GBP and TPM, in terms of withdrawals because of AEs (27). A randomized study in elderly patients has found that fewer patients treated with LTG discontinued because of AEs than those treated with CBZ or GBP (22). In a recent study assessing long-term retention rates in 222 patients with focal epilepsy, the 3-year retention rate was substantially higher with LTG, LEV, and TPM compared with GBP and TGB (28). Retention rates are often viewed as providing a clinically meaningful composite of both efficacy and safety of a drug over time.

In the current study, patients on polytherapy showed a trend toward being more likely to report ≥1 AE than those on monotherapy (OR 1.23, $P = 0.207$). This is in line with previous reports in adult patients that polytherapy is associated with significantly more AEs than monotherapy (9, 11, 12), and polypharmacy reduction has a favorable effect on patient satisfaction (29). Monotherapy also has the added advantages of potentially improving compliance and reducing cost (30).

The use of an AE questionnaire has been shown to significantly increase the number of patients whose AED treatment was changed (8). In our study, treatment modifications occurred at the study visit after the N&SAERS review for almost a quarter of patients. Of those who had treatment modifications, approximately one-third were mainly related to lack of efficacy and one-third were mainly related to AEs. These results are similar to those reported by Carreño et al. (12), where treatment was changed in a quarter of patients, mainly because of lack of efficacy (60%) and AEs (24%). In our study, being seizure-free for ≥1 year and taking either LEV or LTG significantly reduced the chance of altered medication, while presence of tremor significantly increased the chance of medication change. Although not significant, use of newer AEDs, monotherapy, and absence of AEs all reduced the likelihood of medication change.

The main limitation of this study is that it was observational and cross-sectional. Although non-interventional studies can provide a good basis for characterizing associations between different vari-

ables, making cause-and-effect inferences in the absence of randomized controlled trial data can be problematic: all patient's characteristics are not, by default, balanced between the groups, potentially leading to confounding factors. Non-interventional studies can be difficult to analyze and interpret because of the heterogeneity of real-life patient populations and the lack of standardized treatment regimens. Cross-sectional studies are limited by the fact the assessments are performed at one time-point and give no indication of the change over time. It is therefore impossible to infer causality. Although treatment modification (dose or treatment change) was implemented in 22.8% of patients participating in the study, as there was no follow-up assessment, the outcome of the treatment changes made is unknown. Many patients were evaluated at a single visit, but only a limited amount of information was collected. The 'older AED' group also included patients on one older and one newer AED. This approach places all AEDs against 'new AEDs' to avoid over interpretation of their usefulness. Other limitations were lack of control group (all patients were receiving AEDs) and reliability of the structured interview for younger patients (albeit a small number). In addition, as the patient's own physician completed the interview and the treatments were known, some degree of bias may have arisen. This is because the physician may have been more likely to attribute specific AEs to individual AEDs, based on their own clinical experience of using the drug. Finally, different patterns of healthcare use across the six European countries in which the study was conducted may have increased variability; however, the results of individual countries were not compared in this study.

In conclusion, these data provide evidence that patients treated with newer AEDs are significantly less likely to report ≥1 AE than those treated with older AEDs (including a combination of older + newer AEDs), although the non-randomized, cross-sectional study design does not allow the lower rate of AEs to be attributed with certainty to the use of newer AEDs. Among these patients who had been on a stable dose regimen for a median of 13 months, treatment alterations occurred at the study visit for 23%. Patients on the newer AEDs, LEV or LTG, as either monotherapy or part of polytherapy, were significantly less likely to report AEs or change treatment. Overall, a standardized AE instrument appears to be useful for monitoring AEs and in supporting the patient and treating physician in making informed treatment decisions, thus optimizing AED therapy.

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Disclosure of conflicts of interest

Joyce A. Cramer is a consultant for Eisai, Ortho McNeil Neurologics, Pfizer, and UCB. Christel Baukens is an employee of UCB. Sonja Buyle was an employee of UCB at the time of the study, statistical analysis, and the initiation of the manuscript. Pasquale Striano has been a speaker for UCB at the 2009 National congress of the Italian League Against Epilepsy. Arnfin Bergmann is a consultant for sanofi-aventis. Barbara Steinborn, Lenka Hlinkova and Iuliu Bacos have no conflicts of interest.

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