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Self-reported feelings of anger and aggression towards others in patients on levetiracetam: data from the UK antiepileptic drug register

Udo Carl Wieshmann,[1] Gus A Baker[2]

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[1]The Walton Centre for Neurology and Neurosurgery, Liverpool, UK
[2]Department of Neurosciences, University of Liverpool, Liverpool, UK

Correspondence to
Dr Udo Carl Wieshmann; udo.wieshmann@btinternet.com

ABSTRACT

Objectives: To ascertain the frequency of self-reported anger and depression in levetiracetam (LEV).

Design: We compared patients with epilepsy (PWE) taking LEV with PWE taking other antiepileptic drugs (AEDs).

Setting: All PWE and controls submitted information to the UK AED register.

Participants: We analysed the data of 418 PWE and 41 control participants. 158 participants took LEV in monotherapy or as part of polypharmacotherapy, 260 PWE took other AED.

Primary and secondary outcome measures: All PWE and controls completed the Liverpool Adverse Event Profile (LAEP) which includes items on anger and depression quantified on a four-point Likert scale, with 1 indicating that there was never a problem; 2, rarely a problem; 3, sometimes a problem and 4, always or often a problem.

Results: 49% of PWE on LEV and 39% on AED other than LEV reported anger as sometimes or always being a problem (p=0.042). 48% of PWE on LEV and 45% on AED other than LEV reported depression as sometimes or always being a problem (p=0.584). 7% of control participants reported anger as sometimes being a problem and 93% reported anger as never or rarely being a problem. Depression was never a problem in 75% of controls and rarely a problem in 25%.

Conclusions: Anger and depression were more frequently reported as a problem by PWE than by control participants. Our observational register of self-reported symptoms suggested anger being more often a problem in patients taking LEV than in PWE taking other AED. PWE should be informed about this potential problem of LEV.

ARTICLE SUMMARY

Article focus

- Levetiracetam (LEV) is a new and widely used antiepileptic drug (AED).
- We used data from the UK AED register to study the link between LEV and anger.

Key message

- Forty-nine per cent of patients on LEV reported anger as being sometimes or always a problem.

Strengths and limitations of this study

- Adverse effects were self-reported, the register is observational.
- Nevertheless, our register offered insight into the adverse effects of LEV.

INTRODUCTION

Levetiracetam (LEV) is licensed for monotherapy and adjunctive treatment of focal seizures with or without secondary generalisation, for adjunctive therapy of myoclonic seizures in patients with juvenile myoclonic epilepsy and primary generalised tonic–clonic seizures in the UK. LEV is widely used. The market share of LEV in the US measured in drug costs was 15% in 2008 (http://www.wikinvest.com/wiki/Antiepileptic _Drug_Market, accessed 30 Jun 2012). Overall, LEV is a good antiepileptic drug (AED) compared with other AED in terms of rash risks, side effects on liver and kidney and drug interactions. Unfortunately, LEV can have psychiatric adverse effects including irritability, anger, agitation, aggressive behaviour and depression.[1–4] It has been estimated on the basis of collective evidence that 12–15% of all patients will suffer psychiatric side effects[1] but compared with our clinical experience this seemed low. Feelings of anger seemed to be a particular problem, but were often only reported on direct questioning because the patients were embarrassed. The aim of our study was to find out how many patients with epilepsy (PWE) on LEV were suffering from anger. Because doctors may underreport adverse effects[5] we obtained the information directly from the patients using a self-referral register.

METHODS

The UK AED Register is a prospective register to study the efficacy and adverse effects of AED. The register was established at The Walton Centre for Neurology and Neurosurgery, Liverpool in July 2008. Anybody who takes AED can self-refer to the register. The register is independent from the pharmaceutical industry. The register has been approved by the Liverpool North Regional Ethics committee. For the current analysis we included all participants with complete datasets. At the time of the analysis we had 459 participants; 158 patients on LEV in monotherapy or as part of polytherapy, 260 patients on AED other than LEV including carbamazepine, lamotrigine (LTG), topiramate, zonisamide, phenytoin and phenobarbitone and 41 control participants. The control participants were employees at The Walton Centre, students at Liverpool University or patients with single seizures or very infrequent seizures not taking AED. All the data were collected using the Liverpool Adverse Event Profile (LAEP) questionnaire, which was completed by the patients either electronically via http://www.ukaed/info or in paper form in the Mersey Regional Epilepsy clinic at the Walton Centre in Liverpool. The variables recorded in LAEP include 19 self-reported symptoms. It is possible to analyse the scores of individual symptoms as well as calculate overall symptom score. The LAEP includes items on anger and depression quantified on a four-point Likert scale, with 1 indicating that there was never a problem; 2, rarely a problem; 3, sometimes a problem and 4, always or often a problem.[6] The complete dataset is available on request.

We also collected age, gender, epileptic syndrome, severity of epilepsy, number of seizures in the last 4 weeks and other health problems, AED and other medication. We calculated the frequency of aggression occurring sometimes or always in patients on LEV and patients on other AED, and applied the χ^2 test to test for associations of aggression with LEV. We did the same for the item depression.

RESULTS

Forty-nine per cent of patients on LEV and 39% on AED other than LEV reported anger as sometimes or always being a problem (p=0.042). Forty-eight per cent of patients on LEV and 45% on AED other than LEV reported depression as sometimes or always being a problem (p=0.584). In patients taking LEV <1000 mg/day, anger was reported as sometimes or always occurring in 43% and in patients taking LEV >1000 mg/day in 52% (p=0.265). Anger occurred in LEV monotherapy in 48% and polytherapy in 50% (p=0.889). There was a trend for patients on LEV to be less likely to be seizure free than patients on other AED.

