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The EULEV cohort study: rates of and factors associated with continuation of levetiracetam after 1 year

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Levetiracetam has shown good safety/tolerability and efficacy in regulatory trials. This was confirmed in observational investigations performed soon after marketing by using continuation or retention rates as a composite measure.
- When an anti-epileptic drug first becomes available; however, there is evidence of channelling to more severe patients than thereafter.

WHAT THIS STUDY ADDS

- This study was performed several years after marketing of levetiracetam and found high rates of continuation.
- It also further explores this measure by determining the continuation in the absence of initiation of additional anti-epileptic drugs.

AIMS

To investigate real-life effectiveness of levetiracetam in patients initiating treatment in a stable market situation.

METHODS

Epileptic adults who had initiated levetiracetam between 1 January and 31 August in 2005 or 2006 were included and followed for 1 year by hospital or nonhospital neurologists practising in France. One-year continuation rates were estimated using Kaplan–Meier analysis. Among those still treated at end of study, treatment goals were investigated. Factors associated with discontinuation were investigated using Cox proportional hazards regression.

RESULTS

A total of 794 subjects were included in the cohort, and 753 subjects were followed up and included in the analysis. Among these, mean (SD) age was 42.6 (±17.0) years, 51.1% were female, 76.6% had partial epilepsy, 93.5% had seizures in the 6 months preceding levetiracetam initiation and 82.9% had at least one concomitant anti-epileptic drug when starting levetiracetam. One-year levetiracetam continuation rate was 83.5% (95% confidence interval, 80.5–86.0%). Of the 579 patients still using levetiracetam at end of study, 46.8% were seizure free during the last 6 months, and 24% were on levetiracetam monotherapy. Reasons for discontinuation (n = 122) were adverse events (45%), lack of efficacy (38%) or both (9%). Levetiracetam discontinuation was most strongly associated with previous exposure to more than four anti-epileptic drugs, whereas continuation was most strongly associated with presence of seizure-related falls in the 6 months preceding levetiracetam initiation.

CONCLUSIONS

This population-based cohort study in a stable market situation found a high 1 year levetiracetam continuation rate compared with previous studies done sooner after market introduction.

Introduction

The antiepileptic drug (AED) levetiracetam [1] was granted European marketing authorization in September 2000 for the adjunctive treatment of partial onset seizures with or without secondary generalizations in adults with epilepsy, and subsequently to monotherapy in 2006 [2]. During the premarketing clinical trials used to obtain the marketing authorization, it showed good safety, tolerability and efficacy [3–5], but these do not provide the information on postmarketing effectiveness that is increasingly requested for regulatory decision making. For this, pragmatic clinical trials or purely observational designs are more suited [6]. Several observational postmarketing studies performed in the USA and several European countries have sought to fill this gap in understanding [7–16]. Many studies used continuation (retention) rates to measure effectiveness [8–11, 13–16], considered a powerful composite measure of efficacy and tolerability [17]. A common approach employed by studies that did not select a particular population was to include all patients in one (or two associated) clinics initiating levetiracetam over a 2–3 year period following marketing [7–11]. However, during this initial phase, levetiracetam may have been channelled to more severe patients, as reported for lamotrigine when it was first introduced [18]. It has been shown that the 'early adopters' of new drugs may be very different from the prescribers and patients in the later stages of a product's market life [19].

We therefore designed this study to describe the effectiveness of levetiracetam in real-life medical practice in France after several years of market presence, when it can be expected that prescribing becomes less affected by channelling. This study was initiated at the request of the French National Regulatory Authorities.

Methods

Study design

All hospital and nonhospital neurologists in France, identified using a national register of healthcare professionals (CEGEDIM), were contacted by mail in September 2005. Those accepting the invitation to participate were asked to identify retrospectively all patients first prescribed levetiracetam at any time from 1 January to 31 August 2005, and not previously treated by levetiracetam. Exclusion criteria were as follows: refusal to participate, difficult to follow up (homeless, expected relocation in the near future etc.) or current participation in a clinical trial. Patients were included during their subsequent visit, after oral informed consent (in-line with requirements in France for anonymous observational studies). This process was repeated in December 2006 to identify patients initiating levetiracetam between 1 January and 31 August 2006. Physicians were compensated for each patient included, and they received further compensation for each patient followed up. Only adult patients are reported here (aged 16 years or above, the legal cut-off for paediatrics in France).