Seven percent of control participants reported anger as sometimes being a problem, 93% reported anger as never or rarely being a problem. Depression was never a problem in 75% of controls and rarely a problem in 25%. The clinical characteristics of the patients are shown in table 1.

DISCUSSION

We found a small but statistically significant increase in self-reported anger in patients on LEV in monotherapy and polytherapy compared with patients on other AED.

Table 1 The clinical characteristics of the patients

	LEV n=158 median dose 2000 mg/day	No LEV n=260
Gender (f/m)	93/65	139/121
Age (mean (SD) (years))	41.15 (14.88)	42.03 (14.37)
Epilepsy (partial/generalised)	124/34	204/56
Seizure control (seizure free/seizures) (ns)	10/148	29/231
Monotherapy	27	126
2 AED	78	87
3 or more AED	53	47
Adjunctive AED (median dose (mg/day))		
Carbamazepine	43 (800)	92 (800)
Sodium valproate	25 (1600)	67 (1200)
Lamotrigine	43 (400)	92 (300)
Phenytoin	23 (300)	34 (300)
Clobazam	19 (20)	38 (20)
Topiramate	10 (300)	41 (200)
Zonisamide	9 (400)	13 (300)
Primidone	3 (375)	4 (750)
Gabapentin	2 (600)	5 (1200)
Lacosamide	1 (400)	4 (225)
Phenobarbitone	3 (120)	8 (75)
Clonazepam	1 (1.5)	5 (0.5)
Other*	6	12

*Other drugs were rufinamide, pregabalin, escitalopram, diazepam, nitrazepam, lorazepam, piracetam, ethosuximide and acetazolamide.
f/m, female/male; LEV, levetiracetam; ns, not significant.

About half of all patients on LEV reported anger as sometimes or always being a problem. Depression was not significantly associated with LEV. The regulatory trials suggested that LEV influenced affect. Symptoms including agitation, hostility, anxiety, apathy, emotional lability, depersonalisation and depression were reported in 13.3% of patients taking LEV and their standard AED medication compared with 6.2% of patients taking placebo and their standard AED medication.[7] Regulatory trials are not ideal for determination of behavioural adverse effects, as patients on antidepressants and major tranquillisers are often excluded from the trials. LEV has been associated with anger. Many studies reported irritability, anger, agitation, aggressive behaviour and depression in patients taking LEV,[1–4 8] but the incidence of these adverse effects was considered to be relatively low at 12–15%.[1] In our study the prevalence of self-reported anger was much higher. There are a number of possible explanations; doctors may be unaware of relatively subtle mood changes, they may fail to report them or patients may be too embarrassed to spontaneously report anger. In a previous small study using the LAEP we also found a disturbingly high prevalence of self-reported adverse effects suggesting that the burden of taking AED is perhaps much higher than that widely assumed by doctors.[9] This study also showed that even in monotherapy LEV was overall not better tolerated than older AED but had a different adverse effect profile. Feelings of anger were reported as always occurring in 33% of patients on LEV as opposed to 19% on sodium valproate, 16% on carbamazepine and 15% LTG, in keeping with our current study (9). That anger is a particular problem in LEV has also been suggested by a randomised prospective study comparing LEV with LTG.[10]

LEV is a very unusual AED with a probable unique mode of action and is arguably one of the most effective new AED. LEV has a good adverse effect profile. There is low liver toxicity and lack of allergic skin reactions. LEV is likely to have a low teratogenic risk. In addition, LEV has no interactions with the anticontraceptive pill,[11–13] LEV will remain an important AED and will potentially even become a first-line drug in some epileptic syndromes such as juvenile myoclonic epilepsy in women. Having said this, it is important to advise PWE about the potential of affective changes, in particular aggressive moods.

In our unblinded observational study on the effects of LEV on mood we could not exclude all confounding factors. The information came from the patients directly and not as in conventional custom via a physician. Our study therefore critically relied on the truthfulness of the patients. In addition, the median dose of some drugs such as sodium valproate, LTG, topiramate and zonisamide were higher in patients on LEV than in patients not on LEV. There was also a trend for patients on LEV to be less likely seizure free (table 1). LEV was used as second (or third) line drug in those patients with more difficult to control seizures. This must likely have introduced bias and may have affected our findings. Having said this, our data reflected current clinical practice. There are a number of unanswered questions which could be addressed in future studies. These include the effect of LEV on affective changes in monotherapy inpatients with relatively mild epilepsy, the effect of LEV on anger in patients with symptomatic epilepsy and hippocampal sclerosis and the effect of LEV on anger in patients who take LEV and topiramate or zonisamide.

It has to be kept in mind that we have selectively chosen to analyse LEV from our data pool. It is likely that analysing other AED would also demonstrate problems in one or more areas covered by the LAEP. In addition, the risk of adverse effects has to be carefully balanced against the risk of seizures. Patients should be encouraged to take their medication. After all, half of all patients on LEV did not report anger. Nevertheless, PWE should be made aware of this potential problem.

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Contributors UCW and GAB conceived the idea of the UK Antiepileptic Drug (AED) register and the study. UCW was responsible for the data analysis and produced the table. The initial draft of the manuscript was prepared by UCW and then reviewed and amended by GAB. All authors read and approved the final manuscript.

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Competing interests None.

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