The date of levetiracetam initiation was considered as the index date. Throughout the study, physicians were asked to fill out standardized questionnaires from patient medical files. At inclusion, the following data were collected regarding sociodemographic and disease characteristics: type of epilepsy, aetiology, associated medical history, frequency and type of seizures as well as associated hospitalization(s) over the 6 months preceding levetiracetam initiation, previous and index AED use, as well as levetiracetam treatment (initiation date, reason for prescription, daily dose and titration regimen). Follow-up was for 1 year after levetiracetam initiation (index date). During follow-up, AEDs prescribed were recorded retrospectively for the period between index date (levetiracetam initiation) and inclusion, and prospectively at each subsequent patient visit. If the patient discontinued levetiracetam at any point during the 1 year follow-up, the date and reason for discontinuation, as well as the occurrence of any adverse events were recorded. At the end of study (12 months after index date) epilepsy-related hospitalizations during follow-up, and the number and characteristics of seizures over the last 6 months of follow-up were recorded.

The study protocol was approved by the national professional ethics committee (Conseil National de l'Ordre des Médecins), the committee in charge of data protection in biomedical research in France (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé) and the French national commission for data protection (Commission Nationale de l'Informatique et des Libertés). An independent scientific committee composed of five neurologists, one epidemiologist, one pharmacoepidemiologist and one biostatistician supervised the study.

Effectiveness measurements

The following two measures derived from prescriber questionnaires were considered for levetiracetam continuation: 1 year continuation of levetiracetam (regardless of additional AEDs) and 1 year continuation of levetiracetam without addition of a newly prescribed AEDs during follow-up. For those who maintained levetiracetam, epilepsy treatment goals were investigated. These included the following: freedom from seizures during the 6 months before end of study, reduction in the number of seizures during the 6 months before end of study compared with the same period of time before levetiracetam initiation, reduction of number of AEDs used and levetiracetam monotherapy.

Statistical analysis

Survival analyses were performed to estimate levetiracetam continuation rates using the Kaplan–Meier method. A sample size of 700 was chosen to obtain a precision ranging from 3.5 to 5.0% for observed proportions of

10–50% (or 90–50% complementary values) with a 95% confidence interval. Sensitivity analyses for levetiracetam 1 year continuation rate estimation were performed by considering patients without any follow-up to have either all maintained treatment, or all discontinued at day 1. Factors associated with levetiracetam discontinuation were identified using Cox proportional hazards regression. All variables with a value of $P < 0.25$ in univariate analysis were included in the initial multivariate model, and the less significant variables were successively removed. Only statistically significant variables ($P < 0.05$) were retained in the final multivariate model. In light of the sociodemographic, disease and treatment profiles, the study scientific committee decided that patients from both inclusion periods could be pooled for analysis. Statistical analyses were performed using the SAS software (version 9.1; SAS Institute, Cary, NC, USA).

Results

Study population

A total of 2235 neurologists were identified in the CEGEDIM database; 74.3% practised in a hospital setting, 22.5% in a nonhospital setting and 3.2% in both (the latter were considered to practise in a nonhospital setting), and 306 accepted the invitation to participate to the study. Of these, 184 were active and included at least one patient. Of the nonparticipating neurologists, 740 reported that they treated very few or no epileptic patients. Excluding these, the participation rate was 21.6% of the population of neurologists treating epileptic patients.

Participating neurologists included 794 epileptic patients, and 41 were not followed up. The remaining 753 patients were considered for Kaplan–Meier analysis. For these, the sex ratio (male/female) was 0.96 and the mean (SD) age was 42.6 (±17.0) years. Two-thirds of patients were treated in a hospital setting (64.0%). The mean (SD) age at epilepsy onset was 23.7 (±20.4) years. Patients suffered mainly from partial symptomatic epilepsy (47.9%), followed by partial cryptogenic (28.4%) and generalized epilepsy (23.4%), with 71.4% experiencing different types of seizures. The majority had experienced seizures in the 6 months preceding levetiracetam initiation (93.5%), and the median number of seizures experienced during this period was seven (interquartile range, IQR = 3–22). Epilepsy was associated with learning disabilities in 15.5% of patients, motor disabilities in 13.9% and psychiatric disorders in 38.9%. Nearly half (49.0%) had previously been treated with more than four different AEDs during their lifetime (Table 1). The reason given for levetiracetam initiation was lack of previous treatment efficacy for 80.5% of the patients and intolerance to previous treatment for 26.7%. The majority had an initiation dose ≤1000 mg day^{-1} (71.6%) and were on an increasing titration regimen (59.2%). Levetiracetam was most often associated with one or more other AED (82.9%, Table 2).

Table 1

Characteristics of the analysed population at levetiracetam initiation

Characteristic	*n* = 753
Female [*n* (%)]	385 (51.1)
Age [years; mean (SD)]	42.6 (17.0)
Age at epilepsy onset [years; mean (SD)]	23.7 (20.4)
Disabled or invalid [*n* (%)]	219 (29.1)
Missing data	2 (0.3)
Epilepsy treatment setting [*n* (%)]	
Hospital	482 (64.0)
Nonhospital	250 (33.2)
Hospital and nonhospital	21 (2.8)
Type of seizures and/or epilepsy [*n* (%)]*	
Missing data	2 (0.3)
Partial symptomatic	361 (47.9)
Partial cryptogenic	214 (28.4)
Generalized idiopathic	109 (14.5)
Generalized symptomatic or cryptogenic	67 (8.9)
Primary or secondary generalizations [*n* (%)]	546 (72.5)
Presence of multiple seizure types [*n* (%)]	538 (71.4)
Missing data	5 (0.7)
In the 6 months preceding levetiracetam initiation:	
Seizures [*n* (%)]	704 (93.5)
Missing data	14 (1.9)
Number [median (IQR)]	7.0 (3.0 ; 22.0)
Seizure-related falls [*n* (%)]	317 (42.1)
Missing data	8 (1.1)
Number [median (IQR)]	0.0 (0.0 ; 2.0)
Secondary generalizations [*n* (%)]	361 (47.9)
Missing data	12 (1.6)
Number [median (IQR)]	0.0 (0.0 ; 3.0)
Status epilepticus [*n* (%)]	49 (6.5)
Missing data	1 (0.1)
Previous history associated with epilepsy [*n* (%)]	
Learning disability	117 (15.5)
Motor disability	105 (13.9)
Hippocampal sclerosis	40 (5.3)
Missing data	64 (8.5)
Psychiatric disorders	293 (38.9)
Vagus nerve stimulation	4 (0.5)
Missing data	1 (0.1)
Other neurosurgery	88 (11.7)
Lifetime number of AEDs prescribed before levetiracetam initiation [*n* (%)]	
0	36 (4.8)
1	78 (10.4)
2–4	270 (35.9)
>4	369 (49.0)

*LFCE classification. AED, anti-epileptic drug; IQR, interquartile range; SD, standard deviation.

Effectiveness: levetiracetam continuation

At the end of study, 579 patients were still using levetiracetam treatment, 122 had discontinued treatment, five had died and 47 were lost to follow-up. The probability of levetiracetam continuation at 1 year was 83.5% [95% confidence interval, CI, 80.5–86.0) and that of levetiracetam continuation without additional AEDs was 72.5% (95% CI 69.1–75.6). Incidence densities did not vary significantly

Table 2

Characteristics of levetiracetam treatment at initiation

Characteristic	*n* = 753
Reason for levetiracetam initiation [*n* (%)]	
Insufficient efficacy of previous treatment	606 (80.5)
Poor tolerability of previous treatment	201 (26.7)
Levetiracetam dose at initiation [mg day^{-1}; *n* (%)]	
≤1000	540 (71.7)
>1000	213 (28.3)
Titration regimen [*n* (%)]	
Stable	307 (40.8)
Increasing	446 (59.2)
Concomitant AEDs at levetiracetam initiation [*n* (%)]	
Monotherapy (levetiracetam only)	129 (17.1)
Bitherapy (levetiracetam +1 other AED)	363 (48.2)
Tritherapy (levetiracetam +2 other AEDs)	184 (24.4)
Quadritherapy or more (levetiracetam +3 or more other AEDs)	77 (10.2)

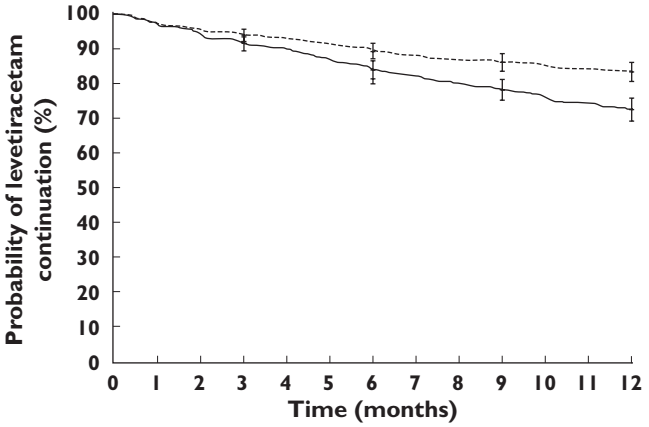

Figure 1

Estimated levetiracetam continuation rates using Kaplan–Meier analysis. Patients with follow-up data (*n* = 753) were considered for analysis of levetiracetam continuation independently of newly prescribed AEDs (dotted line) and in the absence of newly prescribed AEDs (continuous line). The 95% confidence intervals at 3, 6, 9 and 12 months are shown

over time (Figure 1). Sensitivity analyses were performed considering the 41 excluded patients that were not followed up. If these had all maintained treatment, the probability of levetiracetam continuation at 1 year would be 84.4% (95% CI 81.6–86.7) and for continuation without additional AEDs this would be 74.0% (95% CI 70.7–77.0). If these had all discontinued at day 1, the estimated probability of levetiracetam continuation at 1 year would be 79.2% (95% CI 76.1–81.9) and for levetiracetam continuation without additional AEDs this would be 68.8% (95% CI 65.3–71.9).

Of the patients continuing levetiracetam treatment (*n* = 579), 46.8% were seizure free in the 6 months preceding end of study (Table 3). Seizure freedom at end of study was found in 84 (30.0%) of those who had had seven or more seizures before levetiracetam initiation (*n* = 280), in 127 (59.1%) of those who had had two to six seizures before levetiracetam initiation (*n* = 215), in 38 (77.6%) of those who had had one seizure before levetiracetam initiation (*n* = 49) and in 19 (73.1%) of the 26 who were seizure free in the 6 months before levetiracetam initiation. Those with nonstabilized epilepsy at initiation (presence of seizures in the 6 months preceding levetiracetam initiation, *n* = 544) had a mean (SD) reduction of 59.6% (±83.5) in the number of seizures, with 249 (45.7%) being seizure free and 42 (7.7%) having an increase in seizure frequency. Seizure-related falls were experienced by 15% of continuing patients in the 6 months preceding end of study (Table 3). Of 253 having falls preceding levetiracetam initiation, 185 (73.1%) had no falls over the last 6 months. The mean (SD) dose of levetiracetam taken at end of study was 1562.3 mg day^{-1}, and 24% of levetiracetam patients were on levetiracetam alone (Table 3). Of those initially receiving levetiracetam monotherapy (*n* = 106), 86.8% (*n* = 92) were still on monotherapy at the end of follow-up. Of those initially polytreated (*n* = 473), 24.7% (*n* = 117) had a reduction in the number of AEDs used, and 9.9% (*n* = 47) were on levetiracetam monotherapy at the end of follow-up.

Effectiveness: levetiracetam discontinuation

Discontinuation of levetiracetam (*n* = 122 patients) was motivated most often by the occurrence of adverse events (45.1%), insufficient efficacy (37.7%) or both (9.8%). Adverse events (*n* = 67 patients) were mostly behavioural or psychological (32.8%) or fatigue/somnolence (32.8%); the majority were not serious events (92.5%, Table 4). Cox proportional hazards regression, adjusted on inclusion period and age, found that levetiracetam discontinuation was more frequent in patients with a lifetime use of more than four AEDs before levetiracetam initiation (hazards ratio, HR, 1.9; 95% CI 1.3–2.8), in women (HR 1.8; 95% CI 1.2–2.7), in patients included by neurologists practising in a hospital setting (HR 1.8; 95% CI 1.2–2.8), in patients presenting in the 6 months before levetiracetam initiation with multiple types of seizures (HR 1.8; 95% CI 1.1–3.0) and in patients with primary or secondary generalization (HR 1.7; 95% CI 1.1–2.6). Discontinuation was less frequent in those experiencing one or more seizures with falls before levetiracetam initiation (HR 0.4; 95% CI 0.3–0.6). There was confounding between presence of falls and epilepsy type (partial or generalized); 89.3% of those with falls (*n* = 317) were reported to have primary or secondary generalization. Epilepsy type was forced into the final model because it was not significant in univariate analysis.

Discussion

This population-based cohort study of real-life practice in France found a 1 year levetiracetam continuation rate of 83.5% (95% CI 80.5–86.0). This is higher than reported in

Table 3

Treatment and disease characteristics at levetiracetam initiation and end of study for those continuing levetiracetam

Characteristic	At levetiracetam initiation *n* = 579	At end of study *n* = 579
Levetiracetam dose [mg day^{-1}; mean (SD)]	1139.4 (536.5)	1562.3 (721.3)
Concomitant AEDs [*n* (%)]		
Monotherapy (levetiracetam only)	106 (18.3)	139 (24.0)
Bitherapy (levetiracetam +1 other AED)	278 (48.0)	278 (48.0)
Tritherapy (levetiracetam +2 other AEDs)	142 (24.5)	127 (21.9)
Quadritherapy or more (levetiracetam +3 or more AEDs)	53 (9.2)	35 (6.1)
Seizures in the preceding 6 months [*n* (%)]		
Missing data	9 (1.6)	5 (0.9)
Seizure free	26 (4.5)	271 (46.8)
At least 1 seizure	544 (94.0)	303 (52.3)
Number of seizures [median (IQR)]	6.0 (3.0; 20.0)	1.0 (0.0; 6.0)
Seizure-related falls in the preceding 6 months [*n* (%)]		
Missing data	7 (1.2)	5 (0.9)
None	319 (55.1)	487 (84.1)
At least 1	253 (43.7)	87 (15.0)

Table 4

Characteristics of levetiracetam discontinuation

Reasons for discontinuation* [*n* (%)]	*n* = 122
Poor tolerability	55 (45.1)
Insufficient efficacy	46 (37.7)
Both poor tolerability and insufficient efficacy	12 (9.8)
Noncompliance	4 (3.3)
Other	6 (4.9)
Poor tolerability [*n* (%)]	***n* = 67**
Adverse reaction source	
Behavioural and psychological	22 (32.8)
Fatigue/somnolence	22 (32.8)
Neurological	9 (13.4)
Headache	5 (7.5)
Digestive	4 (6.0)
Cutaneous	4 (6.0)
Pancytopenia	1 (1.5)
Seriousness*	
Nonserious	62 (92.5)
Hospitalization	4 (6.0)
Prolongation of hospitalization	1 (1.5)
Life threatening	1 (1.5)

*More than one answer possible.

clinical trials or earlier observational studies; from clinical trials data, 1 year levetiracetam continuation was estimated to be approximately 60% [20, 21]. Postmarketing observational studies of patients treated soon after levetiracetam marketing found 1 year rates that ranged from 60 to 75% [8–11, 13, 22]. The use of continuation rates is recognized as a composite measure of treatment efficacy and tolerability of AEDs [17]. Those patients who discontinued in the present study did so mainly for reasons of poor tolerability or poor efficacy. However, patients may continue treatment if they find only partial efficacy in the absence of undesirable effects, and this may be particularly the case for levetiracetam, which has a good tolerability profile. This was investigated here using the 1 year continuation rate in the absence of addition of other AEDs to the treatment regimen, in a similar manner to Knoester *et al.* [23]. Using such a definition in the present study resulted in an estimated continuation rate of 72.5% (95% CI 69.1–75.6). There are certain limits when interpreting this difference, as the reason for the added AED is not known. However, it could suggest that for those who had additional AEDs the levetiracetam alone was insufficient to obtain disease control (i.e. partial efficacy/effectiveness). Despite being lower, the result does consolidate that found for levetiracetam continuation because it indicates that the majority of patients continuing levetiracetam do so without additional AEDs.

Compared with previous observational studies, the retrospective inclusion of patients by physicians may have contributed to the higher continuation rates. In such a study design, it is possible that participating physicians did not include patients who had rapidly discontinued levetiracetam after initiation and during the retrospective inclusion period. This was addressed by compensating physicians for each patient included, whether they were still on levetiracetam or not. If such a selection bias did occur, it should be limited because the incidence density of discontinuation over the study did not vary significantly (data not shown). Retrospective inclusion was chosen so as not to influence *a priori* the choice of patients put on levetiracetam. Once the patient was included, follow-up was prospective, so that the bias would at worst only affect early discontinuation, mostly related to tolerability issues and not to efficacy. The physician response rate of 20% of potential prescribers is common in our experience. Usual reasons for nonparticipation are not related to the patients the prescriber treats, but to time constraints. For a selection

bias to be relevant, the reasons for nonparticipation would need to have an impact on the prospective 1 year continuation rate, which seems quite unlikely. In another study, we found no difference in characteristics between patients whose prescribers participated and patients whose prescribers did not participate in the study [24].

Another factor to consider is the difference in study populations. While the present study included patients initiating levetiracetam several years after its marketing in France and included patients treated by both hospital and nonhospital neurologists, most of the observational studies cited above explicitly included patients initiating levetiracetam in the 2 years immediately after commercialization of the drug in their respective countries and treated in a specialized epilepsy clinic [8, 9, 11, 22]. This may have led to channelling of levetiracetam to more severely affected patients than those considered here [18]. Evidence to support this hypothesis comes from the characteristics of the populations in these studies, such as the higher previous AED exposure (an approximation of pharmacoresistance) reported by Nicolson *et al*. [11], the higher number of AEDs concurrent to levetiracetam [8–11, 22] and the higher number of seizures experienced in the period before levetiracetam initiation [10, 22]. These differences may explain the higher continuation rates observed in the present cohort. This is further reinforced by the finding that exposure to more than four AEDs before levetiracetam initiation here was the factor most strongly associated with discontinuation, similar to what has been reported elsewhere [9, 11, 15].

Several other factors were also found to be associated with discontinuation. The association with female gender has not yet been reported for levetiracetam in observational studies. Certain AEDs are known to interact with oral contraceptives and/or other AEDs, which is not the case for levetiracetam [25, 26] as reported in the desk reference Summary of Product Characteristics for prescribers in France at the time of the study [27, 28]. In this reference, the potential teratogenicity of levetiracetam is also described, but pregnancy or desire of pregnancy was not evoked as a reason for drug discontinuation. It is possible that in the absence of dose adjustment, undisclosed or unknown pregnancy could have led to inefficacy because it results in higher clearance [29, 30]. However, the association with gender was independent of age, which does not support pregnancy as an explanation of this. Catamenial epilepsy [31] may provide a more plausible line of investigation for future studies, but potential confounding cannot be put aside. Lastly, presence of generalized events (primary or secondary) before levetiracetam initiation was forced into the model owing to confounding with seizure-related falls that were associated with continuation. At this point, it is interesting to note that of the patients who had experienced falls in the 6 months preceding levetiracetam initiation and who were continuing levetiracetam at end of study, nearly three-quarters were free from seizure-related falls during the 6 months preceding end of study. This particular efficacy of levetiracetam could be due to reduced corticospinal excitability [32]. Such an association may also be due to confounding with a particular type of seizure, or with a mechanism of action common to several seizure types, but it was beyond the scope of the present study to investigate this. In fact, the drug might also reduce primary or secondary generalization of seizures that results in falls.

The study also allowed the investigation of treatment goals in epilepsy. Nearly a quarter of those who maintained treatment at end of study had a reduction in the number of AEDs. At the end of follow-up, 9.9% of those initially on multitherapy were treated by levetiracetam alone. Nearly half achieved freedom from seizures, considerably more than reported in other nonselective observational studies [8, 10, 11, 22]. Such direct comparisons may be flawed, as the definition used here differed from that used in other studies with regards to temporal boundaries within which freedom from seizures was measured. However, as noted above, a higher effectiveness may be related to the relative seizure severity of the patients considered here, as it is reported that the magnitude of decrease in the number of seizures is inversely associated with pharmacoresistance for levetiracetam [10] as well as other AEDs [33], but also with the number of seizures experienced before treatment initiation [34]. Concordant with this is the finding here that the proportion of patients attaining seizure freedom decreased with increasing numbers of seizures experienced before levetiracetam initiation.

In conclusion, this population-based cohort study conducted several years after drug authorization in France found a higher 1 year levetiracetam continuation rate than previous studies done soon after market authorization. This might better reflect the effects expected in real-life use in a stable market environment.

Competing interests

H.V. has been reimbursed by UCB pharma, manufacturer of levetiracetam, for attending several conferences, received fees for speaking and consulting. C.M. has been reimbursed by UCB pharma, manufacturer of levetiracetam, for attending one conference. The other authors declared no competing interests. The study was funded by an unconditional grant from UCB Pharma who had no direct role in study design, in the collection, analysis and interpretation of data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

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